Factors That Affect Continuation of Antipsychotic Long-Acting Injections

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Long-acting injection (LAI) is a drug administration method that reduces symptoms and prevents recurrence or relapse of schizophrenia. We examined factors related to the continuation of LAI treatment. The study population included patients with schizophrenia who were undergoing LAI treatment involving risperidone, paliperidone, or aripiprazole at Fujita Health University Hospital between October 2009 and June 2017. We assessed the continuation rate of LAI treatment at six months, and collected patient characteristics such as medication history. Furthermore, we classified patients into two clusters according to the reason for introducing LAI based on a previous study (Prog. Neuropsychopharmacol. Biol. Psychiatry, 2008, Heres et al.). The study included 82 patients (mean age, 44.9 ± 15.0 years); the continuation rate of LAI after six months was 63.4%. Factors that affected LAI continuation included cluster II [adjusted odds ratio (OR): 5.74, \( p = 0.017 \)], switching from the same component as LAI (adjusted OR: 7.13, \( p < 0.001 \)), and diazepam conversion rate (adjusted OR: 0.88, \( p < 0.001 \)). LAI significantly improved the continuation rate of treatment in the patient group belonging to cluster II. Furthermore, based on other factors and reasons for discontinuation, LAI should be preferably commenced in patients with a more stable condition.

Key words schizophrenia; long-acting injection; continuation rate; risperidone; paliperidone; aripiprazole

INTRODUCTION

Long-acting injection (LAI) is a drug administration method that reduces symptoms and prevents the recurrence or relapse of schizophrenia. LAI is useful for improving adherence, which is important for the treatment of schizophrenia. Furthermore, in a meta-analysis of mirror image studies, LAI significantly reduced the frequency of hospitalization compared with that of oral agents in patients with schizophrenia. In contrast, in a meta-analysis based on randomized controlled studies, the rate of treatment discontinuation did not differ between LAI and oral agents.

Continuation of LAI treatment is related to patient characteristics, such as outpatient treatment and tolerability to prior therapeutic drugs. Patients with schizophrenia who undergo LAI treatment are classified into two clusters. Cluster I includes being considered a hazard to others, history of non-compliance, history of suicidal threat, and previous relapse. Cluster II includes an understanding of the illness, high level of education, openness to antipsychotic treatment, high level of insight, good therapeutic alliance, and high level of participation in decision-making. Therefore, cluster I comprises patients with poor adherence, and cluster II comprises those who are completely aware of their illness and want treatment. No previous report has investigated the relationship between this cluster and the LAI continuation rate. Although LAI is known as a tool for maintenance treatment, physicians continue to prescribe LAI to non-adherent patients. Therefore, we classified patients into these two clusters, and analyzed the relationship between cluster type, LAI continuation, and patient characteristics such as medication and life history.

METHODS

Patients The study population included patients with schizophrenia and those with schizoaffective disorder who were given risperidone LAI (RIS-LAI), paliperidone LAI (PAL-LAI), or aripiprazole LAI (ARP-LAI) at Fujita Health University Hospital between October 2009 and June 2017. The exclusion criteria were as follows: 1) patients who switched to an LAI from an investigational drug, 2) those who switched from one LAI to another LAI, and 3) those who could not participate in follow-up examinations for six months after LAI introduction. We excluded patients who switched from one LAI to another to avoid duplication when discontinuing one LAI and introducing another in the same patient. Further, we excluded patients who switched to an LAI from an investigational drug because we did not know the type of investigational drug that was used.

