



An unblinded comparison of the clinical and cognitive effects of switching from first-generation antipsychotics to aripiprazole, perospirone or olanzapine in patients with chronic schizophrenia

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ABSTRACT

The objective of this study, the effect of aripiprazole on clinical symptoms and cognitive function in patients with chronic schizophrenia was compared to that of perospirone and olanzapine. The subjects were 31 patients, they were diagnosed with schizophrenia on the basis of the criteria of the DSM-IV. Clinical symptoms were assessed using Brief Psychiatric Rating Scale (BPRS), and cognitive function was assessed using the Wisconsin Card Sorting Test (Keio Version: KWCST) and the St. Marianna University School of Medicine's Computerized Memory Test (STM-COMET) as executive function and memory/attention function tests at baseline and 8 weeks after switching. As a result, comparison of the BPRS mean total score revealed no significant difference between aripiprazole and the other medications. Aripiprazole resulted in significant changes in the number of categories achieved (CA) and difficulty maintaining set (DMS) compared to olanzapine at the second level of the KWCST. Comparison thus revealed no difference in clinical effect between aripiprazole and the other medications, but might suggest possible differences between aripiprazole and olanzapine in the profiles of the improvement effects on executive function, memory, and attention function.

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1. Introduction

Cognition generally refers to a series of information processing steps involving the acquisition, organization, and use of knowledge. Functions which are held to be related to this process include memory function, attention function, and executive functions such as planning or problem solving skills and monitoring errors, etc (Iwanami and Kamijima, 1999). In schizophrenia, these functions are impaired. The severity of cognitive dysfunction in schizophrenia is intimately related to social and work skills or quality of life, and is therefore an important target symptom in therapy along with positive and negative symptoms (Gibel and Ritsner, 2008; Green, 1999; Iyo, 2007; Keefe et al., 2007; Meltzer et al., 1999; Wykes et al., 1999).

Recently, more and more information has been gathered, primarily overseas, about the effects of antipsychotics on cognitive function in neuropsychological testing, and many reports have found second-

generation antipsychotics to improve cognitive dysfunction (Araki et al., 2006; Cuesta et al., 2009; Janier et al., 2003; Kasai et al., 2004; Kasper et al., 2003; Keefe et al., 1999; Riedel et al., 2010; Tollefson et al., 1997; Yamamoto and Inada, 2007). The results of neuropsychological tests have also shown that the profile of improvement brought about in cognitive dysfunction by second generation antipsychotics varies depending on the type of antipsychotic (Cuesta et al., 2001; Kern et al., 2006; Mori et al., 2004; Purdon et al., 2000; Riedel et al., 2007; Yamamoto and Inada, 2007). In fact, we have also reported that switching from first generation antipsychotic monotherapy to risperidone monotherapy in patients with chronic schizophrenia resulted in improvement primarily of executive function in cognitive dysfunction (Suzuki et al., 2005). Meanwhile, perospirone, the pharmacological action of which includes dopamine D₂ receptor-blocking action as well as serotonin 5-HT_{2A} receptor-blocking action, was introduced in 2001 as the first second generation antipsychotic in Japan (Ishigooka et al., 2006). In 2006, with the introduction to Japan of aripiprazole, a partial dopamine receptor agonist with pharmacological action unlike that of the second generation antipsychotics until then, Japan also joined in the era of drug therapy based on second generation antipsychotics, marking a new turning point. However, as far as we are aware, there have been no reports in Japan on the improvement of cognitive dysfunction by aripiprazole or reports on comparisons of the effect of aripiprazole

Abbreviations: BPRS, Brief Psychiatric Rating Scale; CA, Categories Achieved; DMS, Difficulty Maintaining Set; DVR, Delayed Verbal Recall; DVRG, Delayed Verbal Recognition; IVR, Immediate Verbal Recall; KWCST, Wisconsin Card Sorting Test Keio Version; MFT, Memory Filtering Test; MST, Memory Scanning Test; PEN, Preservative Errors in Nelson; STM-COMET, St. Marianna University School of Medicine's Computerized Memory Test.

