Switching Patients with Chronic Schizophrenia to Aripiprazole: the Improvement in Cognitive Function

Jung Goo Lee1, Ji Heon Lee2, Eun Kyong Ha2, Min Chul Kim2, Young Hoon Kim3

1Department of Psychiatry, Masan Dong Suh Mental Hospital, Masan, 2Department of Psychiatry, Busan Paik Hospital, Inje Medical College, Busan, 3Department of Psychiatry, School of Medicine and Paik Institute for Clinical Research, Inje University, Busan, Korea

Our goal was to evaluate the effects and safety of aripiprazole after switching from prior antipsychotic drugs in patients with chronic schizophrenia. Neurocognitive tests were applied to 21 schizophrenic patients. The schizophrenic patients were retested with the same instruments after 8 and 24 weeks of treatment with aripiprazole. Effects were assessed using the Brief Psychiatric Rating Scale (BPRS), the Hamilton Rating Scale-Depression (HAM-D), and the Clinical Global Impression-Severity (CGI-S). Extrapyramidal symptoms were assessed using the Simpson–Angus Scale (SAS). Levels of prolactin and body weight were also measured. After switching to aripiprazole, no significant changes were observed on the BPRS, the HAM-D, or the GI-S. Significant improvements were found on the Hopkins Verbal Learning Test (HVLT), the Rey Complex Figure Test (RCFT), the Digit Span Forward, Trail-Making Test A, Korean version-Boston Naming Test (K-BNT) 24 weeks after switching to aripiprazole. Aripiprazole induced significant loss of body weight at 4 weeks and decreased prolactin levels at 8 weeks but no changes were observed in the Simpson–Angus Scale (SAS) and body weight at 24 weeks. These data suggest that aripiprazole is effective in improving verbal memory and attention. The drug also demonstrated a favorable safety profile, as observed in the low incidence of hyperprolactinemia.

KEY WORDS: Schizophrenia; Aripiprazole; Switching; Effects; Safety.

INTRODUCTION

Schizophrenia is a disease with heterogeneous characteristics and diverse symptoms including psychotic, cognitive, and mood-altering symptoms. It has been reported that cognitive impairment in schizophrenia results in deficits in various fields, including attention, information processing, working memory, learning ability, and executive function. Such cognitive impairment has been shown to be associated with other deficits of diverse and wide functions in schizophrenic patients. In addition, it has been reported that the social and occupational functions of patients and their quality of life are more closely associated with their level of cognitive function than with their clinical symptoms.

Therefore, since 1990, amelioration of cognitive impairment has been an important treatment aim for schizophrenia, and the effect of newly developed antipsychotics on cognitive function has become an important factor in their evaluation, in addition to their other positive and negative effects on symptoms. In studies on the effect of atypical antipsychotics on the cognitive function of schizophrenic patients, clear evidence showing an improvement of cognitive function has been reported to be absent. However, it has been noted that recently introduced atypical antipsychotics not only improve side effects, negative symptoms, compliance, and mood in comparison with typical antipsychotics but also have a good effect on cognitive function.

Regarding the cognitive effect of atypical antipsychotics, numerous studies on clozapine, risperidone, and olanzapine have been published. Hagger et al. reported that 6 weeks after clozapine was administered to 36 incurable schizophrenic patients, verbal fluency and memory improved significantly, and after 6 months, executive function, attention, and memory improved. In addition, Meltzer et al. demonstrated that clozapine improved memory, verbal fluency, and executive function. Daniel et al. compared risperidone and clozapine in 14 chronic schizophrenic patients, and found that risperidone was effective in terms
of the ability to move to another frame in a visual memory test, and clozapine was effective in terms of alertness in a reaction time test. Purdon et al.\textsuperscript{13} compared the effect of haloperidol, risperidone, and olanzapine on cognitive function in stable ambulatory schizophrenic patients and reported that risperidone significantly improved their overall cognitive function, new learning, and verbal memory, and that olanzapine improved their overall cognitive function, new learning, attention, motion, executive function, and nonverbal memory. Bilder et al.\textsuperscript{12} reported that compared to the haloperidol group, the olanzapine group showed a significant improvement in the perseverative error response of the Wisconsin Card Sorting Test, verbal learning, memory, and attention.