Subjects We collected patient characteristics such as age, sex, presence of employment or studies, marital status, reason for LAI introduction, care setting at initiation (inpatient or outpatient) and medication history (antipsychotic medications, benzodiazepine (BZ) medications, and anti-Parkinson medications) at the time of LAI introduction using medical records. The use of antipsychotic medications, BZ and anti-Parkinson medications were considered in terms of chlorpromazine (CP) and diazepam (DAP), and biperiden (BP) equivalents. The efficacy and safety of previous therapeutic oral drugs with the same components as LAIs were evaluated, but these drugs did not necessarily need to be used prior to LAI treatment. Furthermore the active metabolite of risperidone is paliperidone, and PAL-LAI was permitted in patients with a history of oral risperidone usage. Accordingly, we also evaluated whether oral agents used immediately prior to introducing LAI treatment were similar to that of LAI. Based on the information in the medical record, we evaluated adherence at the time the patient decided to introduce LAI. Patients were classified into two clusters according to the reason for introducing LAI based on the report by Heres et al. Cluster I included patients with poor adherence, and cluster II included those who wished to introduce LAI for recovery. The present study was conducted with the approval of the ethical review committee of Fujita Health University.

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**Outcomes** We evaluated the relationship between LAI treatment continuation and patient’s characteristics and medication history. The primary outcomes were factors that affected the LAI treatment continuation rate at six months, and the secondary outcome was the reason for LAI discontinuation.

**Statistics Analyses** We used Fisher’s exact test to compare frequency and a Student’s t-test to compare mean values for the relationship between treatment continuation and patient characteristics. We adjusted the effect of the difference for each LAI as a covariate. Logistic regression analysis was performed using R version 3.1.1.

**RESULTS**

**Patient Background** In total, 108 patients were candidates for LAI discontinuation. Table 2 presents the reasons for LAI discontinuation for the 30 patients who discontinued.

The six month continuation rate of LAI was 63.4% (52 patients). In univariate analysis, two patient background factors had a significant difference in the LAI continuation rate; 1) switching from the same component as LAI, continuation group: 90.4% and discontinuation group: 53.3%, p < 0.001; and 2) DAP equivalents, continuation group: 4.4 ± 5.2 mg and discontinuation group: 8.0 ± 9.3 mg, p = 0.03. Detailed patient’s characteristics are listed in Table 2.

Information pertaining to the continuation rate and the number of patients in whom each LAI was introduced is presented in Table 2. There was no significant difference between the continuation rate of PAL-LAI and RIS-LAI. However, the continuation rate of ARP-LAI was found to be significantly different.

**Factors Involved in LAI Treatment Continuation** We selected the following four factors as dependent variables: LAI, switching from the same component as LAI, DAP equivalents, and the cluster with p > 0.2 by univariate analysis. By multivariate analysis, the factors that had a significant relationship with LAI treatment continuation were cluster II, adjusted odds ratio (OR): 5.74 and 95% confidence interval (CI): 1.36–24.21; switching from the same component as LAI, adjusted OR: 7.13 and 95% CI: 1.69–30.10; and DAP equivalents, adjusted OR: 0.88 and 95% CI: 0.81–0.97 (Table 3). PAL-LAI and ARP-LAI were not significantly different in multivariate analysis.

**Reason for Discontinuation** Table 4 presents the reasons for LAI discontinuation for the 30 patients who discontinued.

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**Table 1. Cluster Classification According to the Reason for LAI Introduction**

| Reason for introduction | Number of patients | Cluster |
|-------------------------|--------------------|---------|
| Medication non-adherence | 37 (45%)            | I       |
| Inefficacy of previous agent | 16 (20%)          |         |
| Reduction of side-effects | 1 (1%)             |         |
| Remission maintenance   | 20 (25%)           |         |
| Patient wishes           | 3 (4%)             |         |
| Support for independence | 1 (1%)             | II      |
| To reduce the drug-taking burden for social rehabilitation | 1 (1%) |         |
| Single-agent prescription | 1 (1%)            |         |
| To improve QOL           | 1 (1%)             |         |
| To avoid drug-taking perception | 1 (1%) |         |

