Safety and tolerability of aripiprazole in patients with psychosis associated with Parkinson's disease—Results of a multicenter open trial

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Abstract
Aim: To evaluate the effect of aripiprazole on psychosis and motor function in Japanese Parkinson's disease patients.

Methods: Patients with Parkinson's disease and hallucinations and/or delusions were enrolled. They were administered aripiprazole 3 mg/day, with dosage increased or reduced as needed. Patients were evaluated using the Brief Psychiatric Rating Scale (BPRS), Clinical Global Impression-Severity (CGI-S) scale, and Clinical Global Impression-Improvement scale for psychiatric response; Hoehn & Yahr staging and Unified Parkinson's Disease Rating Scale (UPDRS) part III for motor response; Mini-Mental State Examination (MMSE) and Frontal Assessment Battery (FAB) for cognitive response; and Schwab and England Activities of Daily Living scale for daily activities of patients, before and at 2, 4, and 12 weeks after initiation of open-label aripiprazole administration. This study was registered at the University Hospital Medical Information Network Center (registration number: UMIN000007711).

Results: Nine of the 24 enrolled patients discontinued the study. Among them, eight patients discontinued the trial on account of their worsening parkinsonian symptoms. There were no differences in age, disease duration, disease severity, and MMSE and FAB scores at baseline between patients who continued and discontinued the study. However, in patients who continued aripiprazole administration at 3 mg/day or less significantly improved BPRS, CGI-S, and UPDRS part III scores.

Conclusion: Significant improvements in hallucinations and delusions can be expected, although aripiprazole may aggravate parkinsonism in Parkinson's disease patients. Low-dose use of aripiprazole may be useful for managing Parkinson's disease patients with psychosis, but only with close observation of extrapyramidal symptoms.

KEYWORDS
aripiprazole, clinical trial, delusion, hallucination, psychosis
Patients with Parkinson’s disease (PD) often develop hallucinations and delusions that worsen the quality of both the patients’ and the caregivers’ lives. A large multicenter study in Japan reported that the prevalence of psychosis was 20.9% in 1021 PD patients. The incidence may increase with the development of PD pathology in the central nervous system and/or use of dopamine replacement therapy.

Although optimal adjustment of anti-PD drugs, addition of anticholinesterase drugs, and/or increased daily activity may be expected to improve such psychoses, they are not always effective. Atypical antipsychotics may hence be selected in these cases. Clozapine is recommended as a first-line drug for PD psychosis because several randomized studies have revealed significant improvement in hallucinations and delusions without worsening of motor symptoms. However, clozapine is generally not selected, perhaps because it requires special monitoring of agranulocytosis. Pimavanserin is an inverse agonist and antagonist of serotonin 5-HT2A receptors. A randomized controlled trial revealed that this drug improves psychosis without worsening of parkinsonism in PD patients. Pimavanserin, however, has not been approved in Japan. Quetiapine is not known to aggravate parkinsonism and is recommended as a second-line agent against psychosis, although its antipsychotic efficacy is controversial. Other antipsychotics such as risperidone and olanzapine are clinically selected to manage PD psychosis, but they may perturb extrapyramidal symptoms. As these drugs may aggravate parkinsonism frequently, they are not recommended for use against PD psychosis.

Aripiprazole is an atypical antipsychotic that acts as a dopamine D2 and D3 receptor partial agonist and a serotonin 5-HT1a and 5-HT2a receptor antagonist. Since it has different pharmacological properties compared with other atypical antipsychotics and it offers a reduced possibility of patients developing extrapyramidal symptoms, aripiprazole can be selected to manage PD psychosis safely. Weintraub et al reported that aripiprazole was relatively commonly used against PD psychosis in the United States. However, there are no randomized clinical trials or few open-label studies available on this agent. Thus, we tried aripiprazole in PD patients with hallucinations and/or delusions.

2 | METHODS

2.1 | Patients

Patients visiting either Okayama Kyokuto Hospital, the Research Institute for Brain and Blood vessels-Akita, or Asahikawa Red Cross Hospital who met the criteria of the UK Brain Bank, were aged ≥40 and <85 years, presented with hallucinations and/or delusions that were resistant to optimized dopamine replacement therapy and had no serious medical conditions other than PD patients were included in the study (Figure 1).

