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Original Article

Effects of second-generation antipsychotic medications treatment: cognitive improvement in Chinese patients with schizophrenia

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Abstract: Objectives: To evaluate the cognitive improvement and assess the practice effects on patients with first-episode schizophrenia (FES) after accepting second-generation antipsychotic medications (SGAs): olanzapine and risperidone. Methods: A total of 98 patients with a diagnosis of schizophrenia and 63 healthy controls were randomly recruited in this study from Xuzhou East Hospital affiliated to Xuzhou Medical University and Qingdao mental health center and divided into 3 groups (olanzapine, risperidone and healthy controls). The cognitive assessment and the neurocognitive detection would be taken for all groups and compared when appeared at baseline, six weeks later, and sixteen weeks later. The neurocognitive detections were inclusive of measurements of working memory and attention, speed, motor function, episodic memory, and executive function. Results: There was no significant different drug effect on cognitive performance between olanzapine and risperidone groups ($P>0.05$). The cognitive performance of both groups was improved. However, all cognitive evaluations for FES patients were obviously below those of HCs group ($P<0.05$). Besides, drug effects were bigger than practice effects in the cognitive tests in our study ($P<0.005$). Conclusion: To some extent, some cognitive improvements for the FES group may due to practice effects. However, differential medication effects on cognition were tiny in terms of our results in this study.

Keywords: First-episode schizophrenia, second-generation antipsychotic, cognitive improvement

Introduction

Schizophrenia is a mental disorder characterized by abnormal social behavior and failure to perceive reality. Moreover, cognitive impairment is a main feature of such disease [1-3]. Therefore, neurocognition has been considered as a key target in many clinical trials. Patients with first episode schizophrenia (FES), as a kind of significant group, would always be used in neurocognitive studies because it is easy to detect their response to antipsychotics.

Second-generation antipsychotics (SGAs) including risperidone or olanzapine were a group of antipsychotic drugs used to treat psychiatric conditions [4]. Previous studies showed that about eighty percent of patients with FES got symptomatic remission after accepting antipsychotic therapy. However, most of them relapsed within two years. Perhaps it was because of low levels of insight into the illness and non-adherence to their oral medication [5]. Other studies indicated that second-generation antipsychotics (SGAs) improved cognition while a large number of trails examined whether risperidone or olanzapine could improve cognition in patients with FES [6-8]. Nevertheless, many of them didn't include control groups and few studies reported the effects of SGAs on Chinese patients [9].

Schizophrenia is a mentalillness with 1% of the life-time prevalence in the general population worldwide. China is the most populous country in the world, an estimated 1.3 million people in China suffer from schizophrenia [10-12]. Thus, evaluating the effect of SGAs for the cognition improvement of Chinese patients with FES, especially olanzapine and risperidone, is meaningful. Our study would include a healthy control (HCs) group to detect practice effects and

Table 1. Demographic characteristics for olanzapine group, risperidone group and healthy controls

Characteristic	Olanzapine Group	Risperidone Group	Healthy Controls
N	48	50	63
Age (mean ± SD)[a]	23.2±3.8	24.3±4.3	28.5±9.1
CGI score (mean ± SD)[a]	5.35±0.71	5.29±0.68	NA
WRAT-3 reading standard score (mean ± SD)[a]	87.9±14.8	88.3±15.2	101.79±8.78
Education level (mean ± SD)[a]	11.6±2.1	12.3±1.7	13.6±1.9

[a]Results of all variable analysis and X^2 texts were significant (P<0.001), and the olanzapine and risperidone groups differed significantly from thehealthy control group by post hoc analysis. Abbreviations: CGI, Clinical Global Impressions scale; NA, not applicable; WRAT-3, Wide Range Achievement Test 3.

