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Cognitive effects of atypical antipsychotic drugs in first-episode drug-naïve schizophrenic patients☆

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Abstract

Cognitive impairment is a core feature of schizophrenia. The present randomized open study enrolled antipsychotic-naïve patients who were experiencing their first episode of schizophrenia. After baseline neurocognitive tests and clinical assessment, subjects were randomly assigned to olanzapine, risperidone and aripiprazole treatment groups. A battery of neurocognitive tests showed that risperidone produced cognitive benefits in all five cognitive domains, including verbal learning and memory, visual learning and memory, working memory, processing speed, and selective attention; olanzapine improved processing speed and selective attention; and aripiprazole improved visual learning and memory, and working memory. However, the three atypical antipsychotic drugs failed to reveal any significant differences in the composite cognitive scores at the study endpoint. In addition, the three drugs all significantly improved clinical measures without significant differences between the drugs after 6 months. These results suggest that the atypical antipsychotics, olanzapine, risperidone and aripiprazole may improve specific cognitive domains with similar global clinical efficacy. In clinical practice, it may be feasible to choose corresponding atypical antipsychotics according to impaired cognitive domains.

Key Words

neural regeneration; clinical practice; olanzapine; risperidone; aripiprazole; schizophrenia; cognition; memory; grant-supported paper; neuroregeneration

Research Highlights

(1) This study enrolled antipsychotic-naïve patients who were experiencing their first episode of schizophrenia, diagnosed according to the *Diagnostic and Statistical Manual of Mental Disorders* (Fourth Edition).
(2) Risperidone produced cognitive benefits in all five cognitive domains, including verbal learning and memory, visual learning and memory, working memory, processing speed and selective attention.
(3) Olanzapine improved processing speed and selective attention.
(4) Aripiprazole improved visual learning and memory, and working memory.
(5) Aripiprazole was developed later than several other atypical antipsychotic drugs, such as olanzapine and risperidone, so relatively few studies have examined its effects on cognition.

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INTRODUCTION

Cognitive impairment is a core feature of schizophrenia. Cognitive deficits include processing speed, attention/vigilance, working memory, verbal learning and memory, visual learning and memory, and reasoning and problem solving[1]. The deficits may lead to poor functional outcomes, including difficulties in maintaining work and social connections, living independently, and acquiring skills in rehabilitation. Cognitive impairments

associated with schizophrenia have become one of the most important targets of therapeutic intervention.

Numerous studies have reported the relationship between atypical antipsychotic drugs and cognitive function in patients with schizophrenia. Since atypical antipsychotic drugs are available, many studies have found that such drugs may enhance neurocognitive performance in schizophrenia[2-6]. Woodward *et al* [7] compared cognitive changes with haloperidol and atypical antipsychotics in their meta-analysis, observing the broader range of cognitive improvements with atypical antipsychotics. These improvements include both global cognitive function and individual cognitive domains[8]. Significant differences emerged in attention and verbal fluency when comparing different atypical antipsychotic drugs (clozapine, olanzapine, quetiapine, and risperidone). Several limitations in previous studies need to be considered. Most studies use typical antipsychotics (such as haloperidol) as comparators, so some confounding factors (such as anticholinergic drug use or high doses of typical medications) may influence the results. In addition, many schizophrenic subjects have used adjunctive medications such as antidepressants or anxiolytics, which may have detrimental effects on cognitive function and influence the cognitive effects of atypical antipsychotic drugs. Furthermore, chronic schizophrenic patients who perform a short-term follow-up are less likely to benefit from study drugs relative to untreated first-episode schizophrenic patients.

Some studies have directly compared the effects of different atypical antipsychotics on cognitive deficits among patients with schizophrenia[9-11]. Keefe *et al* [12] found that olanzapine, quetiapine and risperidone all made modest improvements in cognition at week 12, but the cognitive effects of these medications at week 52 were small. Riedel *et al* [10] examined 8-week cognitive effects of aripiprazole, olanzapine, quetiapine and risperidone. The results showed that different atypical antipsychotic drugs had different effects in certain cognitive domains. Quetiapine was found to enhance working memory, verbal memory, reaction quality and visual memory. Olanzapine significantly improved working memory, verbal memory and visual memory. Risperidone resulted in significantly improved reaction times. Aripiprazole was found to improve reaction time and reaction quality.