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and several other second generation antipsychotics on cognitive dysfunction to elucidate differences in the profile of improvement.

The objective of this study was to clarify whether or not there were any differences in the profile of improvement in cognitive dysfunction with aripiprazole compared to perospirone and olanzapine by switching treatment from a first generation antipsychotic to second generation antipsychotic aripiprazole monotherapy, perospirone monotherapy, or olanzapine monotherapy in patients with chronic schizophrenia, and comparing clinical symptoms as well as executive function, verbal memory function, and attention function (which are categories of cognitive function used relatively often in research to date) during first generation antipsychotic monotherapy and in the group switching to aripiprazole monotherapy compared to the group switching to perospirone monotherapy and the group switching to olanzapine monotherapy.

2. Methods

2.1. Subjects

The subjects were a total of 31 patients who had been diagnosed with schizophrenia based on the Diagnostic and Statistical Manual of Mental Disorders Fourth Edition (DSM-IV) while hospitalized in the psychiatric department of Seimo Hospital or the psychiatric department of Ashikaga Fujimidai Hospital. 11 (7 males and 4 females) were switched from a first generation antipsychotic to aripiprazole monotherapy, 9 (2 males and 7 females) were switched to perospirone monotherapy, and 11 (6 males and 5 females) were switched to olanzapine monotherapy. The patient characteristics are given in Table 1. 7 subjects in the group switching to aripiprazole, 8 subjects in the group switching to perospirone, and 9 subjects in the group

switching to olanzapine had also been taking anti-Parkinson's medication before switching. The study was an open labeled, flexible-dose, naturalistic observational trial of chronic schizophrenia patients undergoing usual care and who require a change in their medication because of persistent symptoms or troublesome side effects. The allocation of individual patients to a particular antipsychotic therapy was not random. During 2003, most patients were receiving butyrophenone neuroleptics; in 2004, perospirone or olanzapine; 2006 aripiprazole was used. However, the procedure for psychometric and neuropsychological assessment remained the same throughout the entire period of the study. Aripiprazole was given by the method of Kikuyama et al (Kikuyama et al., 2007), and perospirone and olanzapine were given by the method of Weiden (Weiden et al., 1997), as add-on doses, within the range of 6 to 12 mg/day, 8 to 12 mg/day, or 2 to 5 mg/day, respectively, in addition to the previous therapeutic drug, after which the previous drug was tapered down and the new drug was up-titrated over a 3 to 4-week period in all cases to adjust the dose to the optimum dose. When switching, the daily dose was calculated in terms of chlorpromazine using the antipsychotic equivalence conversion tables of Inagaki (aripiprazole 1 mg = chlorpromazine 25 mg; perospirone 1 mg = chlorpromazine 12.5 mg; olanzapine 1 mg = chlorpromazine 40 mg) (Inagaki et al., 1999; Inagaki and Inada, 2006) as a guide for antipsychotic medication. This chlorpromazine equivalent table was developed by Inagaki et al. (1996) based on previously reported world's and Japanese's antipsychotic equivalent tables, and on the estimation of clinical efficacy in previous controlled studies on effects of antipsychotics. Patients with no change in psychotropics other than antipsychotics or other drugs potentially affecting cognitive function before and after switching were selected as patients to compare cognitive function. Only patients who had provided voluntary informed consent in writing to participate in this study upon receiving a full explanation of the purpose and method of the study were enrolled, while patient confidentiality was afforded all due consideration, as were ethical considerations.

2.2. Outcome measures

The following test methods were used to assess clinical symptoms and cognitive function during first generation antipsychotic monotherapy and 8 weeks after the completion of the switch to aripiprazole, perospirone, or olanzapine, the change from baseline to the final observation was calculated, and the effect of aripiprazole in improving clinical symptoms and cognitive function was compared to that of perospirone, and olanzapine.