Given the above findings, the effect of atypical antipsychotics on cognitive function in schizophrenic patients appears to be more positive than typical antipsychotics. However, it is not clear over what timescale and in which areas a definite improvement occurs, or whether it is a secondary effect depending on clinical symptoms or a direct effect of the dynamic mechanism of the drugs.\textsuperscript{13} Animal studies using atypical antipsychotics have reported improvements in memory and learning ability as a result of 5-HT\textsubscript{2} antagonists, and thus the mechanism of their action is believed to be related to the blocking of the 5-HT\textsubscript{2A} receptor. It has been reported that such atypical antipsychotics improve neuronal cognitive function by activating dopamine and acetylcholine in the prefrontal cortex through diverse mechanisms.\textsuperscript{14,15} In addition, it has been speculated that indirect effects are mediated by the improvement of negative symptoms, reduction of extrapyramidal symptoms, and a reduction in the use of anticholinergic drugs.\textsuperscript{14,15}

In these ways, atypical antipsychotics not only improve positive symptoms but also ameliorate negative and cognitive symptoms, inducing fewer side effect extrapyramidal symptoms than typical antipsychotics; hence, they have come to be used as a primary drug in the treatment of schizophrenia.\textsuperscript{16} However, an important issue arising out of the use of atypical antipsychotics is the tolerability of their side effects, which include weight gain, increased blood prolactin, hypercholesterolemia, and prolongation of the QTc interval. Thus, new antipsychotics with better stability and tolerability are required.\textsuperscript{17,18}

It has been reported that unlike other atypical antipsychotics, the recently developed drug aripiprazole has a peculiar reaction mechanism that mediates a partial agonistic effect on the D\textsubscript{2} and 5-HT\textsubscript{1A} receptors, and an antagonistic effect on 5-HT\textsubscript{2A}.\textsuperscript{19,20} It has been reported that aripiprazole has fewer side effects, not only in the extrapyramidal symptoms but also in terms of sedative effect, weight gain, increase in serum prolactin, and prolongation of the QTc interval. In a study comparing aripiprazole and risperidone, Porkin et al.\textsuperscript{21} reported that in both groups, no statistically significant extrapyramidal symptoms were detected, and a study reported by Marder et al.\textsuperscript{19} found that the frequency of extrapyramidal symptoms induced by aripiprazole was similar to that of a placebo. Regarding weight gain, in a 52-week comparative study with haloperidol, those with a body mass index (BMI) lower than 23 in the group receiving aripiprazole showed a slight weight gain, while those with a BMI higher than 27 lost weight.\textsuperscript{21} In a 26-week open study reported by Jody et al.\textsuperscript{22} weight gain in the olanzapine group averaged 3.6 kg, while the aripiprazole group averaged a weight reduction of 0.9 kg. In a metanalysis, McQuade et al.\textsuperscript{23} reported that aripiprazole did not raise the serum prolactin value.

Aripiprazole was introduced to Korea in 2004, and clinical experience of its use is as yet insufficient. Additionally, very few studies to date have examined the effect of aripiprazole on cognitive function in schizophrenia patients, either in Korea or worldwide. Therefore, this study evaluated the treatment effect and safety implications of aripiprazole in schizophrenia, and primarily examined the effects of aripiprazole on cognitive function. Our goal was to determine the treatment effect of aripiprazole on cognitive function in schizophrenia patients who were under antipsychotics before switching to aripiprazole, as well as safety regarding extrapyramidal symptoms, hyperprolactinemia, and weight gain.

**MATERIALS AND METHODS**

**Study Population**

The study was performed on ambulatory patients in the Department of Psychiatry, or inpatients at the Busan Paik Hospital or the Masan Dong Suh Mental Hospital, Korea, who needed to change medications either because the effects of their previous drugs were insufficient or because they had side effects. The subjects were schizophrenic patients satisfying the DSM-IV diagnostic criteria: to rule out any influences of age and education level, their ages were limited to between 18 and 50 years, and their education level was required to be more than 9 years of regular education. Patients with other psychological impairments, those with neurological impairments including head injury, and cases with a history of alcohol and drug abuse were excluded.

The purpose and content of this study were explained to patients who satisfied the recruitment requirements, and their consent was obtained. Through psychiatrists’ interviews, we determined their sex, age, diagnosis, illness
duration, type and dosage of drugs, treatment duration, and education level (Table 1).