2.2 | Aripiprazole treatment

Aripiprazole was prescribed to these patients at a dose of 3 mg/day before bedtime. This dose was fixed for the first 2 weeks. The dose was suitably adjusted according to efficacy or any adverse effects. Medications other than aripiprazole did not change throughout the study.

![Flow chart of the study population](#)
2.3 | Data collection

The psychiatric symptoms of the patients, as well as motor and cognitive conditions and adverse effects, were evaluated before and at 2, 4, and 12 weeks after initiation of aripiprazole. Psychiatric symptoms were evaluated using the Brief Psychosis Rating Scale (BPRS).\textsuperscript{11} the Clinical Global Impression-Severity of illness scale (CGI-S), and Clinical Global Improvement-Improvement scale (CGI-I). The severity of psychiatric symptoms was evaluated by the physician using the CGI-S as follows: 1: normal, not at all ill, 2: borderline mentally ill, 3: mildly ill, 4: moderately ill, 5: markedly ill, 6: severely ill, and 7: among the most extremely ill patients. Each patient was evaluated by the same physician. CGI-I was evaluated by the patient or caregiver as follows: 1, very much improved; 2, much improved; 3, minimally improved; 4, no change; 5, minimally worse; 6, much worse; and 7, very much worse. The severity of PD symptoms was evaluated onsite using Hoehn & Yahr staging\textsuperscript{12} and Unified Parkinson’s Disease Rating Scale (UPDRS)\textsuperscript{13} parts I, II, and III. Cognitive function was evaluated using the Mini-Mental State Examination (MMSE)\textsuperscript{14} and Frontal Assessment Battery (FAB).\textsuperscript{15} Patients’ daily activities were evaluated using the Schwab & England Activities of Daily Living (ADL) scale.\textsuperscript{16} Adverse reactions were evaluated based on the responses during clinical interviews and by blood analyses. The levodopa equivalent daily dose (LEDD) of each patient was calculated using a conversion formula.\textsuperscript{17}

2.4 | Ethics

The trial was registered at the University Hospital Medical Information Network Center (registration number: UMIN000007711). This study was conducted between March 2012 and June 2013, and approved by the ethics committee of each institute. Written informed consent was obtained from all patients prior to the study.

2.5 | Statistical analysis

Differences in baseline characteristics of PD patients who had completed and those who discontinued the study due to adverse effects were compared using the $t$-test for ratio scale, the Mann-Whitney U-test for ordinal scale, and the chi-squared test for nominal scale. Changes in the evaluated scores in patients who completed the study were analyzed using the Friedman’s test, followed by the Wilcoxon signed-rank test. Changes in MMSE and FAB scores before and 12 weeks after aripiprazole administration were evaluated using the Wilcoxon signed-rank test. SPSS Statistics software (version 24.0 for Windows; IBM) was used for all the analyses. Linear regression analysis was performed using the Excel software (Microsoft). Statistical significance was set at $P < .05$.

3 | RESULTS

Twenty-four patients (men, $n = 13$) were enrolled in the present study. All patients presented with hallucinations. Among them, 20 patients presented with visual hallucinations, two presented with both visual and auditory hallucinations, one presented with auditory hallucinations, and one presented with auditory hallucinations and delusions. As shown in Table 1, the mean age $\pm$ SD at initial aripiprazole dosing (visit 1) was 72.4 $\pm$ 6.8 years; age at PD onset was 63.0 $\pm$ 7.2 years; disease duration was 9.4 $\pm$ 4.8 years; median of Hoehn & Yahr stage was 3 (range, 2-5); mean $\pm$ SD of UPDRS part I score was 7.6 $\pm$ 2.9, part II was 16.0 $\pm$ 9.6, and part III was 28.8 $\pm$ 12.9; Schwab and England ADL score was 73.3 $\pm$ 20.6; BPRS score was 39.6 $\pm$ 10.3; MMSE score was 23.6 $\pm$ 3.5; FAB score was 9.0 $\pm$ 3.9; and median of CGI-S score was 5 (2-7); daily dose of levodopa/dopa decarboxylase inhibitor (DCI) was 483 $\pm$ 270 mg; and LEDD was 699 $\pm$ 343 mg at visit 1 (baseline). Five patients were treated with cholinesterase inhibitors (donepezil 4 and galantamine 1), and the other two patients were treated with memantine for neuropsychiatric symptoms.