The relationship between cognitive function and olanzapine or risperidone has been investigated in many studies[6, 13-15]. Consistent results showed that these two atypical antipsychotics had the potential to improve some cognitive domains. Several reports[10, 16-18] have also found that aripiprazole produces a degree of cognitive improvement in patients with schizophrenia. These three atypical antipsychotics are now widely used in clinical practice.

In the present study, we directly compared the cognitive effects of olanzapine, risperidone and aripiprazole. To avoid the confounding factors mentioned above, antipsychotic-naïve first-episode schizophrenic patients were enrolled. The reasons for selection of such a sample receiving 6 months' treatment are as follows: first, relative to chronic, previously medicated patients, antipsychotic-naïve first-episode schizophrenic patients may be particularly susceptible to improvements in cognition; furthermore, first-episode schizophrenia avoids the possible confounding factors relating to age, duration of illness, and prior exposure to antipsychotics. Finally, consistent studies suggest that atypical antipsychotic drugs have been found to continue to improve the positive and negative symptoms of schizophrenia for at least 6 months after initiation of treatment. If the time course of response of cognitive deficits and clinical efficacy are similar, appropriate cognitive improvement trials should also be of a similar duration. Therefore, the principal aim of the present study in first-episode schizophrenic patients was to compare the cognitive effects of olanzapine, risperidone, or aripiprazole after 6 months of treatment.

RESULTS

Quantitative and baseline analyses of participants

One hundred antipsychotic-naïve outpatients who were experiencing their first episode of schizophrenia received cognitive tests and clinical assessments at baseline. Then they were randomly assigned to receive olanzapine (n = 32), risperidone (n = 34) or aripiprazole (n = 34). During the 6-month follow-up period, 26 patients withdrew from the study. As a result, 27 patients took olanzapine, 23 took risperidone and 24 took aripiprazole. Seventy-four patients who completed the whole trial and had intact clinical and neurocognitive data at baseline and after 6 months of treatment entered the statistical analysis.

The demographics of the 74 patients were analyzed at baseline. There were no significant differences in sex, age, education and duration of untreated psychosis

among the different treatment groups for patients who completed the study (Table 1).

Table 1 Demographic and clinical characteristics of the samples at baseline

Variable	Olanzapine (*n* = 27)	Risperidone (*n* = 23)	Aripiprazole (*n* = 24)	χ^2/F	*P*
Sex (M/F, *n*) [a]	20/7	14/9	15/9	1.19	0.552
Age (year)[b]	22.3±5.4	25.0±6.2	23.3±5.9	2.59	0.274
Education (year)[b]	11.5±2.5	11.2±2.4	11.5±2.5	0.68	0.712
Duration of psychosis (month)[c]	11.4±3.5	12.1±4.3	13.4±4.6	1.40	0.254
PANSS scores at baseline					
Positive score[c]	22.5±4.3	23.4±5.5	22.4±5.7	0.30	0.741
Negative score[c]	24.0±7.2	24.5±6.9	23.9±5.3	0.05	0.948
Total score[c]	91.7±13.0	93.7±9.7	93.3±10.0	0.23	0.795

Data except for sex are expressed as mean ± SD. a: Chi-square tests; b: Kruskal-Wallis tests; c: one-way analysis of variance. M: Male; F: female; PANSS: Positive and Negative Syndrome Scale.

Reasons for patient withdrawal from the study were as follows: lost to follow-up (olanzapine *n* = 2; risperidone *n* = 3; aripiprazole *n* = 3), medication noncompliance (olanzapine *n* = 2; risperidone *n* = 3; aripiprazole *n* = 2), lack of efficacy (olanzapine *n* = 1; risperidone *n* = 2; aripiprazole *n* = 3), and intolerable side effects (risperidone *n* = 3; aripiprazole *n* = 2). The flow chart of patients with first-episode schizophrenia through the trial is shown in Figure 1.

Clinical efficacy of the three atypical antipsychotic drugs for first-episode schizophrenic patients

Using paired *t*-tests to compare the means (baseline *vs*. endpoint) within each treatment group, significant clinical efficacy ($P < 0.001$) was obtained from the three medications (Table 2, Figures 2–4) and was not influenced by drugs. At 6 months, the number of patients who received alprazolam was five (19%) in the olanzapine group, eight (35%) in the risperidone group and nine (38%) in the aripiprazole group. The number of patients using anticholinergic medications was zero in the olanzapine group, nine (39%) in the risperidone group and eight (35%) in the aripiprazole group.

