

Continuation of schizophrenia treatment with three long-acting injectable antipsychotics in South Korea: A nationwide population-based study

Sung Woo Joo^{a,1}, Seung-Hyun Shon^{b,1}, GumJee Choi^c,
MinJung Koh^c, Seung Woo Cho^d, Jungsun Lee^{b,*}

^a Republic of Korea Navy, Republic of Korea

^b Department of Psychiatry, Asan Medical Center, University of Ulsan College of Medicine, 88 Olympic-Ro 43-Gil, SongPa-Gu, Seoul 05505, Republic of Korea

^c Medical Affairs, Janssen Korea, Seoul, Republic of Korea

^d Department of Occupational and Environmental Medicine, Ulsan University Hospital, University of Ulsan, Republic of Korea

Received 27 March 2019; received in revised form 27 June 2019; accepted 15 July 2019

KEYWORDS

Long-acting injectable antipsychotic agents; Schizophrenia; Haloperidol decanoate; Paliperidone palmitate; Risperidone

Abstract

Long-acting injectable (LAI) antipsychotics have been developed to prevent symptom relapse in patients with schizophrenia; relapse has a detrimental clinical impact and high social burden. However, data on treatment continuation rates of LAI antipsychotics are inconsistent, primarily because of study design; limited data exist for patients taking oral psychotropic medications taken along with LAI antipsychotics, and factors related to LAI antipsychotics treatment discontinuation. Patients with schizophrenia in the South Korea Health Insurance Review Agency database from 2007 to 2016 who had received LAI haloperidol, LAI paliperidone, or LAI risperidone were included. Treatment continuation rates and proportions of patients using concurrent oral psychotropic medications were calculated. Cox proportional hazard ratios were used for analysis related to discontinuation. There was a significant difference in treatment continuation rates at 6 months after initiation (36.8% LAI haloperidol, 57.5% LAI paliperidone, and 34.5% LAI risperidone). A substantial proportion of patients in all three groups were prescribed oral antipsychotics during LAI antipsychotics treatment. In the LAI paliperidone group, type of hospital was significantly associated with a higher risk of treatment discontinuation, with

* Corresponding author.

¹ These authors share co-first authorship.

E-mail address: js_lee@amc.seoul.kr (J. Lee).

a hazard ratio of 1.195-1.598. Early discontinuation of LAI antipsychotic treatment occurs in a large number of patients with schizophrenia. Intervention strategies for improving the LAI antipsychotics treatment adherence are needed.

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1. Introduction

Schizophrenia is a psychiatric disorder characterized by delusion, hallucination, disorganized thought processes, impaired insight, and negative symptoms (American Psychiatric Association, 2013). Despite remarkable treatment advances in schizophrenia, symptom relapse during maintenance treatment often occurs and contributes to the chronic nature of the disease (Miyamoto and Fleischhacker, 2017). Functional deterioration, one of the long-term consequences from the symptom relapse, makes it difficult for patients with schizophrenia to recover, and causes high social burdens (Vos et al., 2012). To date, several studies regarding relapse prevention and prognosis of schizophrenia have been carried out to address this issue. However, more effective methods for addressing the risk of relapse are still needed (Kishimoto et al., 2013, 2014; Leucht et al., 2012).

According to the clinical guidelines (Kreyenbuhl et al., 2010; National Collaborating Centre for Mental Health, 2014), maintenance therapy should continue after the acute phase of treatment for schizophrenia. Medication nonadherence has been reported to be the major risk factor associated with symptom relapse and inferior outcome in schizophrenia (Nielsen et al., 2015). A previous study has shown that discontinuation of medication increases the risk of relapse nearly two to six times compared with continued treatment in an acute or chronic phase of schizophrenia (Kishimoto et al., 2014). However, poor adherence to antipsychotics is reported in about 40% of schizophrenia patients, indicating low adherence rates during maintenance treatment (Valenstein et al., 2006). Although measurement and identification of medication nonadherence are essential for continued treatment, a prompt and objective estimation for medication nonadherence is challenging in real-world clinical practice (Kane et al., 2013; Nielsen et al., 2015).

