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Switching to antipsychotic monotherapy can improve attention and processing speed, and social activity in chronic schizophrenia patients

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ABSTRACT

Objective: This study sought to examine whether switching polypharmacy therapy to monotherapy would improve the cognitive function and social function of patients with schizophrenia.
Methods: Thirty-nine patients with schizophrenia who were receiving therapy with two antipsychotics were randomly divided into a switch to monotherapy group (switching group) and a polypharmacy continued group (continuing group). For the patients allocated to the switching group, the dose level of one of the two antipsychotic drugs was gradually reduced to zero. Psychotic symptoms, cognitive function and social function scale scores were assessed immediately before and 24 weeks after switching, and the time courses of these scores were compared between the two groups.
Results: Compared with the continuing group, the switching group demonstrated significantly greater improvement in attention after switching ($p = 0.02$). Furthermore, the improvement in daily living ($p = 0.038$) and work skills ($p = 0.04$) was significantly greater in the switching group. In an analysis of the correlation among sub-items with respect to the degrees of improvement, a significant correlation was noted between improvement in executive function and improvement in daily living ($r = -0.64$, $p = 0.005$) and between improvement in work skills and improvement in attention ($r = -0.51$, $p = 0.038$).
Conclusion: In patients with schizophrenia receiving polypharmacy, switching to monotherapy resulted in improvements in attention. Furthermore, improvements in executive function led to improvements in daily living, and improvements in attention led to improvements in work skills. Thus, switching to monotherapy is a useful option.

1. Introduction

Many guidelines on the treatment of schizophrenia recommend antipsychotic monotherapy (American Psychiatric Association. 2004; Miller et al., 2004; National Collaborating Centre for Mental Health. 2009; Buchanan et al., 2010). A lot of schizophrenia patients actually receive antipsychotic polypharmacy (Centorriono et al., 2002; Ganguly et al., 2004; Nakano et al., 2010). Polypharmacy can also be associated with reduced adherence and increased costs and can produce a higher frequency of side effects (Miller and Craig, 2002; Stahl, 2002; Suzuki et al., 2005). It has been observed that polypharmacy can adversely affect not only extrapyramidal symptoms, metabolic syndromes and oversedation but also cognitive functions (Essock et al., 2011; Hori et al., 2012). In other word, total antipsychotic daily dose and antipsychotic number were correlated, a fact that has been mentioned in the literature and both were significant predictors of cognitive performance (Hori et al., 2006; Elie et al., 2010). We previously reported that even combined drug therapy using atypical antipsychotics with less likelihood of inducing adverse reactions produced adverse effects on cognitive functions (Hori et al., 2012). Several components of cognitive dysfunction in schizophrenic individuals also have an impact on social functional outcomes (Aleman et al., 2006) because they are correlated with poor social functional abilities. An enhancement of cognitive functioning is considered to be an important component of schizophrenia treatment (Green et al., 2005; Hofer et al., 2005; Demily and Franck, 2008; Medalia and Choi, 2009). This line of reasoning suggests that improving the cognitive function of

Abbreviations: BACS-J, Brief Assessment of Cognition in Schizophrenia, Japanese-language version; LASMI, Life Assessment Scale for the Mentally Ill; PANSS, Positive and Negative Syndrome Scale.

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schizophrenic patients can lead to improvement in their prognosis or social activity level. We performed the present study to examine the hypothesis that cognitive and social functions are superior in a group that switches from polypharmacy to monopharmacy (switching group) compared with a group that continues with polypharmacy (continuing group).

2. Methods

2.1. Participants

Table 1 presents the characteristics of the subjects in both groups. All of the subjects were outpatients with schizophrenia who had been diagnosed using the DSM-IV-TR at the University of Occupational and Environmental Health in Japan who met the following inclusion criteria: 1) aged 20–60 years; 2) presence of chronic illness without acute exacerbation; 3) continuing a stable dose of both antipsychotics at least 3 months.

Exclusion criteria were 1) comorbid central nervous system disorder; 2) sever psychotic symptoms; 3) meeting DSM-IV criteria for alcohol or other substance dependence; 4) meeting DMS-IV criteria for mental retardation; 5) taking antidepressants; 6) treatment with electroconvulsive therapy in the 6 months preceding the study; and 7) inability to understand the study protocol.

This study enrolled 39 schizophrenia patients with symptoms that had been stable without prescription changes in the past 3 months. The patients were randomly divided into either the switching group or the continuing group using StatView (Abacus Concepts, Berkeley, CA), a computerized statistical package. For participants who were assigned to switch to monotherapy, each participant and physician decided together which of the two antipsychotics to discontinue.