2.3. Symptom assessments

The Brief Psychiatric Rating Scale (BPRS: 18 items) was used to assess clinical symptoms. The BPRS sub-scales were grouped into the following three clusters: group of positive symptoms (5 items: hallucinatory behaviors, conceptual disorganization, suspiciousness, mannerisms and posturing, unusual thought content), group of negative symptoms (4 items: blunted affect, emotional withdrawal, motor retardation, uncooperativeness), and groups of other symptoms (9 items: somatic concern, anxiety, guilt, tension, grandiosity, depression, hostility, excitement, disorientation) (Sumiyama and Kitamura, 1995).

2.4. Cognitive battery

Cognitive function was assessed using the Wisconsin Card Sorting Test (Keio Version: KWCST) (Kashima, 2002) and St. Marianna University School of Medicine's Computerized Memory Test (STM-COMET) (Onodera et al., 1999) as the executive function test and verbal memory function and attention function tests, respectively. Details of the KWCST and STM-COMET are given below.

Table 1
Demographic characteristics^a.

Demographic variables	Aripiprazole (n = 11)	Perospirone (n = 9)	Olanzapine (n = 11)
Age (years) (Mean ± S.D.)	56.1 ± 7.8	56.1 ± 11.7	57.2 ± 11.2
Gender (M : F)	7 : 4	2 : 7	6 : 5
Duration of illness (years) (Mean ± S.D.)	24.8 ± 6.8	30.9 ± 10.4	33.7 ± 13.7
Daily dose (mg/day) (Mean ± S.D.)	428.2 ± 158.2	455.6 ± 123.6	490.0 ± 164.0
Dose equivalent to pre-treatment chlorpromazine dose (mg/day) (Mean ± S.D.)	559.1 ± 233.3	643.6 ± 195.7	637.9 ± 229.3
Biperiden daily dose (mg/day) (before switching) (Mean ± S.D.)	3.0 ± 2.9	3.9 ± 2.3	3.8 ± 2.3
Clinical measures (before switching) (Mean ± S.D.)			
BPRS, total	33.9 ± 3.4	38.3 ± 6.2	36.5 ± 5.9
BPRS, positive	9.7 ± 2.7	11.7 ± 4.5	11.0 ± 3.8
BPRS, negative	12.6 ± 2.1	12.1 ± 2.2	12.2 ± 3.0
Cognitive measures (before switching) (Mean ± S.D.)			
KWCST, First stage, CA	1.8 ± 1.9	1.6 ± 1.6	1.8 ± 1.5
PEN	15.0 ± 9.3	17.3 ± 13.4	19.7 ± 14.6
DMS	1.5 ± 1.3	2.1 ± 2.5	1.3 ± 1.2
Second stage, CA	2.4 ± 2.1	1.8 ± 1.4	2.3 ± 1.6
PEN	9.5 ± 6.7	10.7 ± 7.8	10.2 ± 9.9
DMS	1.8 ± 1.4	1.9 ± 2.4	2.3 ± 1.7
STM-COMET			
IVR	4.2 ± 2.8	5.6 ± 2.1	4.4 ± 2.3
DVR	2.4 ± 1.9	2.9 ± 1.8	2.1 ± 2.0
DVRG	19.5 ± 5.8	18.2 ± 6.3	20.8 ± 3.5
MST	4.6 ± 2.8	5.8 ± 3.0	4.9 ± 1.2
MFT	22.4 ± 13.2	29.3 ± 8.6	21.4 ± 10.5

BPRS, Brief Psychiatric Rating Scale; KWCST, Wisconsin Card Sorting Test Keio Version; CA, Categories Achieved; PEN, Preservative Errors in Nelson; DMS, Difficulty Maintaining Set; STM-COMET, St. Marianna University School of Medicine's Computerized Memory Test; IVR, Immediate Verbal Recall; DVR, Delayed Verbal Recall; DVRG, Delayed Verbal Recognition; MST, Memory Scanning Test; MFT, Memory Filtering Test

^aGroups did not differ in the baseline variables reported in the pooled and individual.

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