Long-acting injectable antipsychotics (LAIAs) have been developed to improve compliance and provide effective alternatives to oral antipsychotics for patients with lack of insight or insufficient compliance (McCreath et al., 2017; Miyamoto and Fleischhacker, 2017). Advantages of LAIAs over oral antipsychotics include infrequent administration, more predictable and consistent plasma drug concentration, and a more accurate assessment of drug noncompliance (Taylor, 2009). However, the utilization rate of LAIAs is low (Heres, 2014) and there is a dearth of evidence about LAIAs treatment discontinuation and related factors. A previous study using a national database reported a significantly higher treatment continuation of long-acting injectable (LAI) paliperidone compared with LAI risperidone and LAI haloperidol (Decuyper et al., 2017). A longer duration of oral antipsychotics treatment before LAIAs treatment increases the risk for discontinuation of LAIAs treatment in schizophrenia (Takaesu et al., 2016).

Several factors inherent in randomized clinical trials (RCT) have been reported to be an obstacle for generalizability of those findings, including recruitment of patients with better insight who are less severely ill, enhanced adherence rates by frequent visits, changes in attitudes of clinicians, and drug education (Haddad et al., 2015; Taipale et al., 2018, 2017; Tiihonen et al., 2017). The patients with poor adherence for whom LAIAs treatment is most indicated are likely to be underrepresented in RCT, because participation in RCT is fully voluntary. Therefore, results using the atypical fraction of adherent patients in RCT do not provide information that is applicable in real-world clinical practice (Taylor et al., 2016). Nationwide cohort studies can overcome some of the limitations above by giving a representative picture of LAIAs treatment in real-world conditions. A nationwide naturalistic database has the advantages of including the entire cohort of treated patients and providing information on treatment approaches in real-world clinical conditions.

The National Health Insurance Service (NHIS), a public medical system in South Korea, is a compulsory social security system operated by the Ministry of Health and Welfare in South Korea. All Koreans must use the National Health Insurance (NHI) or Medicaid service provided by this medical system. The Health Insurance Review Agency (HIRA) is responsible for reviewing medical fees and health care evaluations, and maintains a database for all medical claims records from NHI and Medicaid in South Korea since 2002 (Song, 2009). The Korean standard classification disease (KCD) diagnostic codes, which are based on the International Classification of Diseases, 10th Revision (ICD-10), have been adopted to code diagnoses and related signs and symptoms in the HIRA database. The HIRA provides investigators claim data for purposes of research, which are de-identified for investigators' access. This national claim database advantageously reflects the use of health care resources used by the entire South Korean population.

The main objective of this study was to document treatment continuation in patients with schizophrenia after initiating LAIAs, using the HIRA database. We included patients who were prescribed the three main LAIAs in South Korea—LAI haloperidol, LAI risperidone, and LAI paliperidone. We then compared treatment continuation rates among the three groups. We also described the use of oral medications before and after LAIAs treatment, and explored factors related to the discontinuation of LAIAs treatment.

2. Experimental procedures

2.1. Data source and study population

The claim data were drawn from 10 consecutive years of the HIRA database (2007-2016). The HIRA database included

the following patient information: age, sex, date of admission, days of hospitalization, insurance type, type of hospital, major psychiatric diagnosis codes, comorbid psychiatric diagnosis codes, and history of prescribed medications. We selected patients who had at least one claim for the ICD-10 diagnostic code F20 (schizophrenia) after 2009, and no claims for hospitalization or outpatient care for psychiatric diseases from 2007 to 2009. Currently, four LAIs are available in South Korea: LAI aripiprazole, LAI haloperidol, LAI paliperidone, and LAI risperidone. We excluded patients who were initiated on LAI aripiprazole; the sample size of these patients was small because the end date of our observation period was December 2016, and the approval date of LAI aripiprazole in South Korea was December 2015. We therefore selected patients prescribed the other three LAIs (LAI haloperidol, LAI paliperidone, and LAI risperidone). The present study was approved by the Institutional Review Board of Asan Medical Center (IRB No. 2018-0131). As the HIRA database is anonymous and de-identified, informed consents were exempted by the IRB.