Of the 24 patients, 9 (37.5%) discontinued the study. Eight (33.3%) of them discontinued on account of the worsening of parkinsonism, and one discontinued due to worsening of hallucinations. The time until withdrawal of aripiprazole from the beginning of its dosing was within 2 weeks for 4 patients, 4 weeks for 3 patients, and 12 weeks for 2 patients (Figure 1). An additional patient presented with worsening bradykinesia after initiation of 3-mg aripiprazole; however, this was improved after reducing the dose to 1.5 mg.

There were no statistically significant differences in age at the beginning of the present study, age at PD onset, disease duration, Hoehn & Yahr stage, UPDRS parts I, II, and III scores, Schwab & England ADL score, CGI-S score, BPRS score, MMSE score, FAB score, daily dose of levodopa/DCI, and LEDD between patients who completed the study and those who discontinued the study (Table 1). Although statistically not significant, patients who discontinued aripiprazole administration tended to show older age, higher UPDRS part III score, and lower MMSE score when compared with patients who completed the study (Table 1). These parameters also were not different statistically between patients who presented with and without worsening of parkinsonism (Table 2). All patients (3 patients) who were over 80 years old discontinued the study because of motor deterioration in two patients and worsening of hallucinations in one. If we divided the patient group by baseline age $<80$ and $\geq 80$ years, the ratio of discontinuation was significantly high ($X^2 = 3.073, P < .05$) in the patients’ group over 80 years.

Statistical analysis of the PD patients who completed the study revealed that the reduction in BPRS score, CGI-S score, and UPDRS parts I and III scores were significant (Figures 2 and 3). Hoehn & Yahr staging, the UPDRS part II score, the Schwab & England ADL score, the MMSE score, and the FAB score did not change significantly. With regard to the CGI-I score, 9 patients scored 1 (very much improved) and 6 scored 2 (much improved).
at 12 weeks after aripiprazole dosing. Nine patients complained of adverse symptoms such as the worsening of bradykinesia (1 patient), hypersalivation (1 patient), insomnia (2 patients), binge eating (1 patient), weight gain (1 patient), dry eye (1 patient), and aspiration pneumonia (1 patient). One patient experienced hypersomnia just after increasing aripiprazole dose from 3 to 6 mg; reduction of aripiprazole to 3 mg alleviated hypersomnia. Mild insomnia was also reported in a patient who discontinued the study due to the worsening of parkinsonism.

The daily dose of aripiprazole at 12 weeks was 3 mg/day for 14 patients and 1.5 mg for 1 patient.

### DISCUSSION

Aripiprazole improved hallucinations and delusions without worsening of PD symptoms in 15 (62.5%) of the 24 patients. Nine (37.5%) out of 24 patients reported worsening of parkinsonism. Of these, 8 patients discontinued aripiprazole treatment. One patient continued the treatment because the motor deterioration was reversed after dose reduction to 1.5 mg. It was difficult to predict patients who could not tolerate aripiprazole based on their baseline characteristics (Tables 1 and 2), except for aging. Patients who discontinued aripiprazole dosing, however, tended to show older age, more disease severity and more cognitive impairment when compared with patients who completed the study (Table 1). The prevalence of dropouts was significantly higher in patients over 80 years of age. Patients aged ≥80 years may thus need closer monitoring to detect worsening PD symptoms when using this drug.