Table 2. Cognitive tests

CPT-IP	Executive function
CVLT	Episodic memory
DMS	Working memory
Finger rapping	Motor
Grooved pegboard	Motor
Judgment line orientation	Spatial processing
MMSE	Mental status
Test	Function
Trail making A and B	Speed
Verbal fluency	Speed
WAIS-R digit symbol (scaled score)	Speed
WCST	Speed
WMS-R digit span	Working memory
WMS-R logical memory	Episodic memory
WMS-R visual reproduction	Episodic memory

Abbreviations: CPT-IP, Continuous Performance Test identical pairs subtest; CVLT, California Verbal Learning Test; DMS, Delayed Match to Sample Test; MMSE, Mini-Mental State Examination; WAIS-R, Wechsler Adult Intelligence Test-Revised; WCST, Wisconsin Card Sorting Test; WWSR, Wechsler Memory Scale-Revised.

patients who were drug naive at baseline also would be included. Hopefully, this study could direct the application of SGAs for Chinese patients with FES.

Methods

Participants

A homogeneous collection of 98 patients with FES were enrolled from Xuzhou East Hospital affiliated to Xuzhou Medical University and Qingdao mental health center, and 63 agematched healthy controls were also enrolled in this randomized clinical trial. Controls were recruited either through the patients or among hospital employees. Before the experiment, all people must accept the Structured Clinical Interview for DSM-IV to detect whether they were schizophrenia patients or not. Patients with FES were divided into 2 groups randomly and they needed to take olanzapine and risperdone respectively in this study. In detail, forty-eight patients accepted olanzapine (2.5-20 mg/d) and fifty of them took risperidone (1-6 mg/d). The whole process lasted for sixteen weeks. Exclusion criteria for all groups included medical conditions known to affect the central nervous system and neurological conditions known to affect cognition. All people received cognitive assessments at baseline, sixth weeks and sixteenth weeks.

Cognitive tests and psychopathologic ratings

All cognitive tests had been listed in **Table 2** and would be accepted by every participant. The Schedule for Affective Disorders was used to assess the severity of disorganization in speech, hallucinations, delusions and bizarre behavior [13]. The Schedule for the Assessment of Negative Symptoms (Hillside version) was aimed to rate negative symptoms [14].

Statistical analysis

Statistical analyses were performed with mixed models by In Stat 3.0 software (GraphPad Software Inc). In multiple comparisons after Bonferroni correction, P<0.05 means the significance. The authors had full access to and took full responsibility for the integrity of the data. All authors had read and agreed to the manuscript as written.

A medication type (olanzapine or risperidone) × time interaction would suggest differential medication effects. Group × time interactions would be considered as an assessment of a drug influence and an index to cognitive improvement. Thus, we detected whether the cognitive improvements were changed with treat-

Table 3. Effects of risperidone and olanzapine in patients with FES

Variable	Treatment Week		Medication Group		Treatment Week × Medication group	
	F	P	F	P	F	P
Semantic Fluency	2.72	0.07	1.14	0.34	1.99	0.13
CPT-IP	1.59	0.26	1.35	0.23	1	0.35
CVLT recognition errors	6.77	0.003	0.16	0.73	0.13	0.85
CVLT trials 1-5	12.98	<0.001	0.07	0.83	1.61	0.3
Digit span	5.01	0.02	0.05	0.85	1.89	0.16
Digit symbol	13.12	<0.001	0	0.91	1.76	0.19
DMS	0.02	0.89	0.06	0.89	0.21	0.83
Finger tapping	1.82	0.19	1.24	0.31	0.52	0.57
Grooved peg	2.65	0.07	0.01	0.95	2.75	0.06
Line orientation	7.85	<0.001	0.31	0.62	0.19	0.81
MMSE	36.28	<0.001	0.09	0.81	2.63	0.08
Severity of illness	115.96	<0.001	0	0.92	0.07	0.89
Trail making A and B	26.31	<0.001	0.34	0.58	1.8	0.45
WCST loss of set	3.12	0.05	0.45	0.52	0.35	0.62
WCST% perseveration	9.05	<0.001	0.42	0.53	0.92	0.35
WMS-R logical memory	40.93	<0.001	0.56	0.5	1.64	0.3
WMS-R visual reproduction	26.1	<0.001	0.66	0.46	0.22	0.79