2.2. Definition of variables

Discontinuation of LAIs treatment was defined as (1) change to different LAIs or oral antipsychotics, (2) a period without treatment of more than 28 days, (3) the end of the observation period. The retention period was calculated as the sum of the days from the first prescription of LAIs to the discontinuation. For patients who were prescribed LAIs more than once in the observation period, we used data from only the first LAIA treatment period, and did not include later periods. We divided the retention period into four subperiods (0-60 days, 61-120 days, 120-180 days, >180 days) to calculate proportions of patients within each subperiod. We obtained information on prescribed oral medications, including oral antipsychotics, antidepressants, benzodiazepines, anticholinergics, and beta-blockers to assess usage of these medications with respect to LAIs treatment. The LAIs dose equivalent to olanzapine was calculated according to a previous study (Leucht et al., 2016).

2.3. Statistical analysis

Analysis of variance (ANOVA) test for equal variance or Kruskal-Wallis test for unequal variance were used to compare continuous variables among the three LAIs groups. Chi-square test was performed to measure the significance of associations for categorical variables. The Scheffe test for continuous variables and pairwise comparisons with Bonferroni corrections for categorical variables were adopted for post-hoc analysis. Kaplan-Meier analysis and log-rank test were performed to analyze differences in time to discontinuation among the three LAIs groups. Cox proportional hazard ratio model was used to assess the effect of variables on the retention period. Univariate association of individual variables with respect to the retention period were calculated, and variables with a p -value of <0.2 in the univariate analysis were included in the multivariate model. The significance level was set at 0.05. R software (ver. 3.4.1)

(R Core Team, 2017), package data.table (ver 1.9.6) (Dowle et al., 2017), doParallel (ver. 1.0.10) (Microsoft Corporation and Weston, 2017), foreach (ver. 1.4.3) (Microsoft Corporation and Weston, 2015), and survival (ver. 2.39-5) (Therneau and Lumley, 2015) were used to perform all statistical tests.

3. Results

3.1. Demographic and clinical characteristics of patients

The sample size of the LAI paliperidone group was substantially larger than that of the LAI haloperidol and LAI risperidone groups, which should be considered when drawing conclusions for this population. Patients who were prescribed LAI haloperidol were significantly older and more likely to be male than those in the other two groups. Mean equivalent dosage of LAI paliperidone was significantly higher than those of LAI haloperidol and LAI risperidone. There was a significant difference in the type of hospital in which LAIs treatment was initiated among the three groups. Finally, the LAI haloperidol group had a significantly higher proportion of hospitalizations and longer mean duration of hospitalization than the LAI paliperidone and LAI risperidone groups. Further details on demographic and clinical characteristics of patients are presented in Table 1.

3.2. Treatment continuation

Fig. 1 shows the time to treatment discontinuation curves for the three LAIs groups. The log-rank test showed a significant difference in survival curves among the three groups ($\chi^2 = 365$, $df = 2$, $p < 0.001$). The estimated continuation rate in the LAI paliperidone group was 57.5% at the 6 months, and the LAI haloperidol and LAI risperidone group had continuation rates of 36.8% and 34.5% at 6 months, respectively. We divided the retention period into four subperiods and examined a proportion of patients in each subperiod. The LAI paliperidone group had a significantly higher proportion of patients with greater than 180 days' retention than the LAI haloperidol and LAI risperidone groups. Proportions of patients with less than 60 days' retention in the LAI haloperidol and LAI risperidone groups were 28.8% and 27.8%, respectively, which were significantly higher than the proportion of patients in the LAI paliperidone group (see Supplementary Table 1). Because the subgroup of greater than 180 days' retention included both patients who continued treatment until the end of the observation period and those who discontinued LAIs treatment after the 180 days retention period, we investigated the treatment discontinuation proportion of patients with more than 180 days' observation. The LAI paliperidone subgroup with a greater than 180 days' observation period had a significantly higher continuation proportion (42.5%) than the other two groups (LAI haloperidol: 18.2%; LAI risperidone: 1.0%; $\chi^2 = 163.03$, $df = 2$, $p < 0.001$) (see Supplementary Table 2).

