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# Factors associated with discontinuation of aripiprazole treatment after switching from other antipsychotics in patients with chronic schizophrenia: A prospective observational study

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ABSTRACT

The purpose of the study was to identify factors associated with discontinuation of aripiprazole after switching from other antipsychotics in patients with schizophrenia in real world clinical settings. From January 2011 to December 2012, a prospective, 48-week open-label study was undertaken. Thirty-eight subjects on antipsychotic monotherapy were switched to aripiprazole. Patients who discontinued aripiprazole were compared to those who continued with regards to demographic characteristics as well as treatment factors. Multiple regression analysis was conducted to identify predictors for aripiprazole discontinuation. Thirteen out of 38 patients (34.2%) discontinued aripiprazole during the follow up period. Nine patients (23.7%) discontinued aripiprazole due to worsening of psychotic symptoms. Multiple logistic regression analysis revealed that only the duration of previous antipsychotic treatment was associated with aripiprazole discontinuation after switching to aripiprazole. The receiver operating curve (ROC) analysis identified that the cut-off length for duration of illness to predict aripiprazole discontinuation was 10.5 years. Longer duration of illness was associated with aripiprazole discontinuation. Greater caution may be required when treating such patients with aripiprazole.


## 1. Introduction

Aripiprazole, an antipsychotic agent with partial agonistic activity at the dopamine $D_2$ receptor site (Marder et al., 2003), is recognized as one of the first-line antipsychotics for patients with schizophrenia (Weiden et al., 2007). Because of its unique pharmacological profile, it has been well established that aripiprazole has fewer side effects, including extrapyramidal symptoms, weight gain (Goodnick and Jerry, 2002), hyperprolactinemia, and prolonged QTc interval (Marder et al., 2003). It has been also accepted that aripiprazole is as effective as other antipsychotics with regards to improving psychotic symptoms, as well as neurocognitive function (Kern et al., 2006) compared to other antipsychotics. On the other hand, there are some studies reporting that aripiprazole can worsen psychotic symptoms when used as an adjunct with other antipsychotics or switched from other antipsychotics (Fleischhacker et al., 2010; Newcomer et al., 2008). However, it remains unclear whether or not there are factors that are related to such symptomatic exacerbation leading to discontinuation of aripiprazole. Therefore it would be valuable if we could predict who might benefit from aripiprazole treatment and who might experience symptom exacerbation.

The aim of this study was to investigate factors associated with discontinuation of aripiprazole in patients with chronic schizophrenia after switching from other antipsychotics.

## 2. Materials and methods

### 2.1. Subjects

The study was approved by the ethics committee of Tokyo Medical University and its affiliated hospital. Patients were recruited from outpatient clinics at Tokyo Medical University Hospital and Fuji Psychosomatic Rehabilitation Laboratory Hospital. Study participants were enrolled from outpatient clinics of these hospitals and included in the study if they met the following

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criteria: (1) 18–65 years old with a diagnosis of schizophrenia according to DSM-IV criteria; (2) patients who were being treated with any antipsychotic except aripiprazole as a monotherapy; (3) antipsychotics dosage below 1000 mg/day chlorpromazine equivalents; (4) patients who required a switch of antipsychotics due to intolerability or insufficient efficacy, and aripiprazole was considered to be a reasonable choice as judged by attending physicians. Patients were excluded if they met the following criteria: (1) patients on two or more antipsychotics or on long-acting injectable antipsychotics; (2) patients who are in the acute phase or have suicidal ideation that requires urgent intervention; (3) treatment refractory patients defined as failure to respond to two adequate treatment trials with antipsychotics from two different classes; (4) patients who had physical diseases that might have an impact on the course of schizophrenia, including collagen disease, brain injury/stroke, and diabetes, and those with a history of drug or alcohol abuse within the past 12 weeks.

### 2.2. Study treatment

We applied the "full dose cross taper" method, in that aripiprazole was started from 12 mg/day and gradually increased up to the chlorpromazine equivalent dose of the previous antipsychotics over a period of 4 weeks, whereas the former antipsychotics were continued at the same dosage for 4 weeks and gradually decreased from week 4 and discontinued by week 12. Co-treatment of other antipsychotics was not permitted during the study period. Psychotropic drugs other than antipsychotics were permitted throughout the study based on clinical judgment.

### 2.3. Outcome measures

All subjects were evaluated at baseline, 4 weeks, 12 weeks, 24 weeks, and 48 weeks with the rating scales described as follows; (1) Global severity, Clinical Global Impression scale Improvement (CGI-I) and Clinical Global Impression scale Severity of illness (CGI-S), as assessed by attending physicians; (2) Subjective well-being, Subjective Well-being under Neuroleptics, short version, Japanese edition (SWNS-J) (Watanabe and Matsumura, 2003) filled out by each subject; (3) Extrapyramidal symptoms (EPS), Drug Induced Extra-Pyramidal Symptoms Scale (DIEPSS) (Inada and Yagi, 1996), as assessed by attending physicians; (4) other safety measures including frequency and severity of adverse events, laboratory results, physical examination, vital signs, body mass index (BMI), and metabolic parameters.