To date, several case reports and two open-label trials of aripiprazole against PD psychosis have been published. Two case reports indicated the worsening of extrapyramidal symptoms on administration of aripiprazole, and one described three patients with reduced psychosis without motor deterioration. Aripiprazole at 10-15 mg/day was used in these reports. Fernandez et al. tested aripiprazole in eight patients; however, psychosis improved in only two of them. The other six patients discontinued the trial, and two of them experienced motor deterioration. In their trial, aripiprazole was started at 5-10 mg/day and was slowly increased to 7.5 to 22 mg/day. Higher doses of aripiprazole may be associated with a higher discontinuation rate compared to our results. Friedman et al. studied 14 PD patients with psychosis, and aripiprazole was effective in six (42.9%) patients. Eight patients discontinued the drug, including five patients with motor deterioration. The incidence of motor deterioration caused by aripiprazole was less than 50%; however, 57.1% of patients reportedly needed to discontinue this drug because of adverse effects or inadequate efficacy. Although the effect of aripiprazole on psychosis was higher than that reported by Fernandez et al., discontinuation rate was still higher than that in our study. In this trial, aripiprazole was started at 1 mg/day and increased to a maximum of 5 mg/day. Comparable to

### TABLE 1 Baseline characteristics of patients with Parkinson's disease who completed or discontinued the study

|                      | Total | Completed | Discontinued | P-value |
|----------------------|-------|-----------|--------------|---------|
| Number               | 24    | 15        | 9            |         |
| Sex (male:female)    | 13:11 | 8:7       | 5:4          | ns      |
| Age (years)          | 72.4 ± 6.8a | 71.4 ± 5.7 | 74.0 ± 8.5  | ns      |
| Age at PD onset      | 63.0 ± 7.2 | 62.9 ± 6.1 | 63.3 ± 9.1  | ns      |
| Disease duration (years) | 9.4 ± 4.8 | 8.5 ± 4.6 | 10.8 ± 5.1  | ns      |
| Hoehn & Yahr stage   | 3 (2-5)b | 2 (2-4)   | 3 (2-5)      | ns      |
| UPDRS part I         | 7.6 ± 2.9 | 7.2 ± 2.7 | 8.2 ± 3.4   | ns      |
| UPDRS part II        | 16.0 ± 9.6 | 15.4 ± 10.0 | 17.1 ± 9.5 | ns      |
| UPDRS part III       | 28.8 ± 12.9 | 27.4 ± 12.6 | 31.2 ± 13.9 | ns      |
| Schwab & England score | 73.3 ± 20.6 | 78.7 ± 19.6 | 64.4 ± 20.1 | ns      |
| CGI-S                | 5 (2-7) | 6 (3-7)   | 5 (2-5)      | ns      |
| BPRS                 | 39.6 ± 10.3 | 38.7 ± 8.5 | 41.1 ± 13.1 | ns      |
| MMSE                 | 23.6 ± 3.5 | 24.5 ± 2.4 | 22.0 ± 4.4  | ns      |
| FAB                  | 9.0 ± 3.9 | 8.8 ± 3.8 | 9.3 ± 4.3   | ns      |
| Levodopa/DCI (mg)    | 483 ± 270 | 481 ± 222 | 490 ± 185   | ns      |
| LEDD (mg)            | 699 ± 343 | 678 ± 315 | 753 ± 445   | ns      |

Abbreviations: BPRS, Brief Psychiatric Rating Scale; CGI-S, Clinical Global Impression - Severity; DCI, dopamine decarboxylase inhibitor; FAB, Frontal Assessment Battery; LEDD, levodopa equivalent daily dose; MMSE, Mini-Mental State Examination; PD, Parkinson's disease; UPDRS, Unified Parkinson’s Disease Rating Scale.

*Mean ± SD.

bMedian (score range).

1: Normal, not at all ill, 2: borderline mentally ill, 3: mildly ill, 4: moderately ill, 5: markedly ill, 6: severely ill, and 7: among the most extremely ill patients.
our study, the amount of aripiprazole was maintained at low doses. The mean age of the patients was 74 years (range, 51-90) and the mean UPDRS part III score was 37.3, whereas these values were 72 and 28.8 in our cohort. Higher age and/or more advanced PD state in their cohort could be associated with a higher discontinuation ratio than those in our study. Low-dose use of aripiprazole for PD patients with younger age and milder motor and cognitive impairment may reduce the incidence to stop its administration by adverse effects.

For patients with PD who could tolerate aripiprazole, significant improvements in hallucinations and delusions were observed without worsening of cognitive function. Motor scores measured by the UPDRS part III were also improved in the present study. Improvements in psychiatric symptoms may result in increased physical and/or mental activity, which may improve motor function.