Table 1 Demographic and clinical characteristics of patients with schizophrenia.

Variable	Haloperidol (n = 483)	Paliperidone (n = 5115)	Risperidone (n = 565)	F or χ^2	df	p	Post-hoc
Age at the first prescription of LAIAs, years, mean (SD)	44.62 (11.93)	38.83 (12.89)	39.49 (13.01)	44.925	2, 6160	<0.001	H>P,R
Male, n (%)	234 (48.45)	2177 (42.56)	213 (37.70)	12.307	2	0.002	H>P,R
Olanzapine equivalent dosage of LAIAs, mg, mean (SD)	101.68 (54.52)	203.41 (65.67)	109.33 (41.47)	1651.3	2	<0.001	P>H,R
Duration of LAIAs treatment, person-year	383.9671	5305.9151	322.0658				
Type of hospital, n (%)							
Tertiary hospital	50 (10.35)	1463 (28.60)	170 (30.09)	197.58	8	<0.001	P,R>H
General hospital	66 (13.66)	1118 (21.86)	130 (23.01)				
Hospital	286 (59.21)	2251 (44.01)	250 (44.25)				
Nursing hospital	15 (3.11)	42 (0.82)	2 (0.35)				
Clinic	66 (13.66)	241 (4.71)	13 (2.30)				
Events before LAIAs treatment							
ER visit, n (%)	22 (4.55)	376 (7.35)	43 (7.61)	5.3872	2	0.068	
Hospitalization, n (%)	251 (51.97)	281 (5.49)	41 (7.26)	1133.3	2	<0.001	H>P,R
Duration of hospitalization, days, mean (SD)	460.38 (663.37)	156.61 (210.93)	103.07 (115.13)	74.479	2	<0.001	H>P,R

Continuous variables were compared using Analysis of variance (ANOVA) for equal variance and Kruskal-Wallis test for unequal variance. Chi-square test was used for comparisons of categorical variables. Post-hoc analysis was performed using the Scheffe test for continuous variable and pairwise comparisons for categorical variables with Bonferroni corrections. LAIAs denotes long-acting injectable antipsychotics, H denotes haloperidol, P denotes paliperidone, and R denotes risperidone.

3.3. Use of oral medications before and after LAIAs treatment

The numbers and proportions of patients using oral medications before and after LAIAs treatment are presented in Table 2 and Fig. 2. Supplementary Table 3 shows the treat-

ment durations of oral medications at each time point. We calculated the above statistics, using information on the patients who received the LAIAs or oral medications 1 month before each time point. A substantial proportion of patients received oral antipsychotics during LAIAs treatment in all three groups, and there was a remarkable decreasing trend

Table 2 Numbers of patients prescribed oral medications.