**Study Method**

**Administration of Aripiprazole and Clinical Evaluation**

In the process of switching medications, we first performed a baseline test and then employed the start and tapering method as the drug exchange strategy. On the first day, 15 mg aripiprazole was administered, along with one-half of the usual daily dose of the previous drug. This continued for 3 days. Then one-quarter dose of the previous drug was administered with the 15 mg aripiprazole for an additional 4 days. The antipsychotics administered prior to the exchange were risperidone in 17 cases, olanzapine in 2 cases, amisulpride in 1 case, and chlorprothixene in 1 case. Clinical symptoms were evaluated using the Brief Psychiatric Rating Scale (BPRS), the Hamilton Rating Scale-Depression (HAM-D) and the general Clinical Global Impression-Severity (CGI-S). Extrapyramidal symptoms were evaluated using the Simpson-Angus Rating Scale, CGI-S did not significantly change at any of the test time points (Table 2).

**Cognitive Function Test**

Cognitive function was assessed by a certificated clinical psychologist, and to assess the four major functions defective in schizophrenia, attention, auditory and visual memory, verbal fluency, and executive function, the following tests were performed: the Hopkins Verbal Learning Test (HVLT), the Rey Complex Figure Test (RCFT), the Digit Span Forward and Backward tests, the Stroop Test, the Trail Making Tests A/B, the Digit Symbol Substitution Test (DSST), the Verbal Fluency Test, and the Korean version-Boston Naming Test (K-BNT). Evaluations were made at baseline, 8 weeks, and 24 weeks.

**Statistical Analysis**

We compared scores of the Korean version of the Mini Mental State Examination (K-MMSE), the Brief Psychiatric Rating Scale (BPRS), the Hamilton Rating Scale-Depression (HAM-D), and all cognitive function tests using Wilcoxon’s sign rank test. All of the above statistical analyses were performed using the Korean SPSS version 10.0.

**RESULTS**

**Success Rate of the Switch and Causes of Dropout**

A total of 21 patients was enrolled on the trial, but by 8 weeks, 5 patients had dropped out, and by 25 weeks, a further 5 patients had quit the trial. Thus, 11 patients remained for the full 24 weeks, and the success rate of the switch to aripiprazole was 52.3%. Causes of dropout were insufficient effectiveness in 5 cases, side effects in 2 cases, noncompliance with the drug program in 2 cases, and failure to attend the follow-up observation in 1 case. The daily average dose of aripiprazole was 14.4 mg for the first 8 weeks and 18.3 mg from 8 to 24 weeks.

**Changes in Psychotic Symptoms**

In comparison with the starting point, BPRS, HAM-D, CGI-S did not significantly change at any of the test time points (Table 2).

**Changes in Cognitive Function**

The cognitive function test score prior to and after the administration of aripiprazole showed a significant

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**Table 1.** Demographic and clinical characteristics of subjects

<table>
<thead>
<tr>
<th>Variables</th>
<th>Baseline</th>
<th>1 week</th>
<th>4 weeks</th>
<th>8 weeks</th>
<th>24 weeks</th>
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<tbody>
<tr>
<td>Age (mean years ± SD)</td>
<td>31.1±8.7</td>
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<tr>
<td>Duration of illness (mean years ± SD)</td>
<td>6.5±5.7</td>
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<td>Education (mean years ± SD)</td>
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<td>Gender (%)</td>
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<tr>
<td>Male</td>
<td>7 (33.3)</td>
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<tr>
<td>Female</td>
<td>14 (66.7)</td>
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<td>Previous antipsychotics (%)</td>
<td></td>
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<tr>
<td>Risperidone</td>
<td>17 (81.0)</td>
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<tr>
<td>Olanzapine</td>
<td>2 (9.5)</td>
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<tr>
<td>Amisulpride</td>
<td>1 (4.8)</td>
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<tr>
<td>Chlorprothixene</td>
<td>1 (4.8)</td>
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<td>Use of Anticholinergics (%)</td>
<td>15 (71.0)</td>
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<td>Major cause of switching</td>
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<td>Lack of efficacy (esp. negative sx)</td>
<td>9 (7)</td>
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<td>Overweight</td>
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<td>EPS</td>
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<td></td>
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<tr>
<td>Other adverse events</td>
<td>2</td>
<td></td>
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</table>

SD: Standard deviation
change in various tests, as shown in Table 3.

1) In immediate recall using the Hopkins Verbal Learning Test, a significant improvement was observed at 8 weeks \((p=.004)\) and at 24 weeks \((p=.005)\) compared to the measurement at the base time point; a significant improvement was detected in the delayed recall test at 24 weeks \((p=0.016, \text{Fig. 1})\).