### 2.4. Statistical analysis

We divided the subjects into those who continued aripiprazole treatment until the end of the 48-week follow up period (continued group), and those who discontinued before the end of the follow up period (discontinued group). The Mann–Whitney *U* test and chi-square test were used for comparison of age, sex, BMI, duration of previous antipsychotic treatment, daily doses of antipsychotics before switching, dose of aripiprazole, use of mood stabilizer and benzodiazepines during the switching period (baseline to 12 weeks), SWNS-J score, CGI-S score, and DIEPSS score between these two groups. The factors associated with the discontinuation of aripiprazole were examined using logistic regression analyses with all descriptive variables. All variables were initially examined in univariate models. To control for confounding factors and to determine the main correlates, we then performed multivariate logistic regression analyses with variables that showed a value of $p$ less than 0.25 in the univariate models. As a post-hoc analysis, receiver operator characteristic (ROC) curves (Shapiro, 1999) were plotted and the mean estimated area under the curve (AUC) with 95% confidence interval (CI) for the duration of previous antipsychotic treatment was calculated for predicting discontinuation of aripiprazole treatment. When the slope of the tangent line of the ROC curve was statistically equal to 1 (i.e., AUC = 0.5), the ROC curve was regarded as inaccurate for prediction. The best cut-off value for predicting the discontinuation of aripiprazole treatment was determined on the basis of sensitivity, specificity, and positive likelihood ratio (LR+) and negative likelihood ratio (LR−). According to an established method (Swets, 1988), the cut-off value was assessed as adequate when LR+ was 2.0 or higher and LR− was 0.5 or lower. The Wilcoxon signed rank test was used to evaluate the effect of aripiprazole on rating scales (CGI-I, SWN-J, and DIEPSS), metabolic parameters (BMI, total cholesterol, triglyceride, fasting glucose), and serum prolactin level at each follow-up time point (week 4, week 12, week 24, and week 48) among aripiprazole continuers.

SPSS version 11.5.1J for Windows (SPSS Inc., Tokyo) was used for the statistical analyses. A $p$-value of less than 0.05 was considered to indicate a statistically significant difference.

## 3. Results

A total of 38 patients participated in the study. Patients' characteristics are shown in Table 1. Of 38 patients, 10 patients were on risperidone (26.3%), 10 on haloperidol (26.3%), 9 on olanzapine (23.7%), 3 on quetiapine (7.9%), 2 on blonanserin (5.3%), and 4 on

**Table 1**
Demographic and clinical characteristics between the continued group and the discontinued group.

| | Total subjects ($n$=38) | Continued group ($n$=25) | Discontinued group ($n$=13) | $p$ Value |
|---|---|---|---|---|
| Age (years) | 35.4 ± 11.0 | 33.5 ± 10.3 | 39.0 ± 11.9 | 0.185 |
| Sex (female/male) | 19/19 | 10/15 | 8/5 | 0.170 |
| BMI (kg/m$^2$) | 22.5 ± 5.8 | 22.9 ± 3.6 | 21.5 ± 9.4 | 0.969 |
| Duration of treatment (years) | 11.3 ± 9.7 | 8.1 ± 8.1 | 17.3 ± 10.4 | **0.008** |
| Chlorpromazine equivalent (mg/day) | 508.0 ± 260.4 | 488.9 ± 289.6 | 547.9 ± 190.8 | 0.498 |
| Dose of aripiprazole (mg) | 20.2 ± 7.5 | 20.5 ± 7.7 | 19.8 ± 7.5 | 0.783 |
| SWANS-J total score (points) | 62.6 ± 16.9 | 63.9 ± 16.3 | 60.1 ± 18.4 | 0.450 |
| Use of mood stabilizer (yes/no) | 5/33 | 3/22 | 2/11 | 1.000 |
| Use of benzodiazepine (yes/no) | 18/20 | 13/12 | 5/8 | 0.327 |
| CGI-S score (points) | 4.24 ± 0.6 | 4.2 ± 0.6 | 4.3 ± 0.5 | 0.601 |
| DIEPSS score (points) | 1.2 ± 0.8 | 1.1 ± 0.8 | 1.3 ± 0.9 | 0.395 |

Values are expressed as the mean ± SD. The Mann–Whitney *U* test was used for the comparison of continuous variables between the 2 groups. The chi-square test was used for the comparison of categorical variables between the 2 groups.
BMI = Body Mass Index; SWANS-J = Subjective Well-being under Neuroleptic drug treatment short version, Japanese edition; CGI-S = Clinical Global Impression scale Severity of illness; DIEPSS = Drug Induced Extra-Pyramidal Symptoms Scale.