Variable	Period			
	Before	2 months	4 months	6 months
Number of patients, n (%)				
Haloperidol				
Antipsychotics	373 (77.23)	374 (77.75)	191 (70.74)	129 (69.35)
Antidepressant	66 (13.66)	67 (13.93)	41 (15.19)	26 (13.98)
Benzodiazepine	258 (53.42)	299 (62.16)	154 (57.04)	105 (56.45)
Anticholinergics	265 (54.87)	318 (66.11)	187 (69.26)	132 (70.97)
Beta-blocker	64 (13.25)	91 (18.92)	54 (20)	37 (19.89)
Paliperidone				
Antipsychotics	3707 (72.47)	2530 (49.5)	1756 (46.04)	1360 (45.47)
Antidepressant	768 (15.01)	761 (14.89)	656 (17.2)	525 (17.55)
Benzodiazepine	2476 (48.41)	2588 (50.64)	1788 (46.88)	1323 (44.23)
Anticholinergics	2243 (43.85)	2132 (41.71)	1508 (39.54)	1173 (39.22)
Beta-blocker	1071 (20.94)	1260 (24.65)	847 (22.21)	620 (20.73)
Risperidone				
Antipsychotics	386 (68.32)	310 (58.38)	144 (45)	96 (42.48)
Antidepressant	66 (11.68)	68 (12.81)	48 (15)	37 (16.37)
Benzodiazepine	262 (46.37)	269 (50.66)	146 (45.63)	81 (35.84)
Anticholinergics	232 (41.06)	236 (44.44)	136 (42.5)	88 (38.94)
Beta-blocker	92 (16.28)	109 (20.53)	62 (19.38)	40 (17.7)

The numbers and proportions of patients using oral medications were calculated 1 month before each time point.

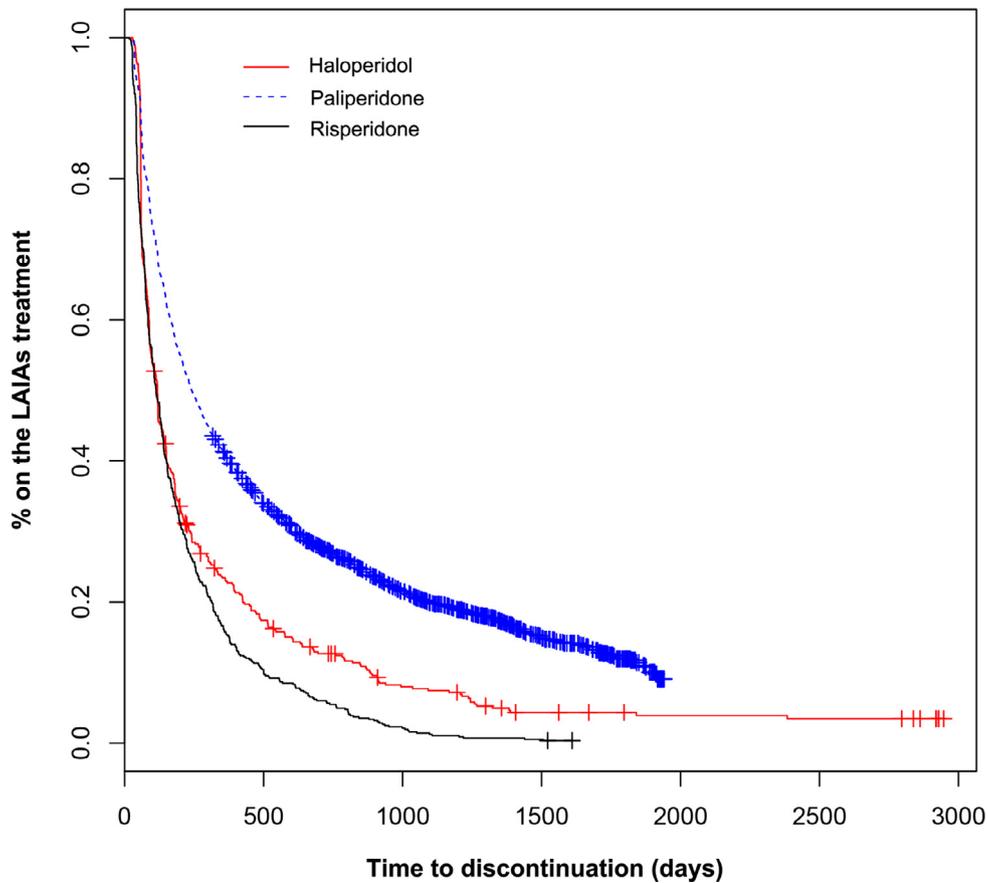


Fig. 1 Time to treatment discontinuation curves of long-acting injectable (LAI) haloperidol, LAI paliperidone, and LAI risperidone. The blue line indicates the LAI paliperidone group, the red line indicates the LAI haloperidol group, and the black line indicates the LAI risperidone group. The + signs indicate censored data. (For interpretation of the references to color in this figure legend, the reader is referred to the web version of this article.)