The study protocol indicated that discontinuation had to occur within 12 weeks, and participants had to continue with their assigned medication regimen for 24 weeks unless this treatment was clinically contraindicated. The doses of antipsychotic drug in the switching group were allowed to strategy as follows. 1) When the patients who were administered first-generation and second-generation antipsychotic drug, the first-generation antipsychotic drug was tapered off. 2) When the patients who were administered second-generation and second-generation antipsychotic drug, the drug with smaller amount (chlorpromazine-equivalent <CPZeq>) was tapered off. Clinical evaluations were performed at baseline and at 24 weeks after baseline (12 weeks after completing the switch to monopharmacy). In contrast, we defined the patients who had been administered two or more antipsychotic drugs and were kept on the same regimen for 24 weeks as the continuing group. The clinical symptoms of the continuing group were evaluated at baseline and 24 weeks after the initial assessment. The doses of antipsychotic drug in the switching group were allowed to change flexibly, depending on the clinical symptoms of each case. The dosages of anxiolytics, mood stabilizers and anticholinergic drugs were not changed during the study period. The raters were blinded about which group the patients belonged to.

Table 1
The demographic and clinical characteristics of schizophrenia patients.

	Switching	Continuing	*p*-Value
Age (years)	36.6 ± 11.9	36.1 ± 10.2	0.89
Sex (Male/Female)	9/8	10/8	0.88
Education (years)	13.5 ± 2.1	13.1 ± 3.0	0.64
Estimated-IQ	101.3 ± 24.4	98.1 ± 9.0	0.63
Handedness (Right/Left)	17/0	17/1	0.32
Smoking (Yes/No)	8/9	8/10	0.88
Onset (years)	24.7 ± 4.8	23.5 ± 6.0	0.51
PANSS-Total	65.3 ± 8.8	69.1 ± 14.1	0.35
Use of anticholinergic drugs, *n* (%)	8 (47.1)	10 (55.6)	0.62

2.2. Cognitive functions, social functions, intelligence test and clinical assessments

The primary outcome measures were the changes in cognitive functions and social functions from baseline to endpoint. The secondary outcome measures were changes in psychiatric symptoms and the severities of psychopathologies. Cognitive functions were assessed by trained psychiatrists using the Brief Assessment of Cognition in Schizophrenia in a Japanese-language version (BACS-J) (Kaneda et al., 2007). The BACS-J has established reliability and validity and is designed to measure cognitive function in schizophrenia (Keefe et al., 2004; Kaneda et al., 2007). The metric includes brief assessments of verbal memory, working memory, motor speed, verbal fluency, attention and processing speed, and executive function. The primary measures from each subtest of the BACS-J were standardized by creating z-scores (the mean of healthy controls was set to zero, and the standard deviation was set to one). All of the data on the healthy controls were obtained from a study by Kaneda et al. (2008), and a composite score was calculated by averaging all of the z-scores for the six primary measures. The influence of age was adjusted using age-matched cohorts of controls to calculate the BACS-J z-scores for each schizophrenia patient in the present study.

We used to assess functional outcomes in this study. The Life Assessment Scale for the Mentally Ill (LASMI) was developed to assess disability in daily life or community functioning (Iwasaki et al., 1994; Iwanami et al., 1999; Inadomi et al., 2005) and is one of the most commonly used scales to evaluate community functioning in Japan. The LASMI is composed of the following five categories: (1) daily living; (2) interpersonal relations; (3) work skills; (4) endurance and stability; and (5) self-recognition. Each category is composed of several items, with each item being rated on a 5-point scale (ranging from no problem = 0 to a serious problem = 4). Lower scores indicate higher degrees of independent living in the community. The mean score for each category was calculated by dividing the total score for that category by the number of items. The LASMI scores were assigned based on observations of the patients' behavior and information from both the patients and their families.

Assessment of intelligence quotient (IQ) of the participants was estimated with the Japanese Adult Reading Test (Hori et al., 2008; Matsuoka et al., 2002), a Japanese version of the National Adult Reading test (Nelson and Wilson, 1991), and those whose estimated-IQ score was less than 80 were not enrolled in the study.

Schizophrenic symptoms were rated using the Positive and Negative Syndrome Scale (PANSS; Kay et al., 1987).

2.3. Statistical analysis

The average values that were obtained in this study are reported in terms of means and standard deviations (SD). Demographic characteristics and test results were compared between the groups. We used the *t*-test and chi-square test to compare various factors between the switching group and the continuing group. The switching-related changes in BACS z-scores and LASMI scores were compared using Student's *t*-test. In addition, the aim of this study was to clarify the effects of switching to monotherapy on cognitive function, as measured by BACS-J. A repeated measures analysis of convariance (ANCOVA) was performed for each cognitive variable with baseline data as convariate. Our main interest in the repeated measures ANCOVA was whether the group-by-time interaction