**Table 2. Patient Background**

| | Number of patients and mean value (n = 82) | Continued (52 patients: 63.4%) | Discontinued (30 patients: 36.6%) | p Value |
|---|------------------------------------------|-------------------------------|-----------------------------------|---------|
| Age | 44.9 ± 15.0 years | 44.4 ± 15.9 years | 45.9 ± 13.7 years | 0.66 |
| Sex | Male | 25 (30.5%) | 17 (32.7%) | 8 (26.7%) | 0.63 |
| Employed/studying | 22 (26.8%) | 16 (30.8%) | 6 (20.0%) | 0.32 |
| Married | 41 (50.0%) | 23 (44.2%) | 18 (60.0%) | 0.25 |
| Care setting at initiation | Outpatient | 55 (67.1%) | 34 (65.4%) | 21 (70.0%) | 0.81 |
| | Inpatient | 27 (32.9%) | 18 (34.6%) | 9 (30.0%) |         |
| Cluster | I | 54 (65.9%) | 30 (57.7%) | 24 (80.0%) | 0.054 |
| | II | 28 (34.1%) | 22 (42.3%) | 6 (20.0%) |         |
| LAI | RIS-LAI | 36 (43.9%) | 17 (32.7%) | 19 (63.3%) | Reference |
| | PAL-LAI | 15 (18.3%) | 8 (15.4%) | 7 (23.3%) | 0.69 |
| | ARP-LAI | 31 (37.8%) | 27 (51.9%) | 4 (13.3%) | 0.001 |
| CP equivalent | 450.7 ± 263.8 mg | 448.6 ± 246.9 mg | 454.2 ± 295.0 mg | 0.93 |
| Switching from the same component as LAI | 63 (76.8%) | 47 (90.4%) | 16 (53.3%) | <0.001 |
| Combined use of multiple antipsychotic agents | 9 (11.0%) | 5 (9.6%) | 4 (13.3%) | 0.72 |
| DAP equivalent | 5.7 ± 7.1 mg | 4.4 ± 5.2 mg | 8.0 ± 9.3 mg | 0.03 |
| BP equivalent | 0.4 ± 1.3 mg | 0.5 ± 1.4 mg | 0.3 ± 1.2 mg | 0.55 |

The frequency was compared using Fisher’s exact test and mean values were compared using Student’s t-test. We adjusted the influence of the difference for each LAI as a covariate. CP: chlorpromazine, DAP: diazepam, BP: biperiden.
a short hospitalization duration, and in those whom treatment continuation is good in patients aged $\geq 55$ years, those with component as LAI, and DAP equivalent. The rate of LAI following three factors: cluster II, switching from the same sociated with LAI treatment continuation. We identified the patient background and LAI treatment to identify factors as -

Table 3. Factors Involved in LAI Continuation

|                | Univariate analysis | Multivariate analysis |
|----------------|---------------------|-----------------------|
|                | Crude odds ratio    | 95% CI          | $p$ Value | Adjusted odds ratio | 95% CI          | $p$ Value |
| ARP-LAI        | 7.52                | 2.18–26.0         | 0.001     | 3.64                | 0.88–14.9       | 0.074     |
| Cluster II     | 2.9                 | 0.94–10.17        | 0.054     | 5.74                | 1.36–24.21      | 0.017     |
| Switching from the same component as LAI | 7.98 | 2.28–33.02 | <0.001 | 7.13 | 1.69–30.10 | <0.001 |
| DAP equivalent | 0.94                | 0.88–1.00         | 0.03      | 0.88                | 0.81–0.97       | <0.001   |

Logistic regression analysis was performed with items showing $p<0.2$ in the univariate analysis as independent variables, with the presence of treatment continuation as the dependent variable, and corrections were made for cofounding factors. In the multivariate analysis, $p<0.05$ was considered significant. CI: confidence interval.

Table 4. Reasons for Discontinuation

| Reason for discontinuation | Number of patients ($n=30$) |
|----------------------------|------------------------------|
| Inefficacy                 | 14 (47%)                     |
| Intolerability             | 6 (20%)                      |
| Discontinued hospital attendance | 3 (10%)                  |
| Injection refusal          | 2 (7%)                       |
| Oral therapy desired       | 2 (7%)                       |
| Expensive                  | 1 (3%)                       |
| Disease name change        | 1 (3%)                       |
| Death                      | 1 (3%)                       |

The most common reason for discontinuation was inefficacy ($n=14$, 47%) followed by poor tolerability ($n=6$, 20%).

**DISCUSSION**

This study was evaluated with three LAIs because the number of cases for each LAI was limited.