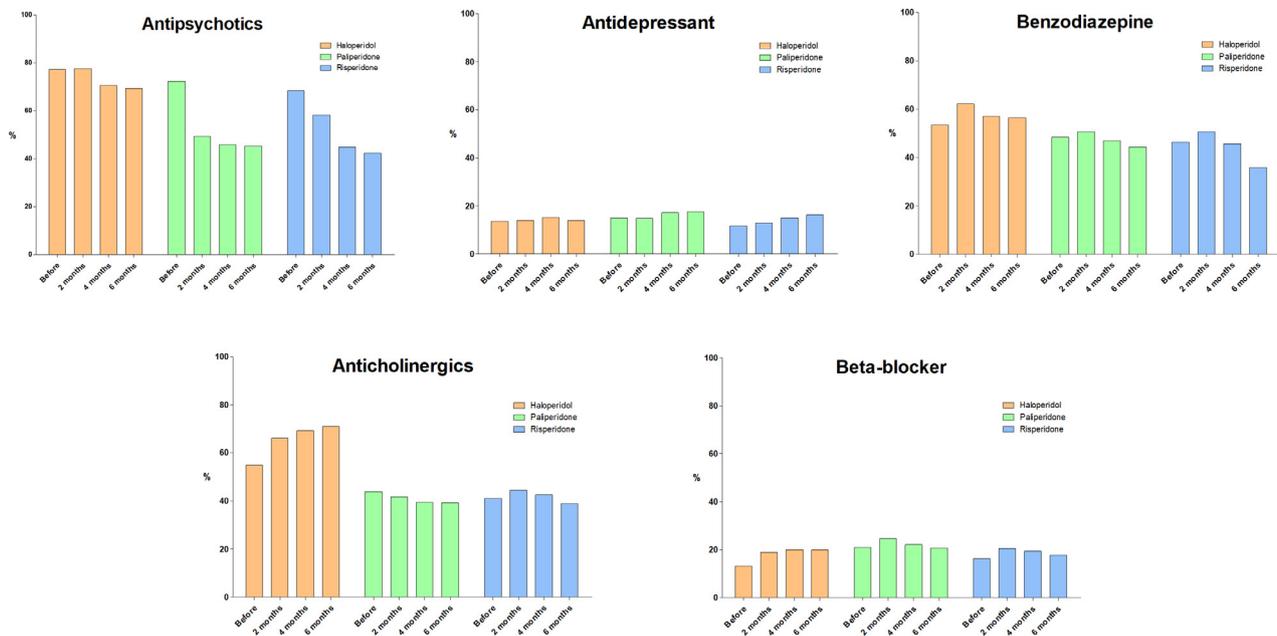


Fig. 2 Proportions of patients prescribed oral medications at each time point. The orange bar represents the long-acting injectable (LAI) haloperidol group, the green bar represents the LAI paliperidone group, and the blue bar represents the LAI risperidone group. (For interpretation of the references to color in this figure legend, the reader is referred to the web version of this article.)

Table 3 Hazard ratio for discontinuation of LAIAs treatment.

