Serum BDNF and catecholamine metabolites predict the cognitive effect of atypical antipsychotic monotherapy in patients with acute schizophrenia

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Background

Neurocognitive impairment is a core feature of schizophrenia, and it is associated with both treatment outcomes and social functions. Although atypical antipsychotics have recently begun to be used with the strong expectation of efficaciously improving neurocognitive function, the effects that actually manifest have been insufficient according to various comparative studies, reviews, and meta-analyses. Summaries of the findings from these studies show that antipsychotics can improve neurocognitive function, but the magnitude of their effect is not high (effect sizes=0.2-0.4) based on refer to the randomized controlled trial data. The present study applied an atypical antipsychotic monotherapy for patients with schizophrenia to (1) examine the percentage of patients who respond well to this treatment, (2) explore the factor the predict response (e.g., the improvement of neurocognition) and (3) identify the factors associated with improvement neurocognitive function.

Methods

This study enrolled 40 patients with acute schizophrenia (DSM-IV-TR) who had received atypical antipsychotic monotherapy for 24 weeks. Demographic data(Gender, Age, Education, Handedness, smoking, onset, duration of treatment, anticholinergic drugs use, first hospitalization, number of hospitalization, total hospitalization period) of these patients were collected before treatment initiation, and clinical symptoms (PANSS), cognitive function (BACS-J: Brief Assessment of Cognition in Schizophrenia Japanese language version), and biological markers (HVA: homovanillic acid, MHPG: 3-methoxy-4-hydroxyl phenyl glycol, BDNF: brain-derived neurotrophic factor) at baseline and 24 weeks after the treatment were assessed. The degree of neurocognitive functional improvement individuals was calculated using the equation for the z-score in Week 24 minus the z-score in Week 0. The improvement was rated on a 6-category scale that ranged from “very much worse” (-3<degree of improvement≤-2) to “very much improved” (2<degree of improvement≤3). The factors that predicted neurocognitive function improvement were explored using a linear model that considered the difference in the BACS z-scores between Week 24 and Week 0 as reflecting improved neurocognitive function. All of the variables observed in Week 0 served as the independent variables. To explore the factors associated with neurocognitive functional improvement, a linear model was created in which the data for the differences between the 2 time points in terms of neurocognitive function psychotic symptoms, and peripheral biological markers served as independent variables. This associations between these variables and neurocognitive functional improvement were evaluated. This assessment was followed by a univariate analysis to calculate the regression coefficient and p-value.

The Ethics Committee of the University of Occupational and Environmental Health approved the study protocols. Written informed consent was obtained from all of the participants of this study.

(Table 1) Demographics of this study

Age(years)	31.1±6.8
M/F	19/21
Education (years)	13.4±2.4
Handedness (R/L)	39/1
Smoking (Yes/No)	10/30
Onset (years)	24.1±6.1
Duration of antipsychotic treatment (years)	5.4±3.8
Number of hospitalization	1.7±1.5
Total hospitalization period (month)	4.7±4.8

(Table 2)

	0W	26W	p-value	Effect size
PANSS-P	28.4±6.3	16.3±3.8	<0.01	2.37
PANSS-N	26.6±7.0	19.6±5.1	<0.01	1.15
PANSS-G	43.9±8.3	34.3±5.0	<0.01	1.42
PANSS-T	98.6±17.7	70.0±11.2	<0.01	1.95
Verbal learning	-1.6±0.9	-1.2±1.1	<0.01	0.47
Working memory	-1.5±0.8	-1.0±0.8	<0.01	0.57
Motor function	-1.4±1.2	-1.2±1.3	0.08	0.21
Verbal fluency	-1.3±0.9	-0.9±1.0	<0.01	0.42
Attention and processing speed	-1.6±0.9	-1.2±0.9	<0.01	0.45
Executive function	-1.3±1.3	-0.9±1.5	0.02	0.33
Composite score	-1.5±0.7	-1.1±0.9	0.01	0.51

PANSS-P: Positive and Negative Syndrome Scale-Positive scale score, PANSS-N: Positive and Negative Syndrome Scale-Negative scale score
PANSS-G: Positive and Negative Syndrome Scale-General Psychopathology subscale score, PANSS-T: Positive and Negative Syndrome Scale-Total score
HVA: homovanillic acid, MHPG: 3-methoxy-4-hydroxyphenylglycol, BDNF: Brain-derived neurotrophic factor

Results

Table 1 shows the demographics in the study. (Table 1)
Table 2 shows the data on the influences of treatment on psychotic symptoms, neurocognitive function and peripheral biomarkers (Table 2)
Marked improvements in neurocognitive function were noted in 17.5 – 25% (Table 2, 3)
Table 4 shows the predicting factors for neurocognitive functional improvement. (Table 4). Some cognitive factors, baseline factor (frequency of hospitalization, and biomarker factor (plasma MHPG levels) predict the cognitive effects of atypical antipsychotics.
Table 5 shows an exploration of the factors associated with neurocognitive functional improvement (Table 5).

(Table 3)

Z-score change ((24W z-score)-(0W z-score))	(-3,-2]	(-2,-1]	(-1,0]	(0,1]	(1,2]	(2,3]
	very much worse	much worse	minimally worse	minimally improved	much improved	very much improved
Verbal learning	0	2	9	18	8	3
Working memory	0	0	8	26	6	0
Motor function	0	3	13	17	3	4
Verbal fluency	0	0	9	26	5	0
Attention and processing speed	0	2	10	20	8	0
Executive function	1	3	15	11	5	5
Composite score	0	1	7	25	7	0

(Table 4) The factors predicting neurocognitive functional improvement

Response variate	Explanatory variate	β	p-value
VL	Number of hospitalization	-0.48	0.005
	Total hospitalization period	0.072	0.155
WM	VL	-0.166	0.032
VF	Number of hospitalization	-0.108	0.049
	MHPG	0.163	0.031
AP	AP	-0.295	0.02
EF	VF	0.348	0.093
	MHPG	0.377	0.025
Composite score	Number of hospitalization	-0.165	0.006

(Table 5) An exploration of the factors associated with neurocognitive functional improvement

Response variate	Explanatory variate	β	p-value
VL	BDNF	0.133	0.018
WM	BDNF	0.061	0.046
VF	PANSS-N	-0.028	0.026
AP	MHPG	0.135	0.033
	BDNF	0.118	0.01
CS	BDNF	0.078	0.046

Conclusion

Approximately 20% of the patients showed good response to treatment with antipsychotics. Frequency of hospitalization, MHPG level, and other parameters predicted responsiveness to these drug therapies. Biological factors such as BDNF and MHPG were associated with the degree of improvement following treatment with these drugs. Thus, it might be useful to apply these factors to predict responses to treatment.

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