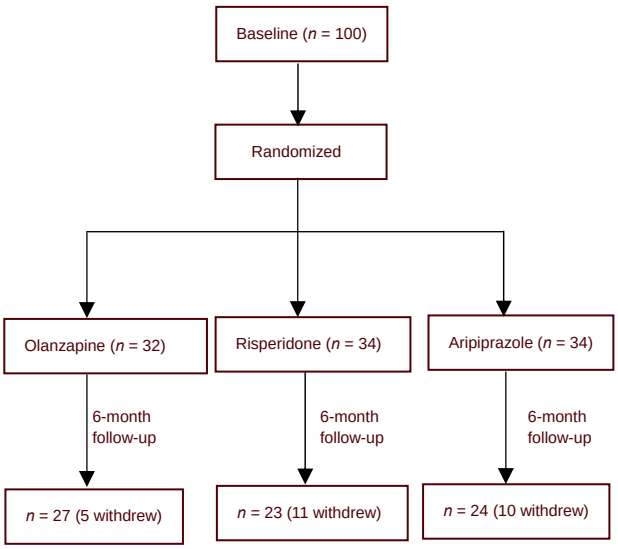

Figure 1 Flow chart of patients with first-episode schizophrenia through the trial.

Neurocognitive effects of the three atypical antipsychotics

A between-group baseline comparison one-way analysis of variance showed no differences in cognitive domains ($P > 0.10$), with the exception of processing speed ($P = 0.02$). Covariance analysis was used to compare change in this domain at two time points among the three treatment groups. No statistically significant difference was observed between the three groups in processing speed ($P = 0.241$). Irrespective of medication type, the patients showed significant improvements in cognitive composite score and the four cognitive domain scores (*z* scores), including processing speed, working memory, selective attention and visual learning over time (Table 3).

Table 2 Psychopathological symptoms: scores of the three treatment groups at baseline and at 6 months

PANSS ratings[b]	Olanzapine (*n* = 27)		Risperidone (*n* = 23)		Aripiprazole (*n* = 24)		Main effects[a]			
							Time		Group-by-time	
	Baseline	6 months	Baseline	6 months	Baseline	6 months	*F*	*P*	*F*	*P*
Positive score	22.5±4.3	14.6±3.6	23.4±5.5	15.2±4.0	22.4±5.7	14.7±3.7	907.20	< 0.001	0.21	0.811
Negative score	24.0±7.2	15.5±5.5	24.5±6.9	15.9±4.9	23.9±5.3	15.4±4.9	524.66	< 0.001	0.24	0.787
Total score	91.7±12.9	58.0±8.4	93.7±9.7	58.0±7.6	93.3±10.0	56.3±8.5	2 271.66	< 0.001	2.55	0.086

Data are expressed as mean ± SD. a: Repeated measures analysis of variance; b: for PANSS subscale scores and total scores, intra-group, *post-hoc* paired *t*-test, and 6 months *vs*. baseline of the three treatment groups, $P < 0.001$. PANSS: Positive and Negative Syndrome Scale.

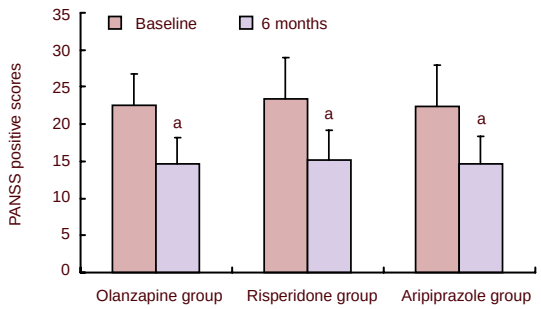

Figure 2 PANSS positive scores at baseline and 6 months after treatment.

Significant intra-group differences between baseline and endpoint score. Data are expressed as mean ± SD. [a]*P* < 0.001, *vs*. baseline (paired *t* test). PANSS: Positive and Negative Syndrome Scale.

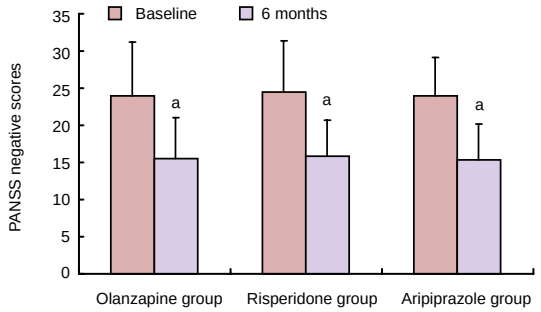

Figure 3 PANSS negative scores at baseline and 6 months after treatment.