Variables	LAI haloperidol				LAI paliperidone				LAI risperidone			
	Hazard ratio	Lower	Upper	<i>p</i>	Hazard ratio	Lower	Upper	<i>p</i>	Hazard ratio	Lower	Upper	<i>p</i>
Type of hospital												
Tertiary hospital	Ref.				Ref.				Ref.			
General hospital	1.042	0.702	1.548	0.837	1.028	0.933	1.132	0.577	1.165	0.921	1.473	0.204
Hospital	0.964	0.683	1.361	0.837	1.195	1.104	1.294	<0.001	1.12	0.913	1.375	0.278
Nursing hospital	0.789	0.402	1.548	0.49	1.479	0.985	2.22	0.059	0.648	0.146	2.867	0.567
Clinic	1.188	0.796	1.774	0.399	1.598	1.372	1.861	<0.001	1.434	0.806	2.551	0.22
Mean olanzapine equivalent dosage of LAIAs	0.998	0.995	1.001	0.125	1.002	1.001	1.002	<0.001	0.99	0.986	0.994	<0.001
Olanzapine equivalent dosage of LAIAs at the second time point from the end	0.999	0.997	1.002	0.676	1.003	1.002	1.003	<0.001	1.006	1.003	1.008	<0.001
Duration from the diagnosis to the first prescription of LAIAs	1	1	1	0.138	1	1	1	<0.001	1	1	1	0.728
Oral medications before LAIAs treatment												
Number of oral antipsychotics	1.089	0.957	1.239	0.198	1.034	0.979	1.091	0.232	1.028	0.879	1.201	0.73
Number of anticholinergics	0.909	0.617	1.339	0.629	1.117	0.984	1.268	0.087	0.846	0.6	1.192	0.338
Duration of antipsychotics treatment	1.002	0.989	1.014	0.799	0.995	0.991	0.999	0.013	0.995	0.985	1.005	0.312
Duration of anticholinergics treatment	0.999	0.983	1.016	0.901	0.992	0.986	0.997	0.003	1.007	0.992	1.023	0.356
Mean dosage of antipsychotics	1.004	0.998	1.01	0.223	0.995	0.991	0.999	0.01	0.995	0.985	1.005	0.356
Events before LAIAs treatment												
Number of hospitalization	1.036	1.001	1.071	0.042	1.045	1.014	1.078	0.005	1.12	0.986	1.273	0.082
Mean duration of hospitalization	1	1	1	0.648	1	1	1.001	0.976	0.999	0.996	1.001	0.257

Cox proportional hazard ratio model was used. Included variables had a *p*-value <0.2 in the univariate analysis. LAIAs denote long-acting injectable antipsychotics.

in the proportions of patients using oral antipsychotics in the LAI paliperidone and LAI risperidone groups. Proportions of patients taking an antidepressant, benzodiazepine, anticholinergic, or beta-blocker were relatively constant before and after LAIAs treatment in all the three groups, except for an increasing proportion of those taking anticholinergics in the LAI haloperidol group and a decreasing proportion of those taking benzodiazepine in the LAI risperidone group. Regardless of the type of oral medication and LAIAs group, the treatment duration of oral medications decreased after 2 months of LAIAs treatment, and continuously increased after 4 and 6 months of LAIAs treatment (see Supplementary Table 3).

3.4. Risk factors for LAIAs treatment discontinuation

Univariate analysis with a Cox proportional hazard ratio model was performed and resulted in variables with *p*-values of less than 0.2. Table 3 shows the results of multivariate analyses using these variables. In the LAI haloperidol group, the number of hospitalizations before LAIAs treatment was significantly associated with a higher

risk of treatment discontinuation. In the LAI risperidone group, the mean olanzapine equivalent dosage of LAIAs was significantly associated with a lower discontinuation risk, and olanzapine equivalent dosage of LAIAs at the second time point from the end had a significantly higher risk of treatment discontinuation. The variables with significant associations with risk of treatment discontinuation in the LAI paliperidone group included type of hospital, mean olanzapine equivalent dosage of LAIAs, olanzapine equivalent dosage of LAIAs at the second time point from the end, duration from the diagnosis to the first prescription of LAIAs, treatment duration of oral antipsychotics and anticholinergics before LAIAs treatment, mean dosage of oral antipsychotics before LAIAs treatment, and number of hospitalizations before LAIAs treatment. Although the hazard ratios of most of these variables were near 1.000, the hazard ratios of the hospital type were 1.195 (Hospital) and 1.598 (Clinic).