Table 4. Healthy controls compared with patients with FES on cognitive measures

Variable	Treatment Week		Medication Group		Treatment Week × Medication group	
	F	P	F	P	F	P
CVLT recognition errors	9.32	<0.001	41.79	<0.001	0.18	0.75
CVLT trials 1-5	35.11	<0.001	158.76	<0.001	3.59	0.04
Digit symbol	19.69	<0.001	67.95	<0.001	1.34	0.2
Line orientation	9.91	<0.001	30.82	<0.001	2.16	0.13
MMSE	35.72	<0.001	91.02	<0.001	17.86	<0.001
Trail making A and B	43.68	<0.001	86.23	<0.001	16.92	<0.001
WCST% perseveration	14.69	<0.001	57.96	<0.001	4.55	0.02
Logical memory	79.35	<0.001	182.67	<0.001	0.32	0.81
Visual reproduction	18.76	<0.001	49.91	<0.001	15.72	<0.001
CVLT recognition errors	9.32	<0.001	41.79	<0.001	0.18	0.75

ment time and the difference was appeared due to the different medication types.

Then, we tried to determine if cognitive change could be attributed to causes other than drugs or practice using multiple regression analyses. Thus, we sought to determine whether measures of baseline state variables or changes from baseline to sixteenth weeks (positive, negative, or disorganized symptoms) could predict cognitive changes. We also conducted many linear regressions for each group. In this section, we set significance for entrance of predictors at P<0.10 for multiple regressions.

Results

All patients with FES and controls were recruited from Xuzhou East Hospital affiliated to Xuzhou Medical University and Qingdao mental health center, aged 18-35 years old. All patients had evidently psychotic symptoms when they were enrolled into this study. The concrete demographic characteristics could be seen in **Table 1**.

Table 3 showed that two groups (olanzapine vs. risperidone) had no significant differences on cognitive performance (P>0.05). We also found that SGAs had different effects on cognitive improvement by medication group × treatment time interaction. There was no interaction for all variables. Besides, we observed that performance on cognitive assessments was improved regardless of whatever patients took, olanzapine or risperidone.

Based on the above results, we compared the cognitive changes between healthy controls and FES patients. All tests showed that as the treatment time went by, there was a significant cognitive difference between healthy controls and FES patients (P<0.001). And whether patients took olanzapine or risperidone, they all had significant cognitive difference compared with health controls (P<0.001). When we detected the interaction of treatment week × medication group, most tests showed the difference, which indicated that the treatment time and medica-

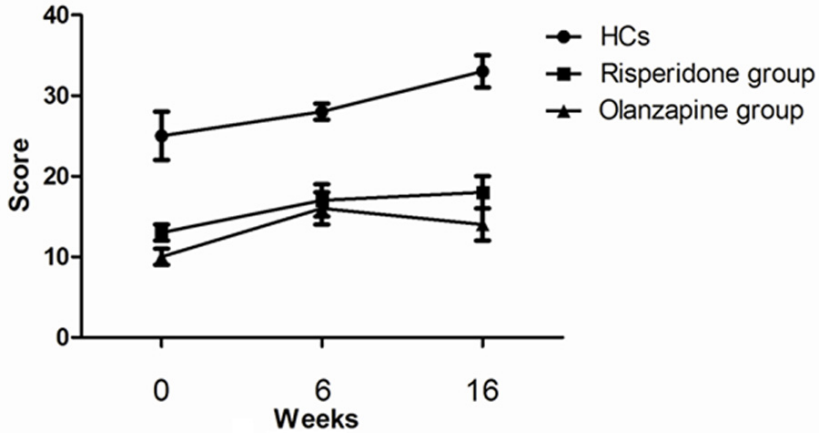

Figure 1. Performance of logical memory for the patients with first-episode schizophrenia (FES) who have taken two kind of drugs and the healthy controls (HCs) at baseline, 6 weeks, and 16 weeks. The graph represents most tests because the difference among those FES groups is small, the rate of improvement between the FES and HC groups is similar, and the difference between the FES and HC groups persists throughout the study.