Significant intra-group differences between baseline and endpoint score. Bars represent mean ± SD. [a]*P* < 0.001 *vs*. baseline (paired *t* test). PANSS: Positive and Negative Syndrome Scale.

Paired *t*-tests showed that the cognitive composite scores of all three treatment medications increased over time (olanzapine, $t_{(26)} = -2.12$, $P = 0.044$; risperidone, $t_{(22)} = -5.48$, $P < 0.001$; aripiprazole, $t_{(23)} = -3.43$, $P = 0.002$.

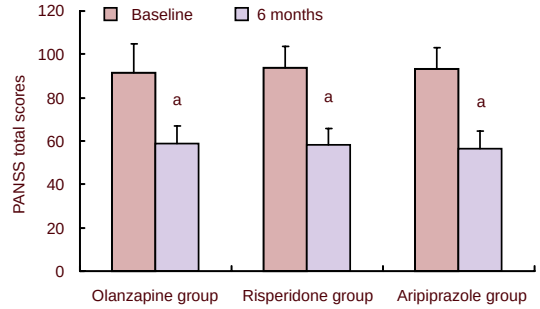

Figure 4 PANSS total scores at baseline and 6 months after treatment.

Significant intra-group differences between baseline and endpoint score. Data are expressed as mean ± SD. [a]*P* < 0.001, *vs*. baseline (paired *t* test). PANSS: Positive and Negative Syndrome Scale.

A paired *t*-test showed that olanzapine improved two of the five domain scores, including processing speed ($t_{(26)} = -2.11$, $P = 0.045$) and selective attention ($t_{(26)} = -3.30$, $P = 0.003$). Risperidone improved all five cognitive domains, including verbal learning ($t_{(22)} = -2.25$, $P = 0.035$), processing speed ($t_{(22)} = -4.05$, $P = 0.001$), visual learning ($t_{(22)} = -4.59$, $P < 0.001$), selective attention ($t_{(22)} = -4.42$, $P < 0.001$) and working memory ($t_{(22)} = -2.70$, $P = 0.013$). Aripiprazole improved visual learning ($t_{(23)} = -2.48$, $P = 0.021$) and working memory ($t_{(23)} = -2.61$, $P = 0.016$). Although group-by-time main effects revealed significant differences in mean *z*-score changes of cognitive composite scores ($P = 0.034$) for the three antipsychotics after 6 months of treatment, differences disappeared between treatment groups after Bonferroni correction for multiple comparisons. The effect sizes of the three atypical antipsychotics on cognitive composite scores and five cognitive domains over time are shown in Table 4.

Table 3 Mean *z* scores of cognitive composite scores and individual cognitive domains at baseline and 6 months

Domains	Olanzapine (*n* = 27)		Risperidone (*n* = 23)		Aripiprazole (*n* = 24)		Main effects[a]			
							Time		Group-by-time	
	Baseline	6 months	Baseline	6 months	Baseline	6 months	*F*	*P*	*F*	*P*
Global score[b]	0.09±0.61	0.30±0.51[d]	–0.26±0.73	0.28±0.53[e]	0.15±0.66	0.42±0.51[e]	39.72	< 0.001	3.55	0.034
Verbal learning	0.15±0.78	0.05±0.70	–0.28±1.06	0.14±0.80[d]	0.09±0.91	0.29±0.77	3.03	0.086	2.52	0.088
Visual learning	0.15±0.90	0.52±0.80	–0.33±1.11	0.70±0.87[e]	0.14±0.96	0.74±0.75[d]	27.57	< 0.001	2.33	0.105
Processing speed[c]	0.17±0.77	0.37±0.76[d]	–0.41±0.83	0.01±0.69[e]	0.23±0.89	0.21±0.78	NA	NA	NA	NA
Working memory	0.08±0.82	0.21±0.77	–0.10±0.94	0.28±0.64[d]	0.01±0.89	0.39±0.74[d]	14.75	< 0.001	1.18	0.310
Selective attention	–0.06±0.85	0.37±0.64[e]	–0.23±0.84	0.25±0.75[e]	0.29±0.82	0.48±0.91	28.80	< 0.001	1.74	0.184

Measurement data are expressed as mean ± SD.

a: Repeated measures analysis of variance; b: Bonferroni *post-hoc* multiple comparisons (no significant differences found between treatment groups; $P > 0.041$); c: analysis of variance used to compare mean *z* scores across the cognitive domains. Intra-group, paired *t* test of 6 months *vs*. baseline, [d]*P* < 0.05, [e]*P* < 0.01. NA: Not assessed.