We retrospectively examined the relationship between patient background and LAI treatment to identify factors associated with LAI treatment continuation. We identified the following three factors: cluster II, switching from the same component as LAI, and DAP equivalent. The rate of LAI continuation is good in patients aged $\geq 55$ years, those with a short hospitalization duration, and in those whom treatment was introduced on an outpatient basis. However, each of these studies differ in the target drugs and observation period, and all factors associated with continuation and discontinuation were not consistent. For example, one report indicated that the reason for introducing LAI had no significant impact on the risk of discontinuation, whereas another indicated that the rate of continuation was low in patients who were given LAI because of medication non-adherence and intolerability. Our study had no correlation between age and continuation rate. We did not evaluate the effect of hospitalization period because of the small number of cases of hospitalization included in the study.

In the present study, we classified patients into two clusters based on a previous study, and we found that the rate of LAI treatment continuation was high among patients in cluster II. The efficacy and safety of oral agents in several patients in cluster I could not be sufficiently verified because the patients had poor adherence and lack disease awareness. In contrast, the efficacy and safety of oral agents in patients in cluster II was adequately verified, and LAI was introduced based on a satisfactory physician–patient relationship and good adherence. Thus, patients in cluster II had a higher rate of LAI treatment continuation than patients in cluster I who were given LAI because of medication non-adherence.

For oral agents administered immediately prior to LAI introduction, patients who switched from an oral agent with the same component as the LAI had a significantly higher rate of LAI continuation than those who switching from a different oral antipsychotic agent. Similarly, in a study of PAL-LAI introduction, switching from a different class of oral antipsychotic agents significantly reduced the rate of LAI continuation. The protocol of clinical trials at LAI approval recommends switching from an oral antipsychotic agent with the same component, but the package insert specifies that LAI introduction is permitted if oral agents with the same component as the LAI had been used once in the past, and efficacy and safety were confirmed. However, repeated recurrences and relapses reduce patient responsiveness to drugs, and responsiveness may differ from that of previous drugs. Therefore, that the rate of LAI continuation may be improved by carefully verifying the efficacy and safety of oral agents with the same components immediately prior to introducing LAI. Furthermore, approximately 70% of the reason for discontinuing LAI was inefficacy or intolerability; and outcome and adverse effects need to be monitored when changing from an effective drug.

Caution should be exercised when interpreting DAP equivalent, that is BZ dosage. Although we found no relationship between LAI treatment continuation and BZ dosage in previous study, patients who do not use BZ are more stable than those who needed high-dose BZ in clinical practice. However, it is difficult to generalize because we did not evaluate psychological symptoms. Patients with schizophrenia who use antipsychotic agents and BZ have an increased the risk of oversedation, motor ataxia, dependency, and death compared with patients treated by a single antipsychotic agent. Therefore it is preferable to minimize the combined use of BZ.

The present study was limited because it was retrospective, and information that could not be obtained from medical records was not evaluated, such as psychiatric symptoms and the onset of adverse effects after LAI introduction. These factors were associated with the main reasons for LAI discontinuation, and it is preferable to accurately measure these items using a scale such as the positive and negative syndrome scale or the drug-induced extrapyramidal syndrome scale. Second, Cluster selection must be performed with the consideration that there is a possibility of bias on the part of medical staff. In Heres’s report, physicians answered to questionnaires about patient characteristics that may affect LAI treatment, as a result the patient was divided into two clusters. In the present study, physicians actually introduced LAI to patients for
some reasons and we investigated the reasons for introduction using medical records and classified patients into two clusters. Finally, based on the results reported previously, we investigated LAI continuation six-months after its introduction. This six month observation period was shorter than that used in previous studies, and a longer observation period is warranted for future studies.

LAI was introduced because of poor adherence to the existing agent, and patients belonging to cluster II had a higher rate of continuation. Furthermore, LAI introduction will enable more stable and long-term treatment continuation, and the efficacy and safety of previous oral therapeutic agent with same components as LAIs should be verified.

Conflict of Interest The authors declare no conflict of interest.

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