2) In immediate recall using the Rey Complexity Figure Test, a significant improvement was found at 8 weeks \((p=.044)\) and 24 weeks \((p=0.023)\) compared to the measurement at the base time point. In delayed recall, a significant improvement was found at 8 weeks \((p=0.016)\) and 24 weeks \((p=.026)\), and recognition showed a significant improvement at 24 weeks \((p=0.006, \text{Fig. 2})\).

3) In the Digit Span Forward Test, a significant improvement was found at 24 weeks \((p=0.046, \text{Fig. 3})\).

4) In Trail-Making Test A, significant improvement was shown in the tests at 8 weeks \((p=0.007)\) and 24 weeks \((p=.026, \text{Fig. 3})\).

5) In the Korean version-Boston Naming Test, significant improvement was detected in the tests at 8 weeks \((p=0.001)\) and 24 weeks \((p=0.003, \text{Fig. 3})\).

**Change of Abnormal Response**

1) In the Simpson-Angus evaluation scale assessing extrapyramidal symptoms, no significant change was detected at 24 weeks (Fig. 4).

2) The prolactin value showed a significant reduction at the last time point after 8 weeks compared to the base time point \((p=0.001, \text{Fig. 4})\).

3) Weight reduction showed statistical significance at 4 weeks \((p<0.01)\), but did not at 24 weeks (Fig. 4).

**DISCUSSION**

Although the previously used antipsychotic drugs may have had a therapeutic effect on schizophrenia, patients have switched to other antipsychotics because of an inefficient treatment response to positive or negative symptoms, the reduction of cognitive function, or other side effects. As exchanging drugs may cause aggravation of psychotic symptoms or other side effects, the method by which drugs are safely switched needs consideration. Generally, the methods of exchanging antipsychotics are the direct exchange method, which terminates previous drugs completely and administers new drugs immediately, and the cross-exchange method, whereby new drugs are added and previous drugs are gradually decreased. Because of the possibility of causing withdrawal symptoms or the exacerbation of psychotic symptoms, however, the direct ex-
change method is not used widely. The cross-exchange method may augment side effects or possibly exacerbate symptoms depending on the reduction speed.

During the exchange of drugs, not only clinical conditions, but also the pharmacological characteristics of the switched drugs should be considered. Systemic studies on the switch to aripiprazole are rare. Casey et al.\(^25\) compared the effectiveness and safety of three methods for exchanging aripiprazole: first, previous drugs were terminated immediately and 30 mg aripiprazole was administered immediately; second, 30 mg aripiprazole was administered immediately and previous drugs were reduced over 2 weeks; and third, previous drugs were reduced over 2 weeks and aripiprazole was gradually increased to 30 mg. The average exchange rate was 72%, and the three methods were found to be comparably effective and safe. In our study, we selected to use the cross-tapering method, which is used most widely in clinics and involves the administering of 15 mg aripiprazole immediately while reducing previous drugs over 1 week. Of the 21 enrolled patients, 10 dropped out during the course of the 24-week trial, and 11 completed the study. The exchange success rate of aripiprazole was 52.3%. However, our study was 24 weeks in duration, as compared to previous studies that were only 8 weeks in duration, in which the exchange rate at the 8th week was 76.1%.

Due to the impairment of cognitive functions such as attention, executive function, and memory, schizophrenic patients show social and professional functional impairment, and their quality of life also declines.\(^26,27\) A more severe level of cognitive defect leads to a lower degree of clinical improvement and rehabilitation; similarly, with more severe levels of cognitive defect, insufficient data...
exist regarding the need for compliance with therapeutic intervention. Therefore, numerous studies have been conducted on the effect of antipsychotics on cognitive function. Their common conclusion is that although typical psychotics may be clinically effective in acute or chronic schizophrenia, they have little effect on cognitive function. In addition, after the administration of anticholinergic drugs for the control of side effects such as extrapyramidal symptoms, a decline in cognitive function may be experienced.

It has been reported that atypical antipsychotics may partly ameliorate cognitive function, resulting in an improvement in the quality of life. In studies on clozapine, results have shown a consensus with regard to improvements in attention, verbal fluency, and executive function. However, the results for working memory, verbal memory, and spatial memory have been inconsistent. In studies of olanzapine, a consensus exists regarding an improvement in verbal learning and memory, verbal fluency, and executive function. However, the results for attention, working memory, visual learning, and memory have differed. In our study, clinical symptoms evaluated following the exchange of antipsychotics to aripiprazole and after 24 weeks of administration did not show a significant change.