Table 4 Effect sizes (Cohen's d) of global cognitive score and different cognitive domains over time for the three treatment groups

Group	Global score	Verbal learning and memory	Visual learning
Olanzapine	0.37	–0.13	0.43
Risperidone	0.85	0.40	1.03
Aripiprazole	0.46	0.22	0.70

Group	Processing speed	Working memory	Selective attention
Olanzapine	0.26	0.16	0.57
Risperidone	0.55	0.47	0.56
Aripiprazole	0.02	0.46	0.60

Relationship between cognitive change and negative symptom change of the three treatment groups

Pearson correlations did not reveal a relationship between the z change scores of the cognitive composite score and individual cognitive domains and the treatment-related change scores in the clinical Positive and Negative Syndrome Scale (PANSS) negative score for the entire sample (composite score, r = –0.15, P = 0.209; verbal learning and memory, r = –0.18, P = 0.134; visual learning and memory, r = –0.09, P = 0.468; processing speed, r = –0.01, P = 0.904; working memory, r = –0.07, P = 0.572; selective attention, r = 0.05, P = 0.701) after the 6-month follow-up. For each group, the Pearson correlations showed no correlation between change in cognitive performance and change in negative symptoms scores (olanzapine group: composite score, r = –0.15, P = 0.245; verbal learning and memory, r = –0.22, P = 0.272; visual learning and memory, r = –0.20, P = 0.324; processing speed, r = –0.26, P = 0.196; working memory, r = –0.143, P = 0.476; selective attention, r = –0.17, P = 0.398; risperidone group: composite score, r = –0.19, P = 0.395; verbal learning and memory, r = –0.21, P = 0.331; visual learning and memory, r = –0.10, P = 0.804; processing speed, r = 0.08, P = 0.715; working memory, r = –0.32, P = 0.885; selective attention, r = 0.18, P = 0.424; aripiprazole group: composite score, r = –0.01, P = 0.956; verbal learning and memory, r = –0.10, P = 0.639; visual learning and memory, r = –0.02, P = 0.918; processing speed, r = 0.00, P = 0.99; working memory, r = –0.05, P = 0.825; selective attention, r = 0.08, P = 0.729).

DISCUSSION

In the present study, we observed and compared the cognitive effects of three atypical antipsychotics in drug-naïve subjects with first-episode schizophrenia after 6 months of treatment. The results demonstrate that atypical antipsychotics can enhance cognition after 6 months of treatment.

It has been reported that atypical antipsychotic drugs produce improvements in some but not all cognitive domains in patients with schizophrenia. Different atypical antipsychotics may have differential effects regarding improvement of certain cognitive domains. Meltzer *et al* [19] summarized the effects of atypical antipsychotics on cognition in schizophrenia. Preliminary evidence showed that olanzapine enhanced verbal learning and memory, verbal fluency, and executive function, but not attention, working memory, or visual learning and memory. With regard to risperidone, consistent studies showed its improvement on working memory, executive functioning, and attention. In this trial, when comparing baseline cognitive performance with follow-up performance, risperidone showed improvement in all five cognitive domains and olanzapine in two domains (processing speed and selective attention). The results are consistent with previous studies that have found atypical antipsychotics producing improvements in neurocognitive performance in early psychosis[2, 20-21]. The wide-ranging cognitive improvement associated with risperidone in this study is consistent with a previous study that showed improvements in episodic memory, verbal fluency, vigilance, executive functioning, and visuomotor speed after 3 months of treatment[21]. However, Malla *et al* [22] failed to find significant cognitive improvements in first-episode psychosis patients after treatment with olanzapine or risperidone for 1 year. The inconsistent results may be associated with study samples, cognitive test batteries, and medication status in different studies.

Reports of aripiprazole's effects on cognition are limited. In a case study, Mucci *et al* [16] observed that aripiprazole has cognitive enhancing effects compared with olanzapine and amisulpride. Other studies found that aripiprazole improved reaction time, reaction quality[23] and motor speed[18]. Here, the aripiprazole group showed significant improvement in working memory, and visual learning and memory, but no improvements in other domains. Risperidone (effect size = 0.55) showed better processing speed improvement than aripiprazole (effect size = 0.02). Ceiling effects and baseline differences in processing speed between the two groups may account for the small effect size of aripiprazole. A recent report showed that the cognitive profile of aripiprazole was different from that of olanzapine and risperidone because of its unique pharmacology[17]. More studies, particularly

those using a larger sample size, are required to verify these results. The various results between the different studies may be attributed to the sample size, the cognitive tests employed and the medication status prior to enrollment.