The limitations of this study included its design, this being an open-label study, and the fact that it had a small sample size. These conditions make the evidence less potent and enable the analysis of adverse effects precisely. Since aripiprazole can aggravate parkinsonism, potentially resulting in falls, dysphagia, pneumonia, neuroleptic malignant syndrome, or death, close observation is necessary when selecting this drug to manage PD psychosis.

In conclusion, low-dose use of aripiprazole to treat PD patients with hallucinations and/or delusions may worsen motor symptoms in one-third of the patients. However, for PD patients who can tolerate aripiprazole, this drug may be useful for treatment of their psychiatric symptoms.

### TABLE 2 Baseline characteristics of the patients who presented with or without worsening of parkinsonism by aripiprazole

|                     | No worsening | Worsening | P-value |
|---------------------|--------------|-----------|---------|
| Number              | 15           | 9         |         |
| Sex (male:female)   | 7:8          | 6:3       | ns      |
| Age (years)         | 72.0 ± 6.5[^a] | 73.0 ± 7.6 | ns |
| Age at PD onset     | 62.5 ± 6.1   | 63.8 ± 9.4 | ns |
| Disease duration (years) | 9.5 ± 4.9 | 9.3 ± 5.0 | ns |
| Hoehn & Yahr stage  | 2 (2-5[^b])  | 3 (2-4)   | ns      |
| UPDRS part I        | 7.5 ± 2.7    | 7.7 ± 3.5 | ns      |
| UPDRS part II       | 16.4 ± 10.9  | 15.4 ± 7.7 | ns |
| UPDRS part III      | 28.5 ± 13.5  | 29.3 ± 12.8 | ns |
| Schwab & England score | 75.3 ± 23.3 | 70.0 ± 15.8 | ns |
| CGI-S[^c]           | 6 (3-7)      | 5 (2-7)   | ns      |
| BPRS                | 39.7 ± 10.2  | 39.3 ± 11.0 | ns |
| MMSE                | 24.1 ± 3.4   | 22.8 ± 3.6 | ns      |
| FAB                 | 8.7 ± 3.8    | 9.6 ± 4.2 | ns      |
| Levodopa/DCI (mg)   | 496 ± 225    | 458 ± 183 | ns      |
| LEDD (mg)           | 709 ± 307    | 677 ± 439 | ns      |

Abbreviations: BPRS, Brief Psychiatric Rating Scale; CGI-S, Clinical Global Impression - Severity; DCI, dopa decarboxylase inhibitor; FAB, Frontal Assessment Battery; LEDD, levodopa equivalent daily dose; MMSE, Mini-Mental State Examination; PD, Parkinson’s disease; UPDRS, Unified Parkinson’s Disease Rating Scale.

[^a]: Mean ± SD.
[^b]: Median (score range).
[^c]: 1: Normal, not at all ill, 2: borderline mentally ill, 3: mildly ill, 4: moderately ill, 5: markedly ill, 6: severely ill, and 7: among the most extremely ill patients.

### FIGURE 2 Effect of aripiprazole on Parkinson’s disease psychosis evaluated by Brief Psychiatric Rating Scale (BPRS) and Clinical Global Impression-Severity (CGI-S) scale. The graph represents mean ± SD. *P < .05
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CONFLICT OF INTEREST
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AUTHOR CONTRIBUTIONS
Study conception and organization: KK, TM, and KY; Study conduct: KK, TM, and KY; Data and statistical analysis: K.K; Manuscript preparation: KK. All authors reviewed and approved the final draft of the manuscript.

ETHICAL APPROVAL
This study was approved by the ethics committee of each institute.

INFORMED CONSENT
Written informed consent was obtained from all patients.

REGISTRY AND THE REGISTRATION NO. OF THE STUDY
This work was preregistered as “Effect of aripiprazole on psychiatric symptoms in patients with Parkinson disease” on the University Hospital Medical Information Network Center (registration number UMIN000007711).

PATIENT CONSENT
Written informed consent was obtained from all patients prior to the study.

PERMISSION
Contents of this article have not been published in any other sources.

DATA AVAILABILITY STATEMENT
The data that support the findings of this study are available in the Supplementary Material of this article.

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