Nonetheless, in cognitive function tests, significant improvements were detected in 8 of the 16 test categories, and none of the tests revealed any deterioration. In sum-

![Graphs showing mean changes in cognitive tests and adverse events after switching to aripiprazole.](image-url)
mary, a significant improvement was detected in immediate and delayed recall in the Hopkins Verbal Learning Test and immediate recall in the Rey Complex Figure Test, as well as in delayed recall and recognition in the following tests: the Digit Span Forward and Backward tests, Trail-Making Test A, and the Korean version-Boston Naming Test. Performance on the Hopkins Verbal Learning Test, which evaluates learning and verbal memory, showed improvement in the immediate recall and delayed recall components. The Rey Complex Figure Test evaluates visual memory, and there were improvements in the immediate recall, delayed recall, and recognition components. The improved Digit Span Test and Trail-Making Test A evaluate attention, and the Korean version-Boston naming test primarily evaluates verbal function. Among the cognitive function test categories that showed significant improvement by 24 weeks, all tests except for the delayed recall component of the Hopkins Verbal Learning Test and the recognition components of the Rey Complex Figure Test and the Digit Span Test, demonstrated significant improvement from 8 weeks that was sustained until 24 weeks. However, such significant improvement in the various cognitive function test categories may have been influenced by the practice effect. To examine this possibility, we studied the results of cognitive function tests in a placebo group, who were participants in two other studies and had performed cognitive function test categories identical to those of the chronic schizophrenic patients. In one study, the placebo group showed no significant improvement in any of the test categories, but in the other study, significant improvements were found in immediate recall and recognition using the Rey Complex Figure Test and Korean version-Boston Naming Test. The results allow the possibility that the above two tests, which evaluate visual memory and verbal function, were influenced by practice effects. This finding is similar to part of our present study, which appears to have been influenced by practice effects. However, unlike our study, no significance was detected in the placebo group for the Hopkins Verbal Learning Test, the Digit Span Test, or Trail-Making Test A. Therefore, the likelihood is low that the improvements in these tests, which evaluate verbal memory and attention, are practice effects: indeed, they are clearly the effects of aripiprazole. However, the characteristics of the patients in our study were different from those of the patients in the other two studies, so these results need further verification.

In previous studies comparing the effect of aripiprazole and olanzapine on neuronal cognitive function in stable chronic schizophrenic patients, the use of aripiprazole resulted in a significant improvement in verbal memory, which partially agrees with the results of our study. It is anticipated that such improvement in various areas of cognitive function may help increase the degree of patient insight, which is important for treatment compliance, as well as clinical improvement and rehabilitation. As well as the effect of aripiprazole on cognitive function, other remarkable aspects of this study are related to the safety and tolerability of aripiprazole.

In several previous studies, increases of prolactin, weight gain, and extrapyramidal symptoms have been almost absent. In our study, 8 weeks after the switch to aripiprazole, we found a significant reduction in prolactin; we also detected significant weight reduction after 4 weeks and a weight reduction of approximately 6 kg on average at 24 weeks, although this figure was not significant. Weight gain due to antipsychotics mediates a negative effect on drug compliance, which may be a reason for switching drugs. In the Simpson-Angus evaluation scale, which assesses extrapyramidal symptoms, no statistically significant improvement was detected after 24 weeks, although a decrease did occur. At the base time point, 15 of the 21 patients used anticholinergic drugs; subsequently, most cases stopped taking the drugs, and only 3 patients were still taking them at 24 weeks. The improved cognitive function detected in our study following the exchange to aripiprazole may have been due to the reduced dose of anticholinergic drugs. It has been reported that verbal memory and spatial memory are influenced greatly by anticholinergic drugs, which is in partial agreement with the results of our study.

Two limitations to the present study must be acknowledged. First, 21 subjects comprise a relatively small number; it was an open trial, and a control group was absent. Hence, it was difficult to compare previous antipsychotics directly with aripiprazole. However, in reality, it is difficult to conduct a study of this kind with a control group as it would involve administering placebo drugs to schizophrenic patients in clinics. Second, the possibility that the change of cognitive function resulted from changes in anticholinergic drug use was not considered. Our study did not elucidate whether the improvement in cognitive function was due to decreased use of anticholinergic drugs; however, lowering the use of anticholinergic drugs may have a clinical advantage. Despite these limitations, our study suggests that the new atypical antipsychotic aripiprazole partially improves cognitive function.

REFERENCES
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