When comparing the three antipsychotics, we found no significant differences in cognitive changes of any domain after 6 months of treatment (after Bonferroni correction). The result is consistent with previous studies, which suggest that atypical antipsychotics have similar effects on cognition[9, 12]. The effects may be independent of the duration of treatment. In a 1-year double-blind study of schizophrenia, olanzapine and risperidone were equivalent concerning cognitive amelioration at 8, 24, and 52 weeks of treatment[24]. Keefe *et al*[12] obtained a similar result in their randomized, double-blind 52-week cognition comparison of olanzapine, quetiapine and risperidone. However, another multicenter, double-blind study over 1 year showed a significantly greater benefit from treatment with olanzapine than with risperidone[25]. For the three study medications, the global cognitive effect sizes, from moderate (0.37) to large (0.85), are greater than those observed in the Clinical Antipsychotic Trials of Intervention Effectiveness study[26]. This may be due to differences in baseline characteristics of the sample, such as short duration of illness, relatively young patients, lack of previous exposure to any other antipsychotic medication and over 9 years of education.

Atypical antipsychotic drugs have been reported to improve cognitive function. However, the mechanisms for such effects are not well understood. Multiple neurotransmitter systems may be involved in cognitive efficacy. Many studies on the cognitive effects of olanzapine have focused on reduced dopaminergic activity, along with more pronounced serotonergic, adrenergic or histaminic effects[19]. For risperidone, the cognition-enhancing effect may be correlated with the combination of low-affinity antagonism of D_1 and high-affinity antagonism of 5-HT2A/2C[27]. With regard to aripiprazole, the cognitive mechanism may be related to its unique pharmacology, since aripiprazole is a partial agonist at D_2 and D_3 dopamine receptors and increases dopamine transmission in the prefrontal cortex and hippocampus[28].

Here, we observed a significant reduction in positive and negative symptoms, as well as the total score, as rated by PANSS. In addition, no difference was observed between the degrees of improvement in the three groups. Because the patients enrolled at baseline, had never taken any antipsychotics and had experienced only a short duration of untreated psychosis, they may be susceptible to obtaining particularly large clinical benefits from treatment with atypical antipsychotics.

Cognitive dysfunction and negative symptoms share many similar features and often correlate in their severity when examined cross-sectionally[29]. Changes in negative symptoms may influence cognitive effect. However, the current study revealed no correlations between improvement in negative symptoms, as assessed by PANSS, and change in the cognitive composite score, irrespective of treatment group. These results may indicate that negative symptoms and cognition should be viewed as relatively independent targets for intervention. Gold[30] has offered four lines of evidence for the hypothesis: (1) the developmental course of the two domains is distinct; (2) the response to antipsychotic medication is distinct; (3) the cross-sectional correlations are weak; and (4) cognitive impairment seems to be a risk factor for schizophrenia.

Some studies have proven that practice effects may partially contribute to cognitive improvements in first-episode schizophrenia patients[6, 31]. In a study on first-episode schizophrenia, Goldberg and colleagues[31] compared the effects of two atypical antipsychotics (olanzapine and risperidone) on cognition. The study also assessed healthy controls on the same battery and points as the patients. The results showed that the composite effect size for cognitive change (0.36) in first-episode schizophrenia was consistent with that of the healthy control group (0.33), but may be attributed to practice effects. Because of the lack of a healthy comparison group, we could not separate out the magnitude of the cognitive results from the practice effects. To minimize practice effects, parallel versions of the Hopkins Verbal Learning Test-Revised™/Brief Visuospatial Memory Test-Revised™ were applied at the 6-month retest. In addition, the 6-month interval is long enough to attenuate the practice effects[5].

However, our study has a number of limitations. First, the study lacks a matched control group using the same cognitive tests to retest their cognitive function over a similar time interval, so it is difficult to determine how practice effects influence cognitive performance during the retest. Second, because of the small sample size, it was not possible to perform any subgroup analysis. So any potential differences between subgroups were not recognized. Third, while the cognitive tests were objective, the nature of the open-label study may lead to

expectations of patients and their relatives, thus influencing the study results. Future studies should use a larger sample size, a double-blind design, a multicenter study with longer follow-ups, and standard cognitive testing tools.