Table 5. The composite effect size (Cohen d) in patients with FES and healthy controls within each treatment period

Variable	Patients with schizophrenia			Healthy controls		
	0-6 Weeks	6-16 Weeks	0-16 Weeks	0-6 Weeks	6-16 Weeks	0-16 Weeks
Semantic Fluency	-0.18	0.05	-0.12	0.03	0.02	0.07
CPT-IP	NA	0.16	NA	NA	0.05	NA
CVLT recognition	0.36	0.49	0.39	0.41	0.1	0.42
CVLT trials 1-5	0.39	0.45	0.51	0.63	0.21	0.69
Digit span	0.21	0.15	0.32	0.43	0.06	0.41
Digit symbol	0.41	0.06	0.42	0.16	-0.09	0.65
DMS	NA	0.06	NA	NA	0	NA
Tapping	0.11	0.12	0.27	0.12	0.3	0.28
Line orientation	0.38	-0.02	0.35	0.16	0.04	0.21
MMSE	0.69	0.15	0.82	0.03	0.36	0.42
Severity of illness	1.19	0.52	1.43	NA	NA	NA
WCST set	-0.21	0.14	-0.05	-0.11	0.03	-0.04
WCST% perseveration	0.36	0.04	0.38	0.41	-0.02	0.43
WMS-R logical memory	0.72	0.31	0.81	0.75	0.26	1.02
WMS-R visual reproduction	0.61	0.05	0.72	0.13	-0.15	-0.06
Tapping	0.13	0.15	0.24	0.11	0.1	0.32
Pegboard	0.22	0.03	0.16	0.49	0.21	0.69
SANS	0.35	-0.25	0.12	NA	NA	NA
Hallucinations	1.26	0.12	1.5	NA	NA	NA
Delusions	0.97	0.53	1.45	NA	NA	NA
Disorganization	0.63	0.23	0.81	NA	NA	NA

tion affected the cognitive changes together (**Table 4**).

Figure 1 also revealed the individual improvement of logical memory for those groups. Those FES patients presented almost same forms of changes for all tests. All cognitive evaluation for FES patients were significantly below those of HCs group.

The composite effect size in patients with FES for all sixteen tests firstly detected was 0.31. But the Cohen's d of control group was similar (0.28) (**Table 5**), which meant that the cognitive improvements were more obvious in treatment in the first six weeks in both groups.

Discussion

SGAs, which remained its superiority with better tolerability, superior quality of life and lower risks of relapse than first-generation anti-psychotics, was firstly applied in the early 1990s [15-17]. However, subsequent studies questioned its clinical superiority and adverse effects. Especially, several drugs of the SAGs had been proved to have a greater probability in causing weight gain and metabolic syndrome than first-generation anti-psychotics, despite having fewer extrapyramidal effects [18, 19]. Additionally, SGAs sometimes caused serious side effects, such as the pneumonia [20]. But for pati-ents with FES, SGAs was confirmed to have cognitive improvement in previous studies.

In this study, we applied multiple series of statistical analyses. We found notable cognitive improvements for Chinese FES in tests of speed of processing and executive functions, which were related to set shifting and episodic memory.

Compared with previous studies, webrought HC group into our study and assessed the practice effects on Chinese patients with FES. We also found that drug influence was more evident than practice effects in FES group. Nonetheless, such phenomenon could not be considered that it was due to high co-variation with positive or negative symtoms. But they may represent valid cognitive enhancement. These results were consistent with some recent studies about SGAs effects on cognition [7].

However, there still have several limitations in our study. For one, we cannot detect practice effects when patients are under drug-free condition due to some moral rules. Therefore, to some extent, our results are probably be considered as inferential. For another, although we have attempted to offer considerable evidence to support our opinion, it is probably suitable to hold the attitude that practice effects should be included when conducting clinical trials.

Conclusion

Second-generation anti-psychotic medication is associated with cognitive improvement. Although practice effect may play a role in some cognitive improvement, the drug effect is also significant. It is the first study that probed into the relationship between SGAs effect and practice effect on Chinese FES patients. Fur ther studies need to repeat related clinical trials in larger samples in order to support our conclusion.

Disclosure of conflict of interest

None.

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