In conclusion, we have shown that the degree of global cognitive function improvement varies depending upon the antipsychotic administered during a 6-month follow-up. Different atypical antipsychotics tend to enhance different individual cognitive domains. The improvements are independent of negative symptoms, consistent with previous studies. However, practice effects cannot be completely excluded.

SUBJECTS AND METHODS

Design

An open-label, randomized, follow-up clinical trial in a natural setting.

Time and setting

This study was performed at the outpatient clinic of the Second Xiangya Hospital of Central South University, China, from October 2008 to April 2010.

Subjects

One hundred outpatients were recruited. Schizophrenia or schizophreniform disorder was diagnosed by two qualified psychiatrists using the Structured Clinical Interview according to the *Diagnostic and Statistical Manual of Mental Disorders* (Fourth Edition) criteria (American Psychiatric Association, 1994).

The following criteria were met for inclusion in the study: Han Chinese (chosen to maintain a homogeneous sample); aged 16 to 35 years; first-episode patients without previous exposure to any antipsychotic or other medication affecting cognitive function; course of illness lasting for at least 1 month but no longer than 2 years; PANSS[32] total score higher than 60 at baseline; education over 9 years; agreeable to take part in a neurocognitive assessment and to sign the informed consent form.

Patients were excluded for the following reasons: history of brain injury; significant substance abuse; pregnancy or nursing; serious risk of suicide; severe, unstable medical illness; unwilling to take any research medication or accept cognitive testing; refusal to sign informed consent form.

All study procedures were performed in accordance with the *Administrative Regulations on Medical Institution*, issued by the State Council of China[33]. All patients or their legally authorized representatives gave written informed consent for their participation after receiving a detailed description of the study procedures, including risks and benefits.

After obtaining written informed consent from the patients or their legally authorized representatives, and completing the baseline assessments, patients were randomly assigned to take olanzapine, risperidone or aripiprazole in a natural setting. Patients were given antipsychotic medication from low to high doses: olanzapine (2.5–20 mg per day), risperidone (1–4 mg per day), and aripiprazole (5–20 mg per day). In general, the initial dose of olanzapine was 2.5 mg per day, risperidone was 1 mg per day, and aripiprazole was 5 mg per day. After 2 days, the doses of the three medications were gradually increased until they reached the recommended maximum therapeutic dose. Researchers could flexibly adjust the medication dose according to the response of different patients. Anticholinergic medications (benzhexol hydrochloride, 2–4 mg per day) were used to relieve extrapyramidal side effects, and alprazolam could be prescribed to treat agitation and insomnia in the study-recommended dose ranges (0.4–0.8 mg per day). Patients should discontinue these medications within 24 hours prior to clinical or cognitive assessments.

Methods

Clinical measures of samples

Symptoms were assessed by PANSS[32], which was also used to assess clinical efficacy.

The PANSS consists of 30 items rated on a seven-point scale (1 = absent, 7 = extreme). It has three subscales: positive (seven symptoms: P1–P7), negative (seven symptoms: N1–N7), and general psychopathology (16 symptoms: G1–G16). The measurements included PANSS positive score (7–49), negative score (7–49) and total score (30–210). The higher the score, the more severe the symptoms.

Cognitive test battery of the samples

Patients underwent a battery of cognitive tests at baseline, and again following 6 months of treatment. The tests were performed in a fixed order on every patient and were conducted by the same rater trained in cognitive testing. The test battery, which comprised six tests, is described in detail as follows.

Hopkins Verbal Learning Test-Revised[34]: This test assesses verbal memory and learning ability. The rater reads a list of 12 words to the subjects three times. After these readings, the subjects are asked to freely recall these words, and the rater records the number of correctly recalled words every time. After 25 minutes, the number of delayed recall words is also recorded. The total score of the three trials and delayed recall were used as outcome measures in this study. The total score is between 0 and 36; the score of delayed recall is between 0 and 12. Higher scores represent better performance.

Brief Visuospatial Memory Test-Revised[35]: This test consists of six geometric figures that are printed in a 2 × 3 array on a page. The subject is shown the page for 10 seconds and then asked to draw the figures as accurately as possible in the correct location on the answer sheet. The score is assessed according to the criteria provided in the test manual. Each reproduction is given 2 points if both figure and location are correct. One point is given if either the figure or location is correct. The range of possible scores is 0–12 for each free recall trial. Total recall score over three learning trials was used as the outcome measure in the present study, giving a total recall score between 0 and 36. A higher score indicates better performance.

Spatial span subtest[36]: Nonverbal working memory (forward and backward spatial span) is assessed in this test, using a three-dimensional board with 10 irregularly arranged numbered cubes. The test examiner taps a series of blocks at a rate of about 1 per second per block in a specific, predetermined pattern. Subjects must then tap the cubes in the same (or reverse) sequence. One point is awarded for each correct answer and the test is terminated after two incorrect consecutive trials. The score ranges from 0 to 16, whether forward tapping or reverse tapping. The total scores of forward and backward spatial span were used as outcome measures in the present study, resulting in scores for each subject ranging from 0 to 32, with a higher score indicating better performance.

Verbal Fluency Test (animal naming)[37]: This psychological test requires subjects to say as many words as possible from a given category in 1 minute. The category can be phonemic or semantic. Animal naming is a semantic verbal fluency test. The total number of animals named in 1 minute, excluding repetitions and intrusive errors, was used as the outcome measure in this study, a higher score indicating better performance and reflecting both intact lexical storage and an ability to retrieve information from semantic memory.

Stroop Color and Word Test[38]: This test consists of three trials: stroop word, stroop color, and stroop color/word. First, the subjects read the name of the word (red, blue, or green) printed in black. Second, they name the color in which a word is printed. Finally, the names of colors are printed in colors that do not correspond to the words (***e.g.*** "blue" printed in red), and subjects must read aloud the color, but not the word (***i.e.*** "red" for this example). Every trial contains 100 items, and the subjects must read as quickly as possible for 45-second intervals. The number of correct names is recorded for every trial. Again, the higher the score, the better the performance in the test.

Digit symbol coding[36]: This test consists of 133 digit-symbol pairs and requires the subjects to copy the corresponding symbol for a given number, as fast as possible. The number of correct symbols listed within 120 seconds was measured in the study. A higher score indicates a better performance.

Patients were required to complete the entire test battery in 30–40 minutes. Two different parallel versions of Hopkins Verbal Learning Test-Revised™ and of the Brief Visuospatial Memory Test-Revised™ were used to limit practice effects. These six tests include 10 variables and comprise five cognitive domains: verbal learning and memory (Hopkins Verbal Learning Test-Revised), visual learning (Brief Visuospatial Memory Test-Revised), processing speed (animal naming and digit symbol coding), working memory (spatial span subtest), and selective attention (Stroop test).

For neurocognitive tests, all test measures were first converted to standardized ***z*** scores by setting the sample mean of each measure at baseline to 0 and the standard deviation to 1 for each test variable. The ***z*** scores were computed by using the baseline means and standard deviations from patients who completed that test at both baseline and follow-up. Because three domains (verbal learning, processing speed and selective attention) were examined using more than one test or variable, we used their summary scores, which were calculated by averaging the ***z*** scores for the contributing variables. A cognitive composite score was computed by averaging ***z*** scores of five cognitive domains for each treatment group.

Statistical analysis

Measurement data were expressed as mean ± SD. SPSS 15.0 software (SPSS, Chicago, IL, USA) was

used to analyze the data. Continuous variables were checked to determine whether they satisfied normal distribution assumptions. All variables except for age and education fell within the normal distribution; the Kruskal-Wallis test was performed to compare these two variables. Categorical variables were analyzed using the chi-square test. One-way analysis of variance was used to analyze PANSS scores and cognitive variables of three treatment groups at baseline. A repeated measures analysis of variance was used to examine the clinical and cognitive effects of the three antipsychotics after 6 months of treatment, with the three independent treatment groups (olanzapine; risperidone; aripiprazole) used as between-subjects factors, and the two time points (baseline and 6 months) used as within-subjects factors. When a time or group-by-time interaction effect was significant on a particular domain, paired *t*-tests were used to examine within-group changes over time in a *post-hoc* analysis. Multiple comparisons were also performed using the Bonferroni test if there were significant differences in the between-group comparisons. The Pearson correlation was used to examine the relationship between treatment-related changes in an individual's neurocognitive domain z scores and treatment-related change scores in the PANSS negative subscale. Effect sizes were determined using Cohen's formula[38-39]. All analyses used two-tailed levels of significance. Statistical significance was set at $P < 0.05$. When doing multiple comparisons, the Bonferroni adjustment *P* value was set at $P < 0.017$.

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