4. Discussion

In this study, we aimed to document treatment continuation rates of LAI haloperidol, LAI paliperidone, and LAI

risperidone. We used the HIRA database, which reflects the use of health care resources for the entire South Korea population. We also investigated the use of oral psychotropic medications before and after LAIAs treatment and the risk factors for LAIAs treatment discontinuation. The proportion of patients with >180 days of LAIAs treatment was significantly higher in the LAI paliperidone group than in the LAI haloperidol and LAI risperidone groups. More than a quarter of patients in the LAI haloperidol and LAI risperidone groups discontinued LAIAs treatment <2 months after initiation of the treatment. Patients in the LAI paliperidone group who had greater than 180 days' observation had a continuation proportion of 42.5%, which was significantly higher than the other two groups. A large number of patients continued oral antipsychotic treatment even after the initiation of LAIAs treatment. Among the factors significantly associated with LAIAs treatment discontinuation in the LAI paliperidone group based on hazard ratio, type of hospital was most likely to be a useful indicator of discontinuation of LAIAs treatment.

In the present study, LAIAs treatment estimated continuation rates 6 months after initiation of treatment was 36.8% in the LAI haloperidol group, 57.5% in the LAI paliperidone group, and 34.5% in the LAI risperidone group. A previous study reported that fewer than 1 in 10 patients continues on LAI haloperidol (9.7%) and LAI risperidone (2.6%) for at least 6 months (Olfson et al., 2007). The continuation rates of LAI risperidone were reported as 80.4% in the first month and 54.3% in the first year of the treatment (Mohamed et al., 2009). The treatment continuation rates of LAI paliperidone were reported as 33-59% after 6 months of treatment, and significantly higher treatment continuation of LAI paliperidone was also found over that of LAI haloperidol or LAI risperidone (Decuyper et al., 2017). As these previous studies show, this study showed that patients started on LAI paliperidone were more likely to continue the treatment compared with those on LAI haloperidol or LAI risperidone treatment.

In this study, the LAI haloperidol and LAI risperidone groups showed more than 25% discontinuation in the first 2 months after starting the treatment, indicating high early discontinuation rates. According to a previous study (Olfson et al., 2007), means of treatment duration are 71.7 days in the LAI haloperidol group and 60.5 days in the LAI risperidone group, which also suggests that a majority of patients discontinue LAIAs treatment within the first few months. It is suspected that confounding factors such as the severity of psychopathology and level of insight might affect these significant group differences in early discontinuation rates. Further studies with adjustment of confounders are required to deepen the understanding of factors affecting the early discontinuation of LAIAs treatment.

The continuation proportions of patients with more than 180 days' observation was 42.5% in the LAI paliperidone group, 18.2% in the LAI haloperidol group, and 1.0% in the LAI risperidone group. These results suggest higher long-term treatment adherence to LAI paliperidone treatment. Given the evidence reporting that a large number of patients discontinue LAIAs treatment in the first few months (Olfson et al., 2007), patients with more than 180 days' observation were an atypical fraction of the total patients with LAIAs treatment. In this study, nearly half of the

patients in the LAI paliperidone group discontinued treatment after 180 days, whereas more than 8 in 10 patients in the LAI haloperidol group and 99% of patients in the LAI risperidone group discontinued treatment eventually. The factors accounting for this remarkable difference in the treatment adherence among the three groups were not investigated in this study, and, to our knowledge, have not been investigated in any other study. Because the HIRA database does not include information on illness insight, severity of psychiatric symptoms, and familial support, which may be related to long-term LAIAs treatment adherence, we could not include these factors in this study. Future research with more available information is required to address this issue.

Here, we investigated the use of oral medications before and after LAIAs treatment. Specifically, the number and proportion of patients prescribed oral medications and the treatment duration of oral medications at each time point were analyzed. According to a previous report (Olfson et al., 2007), up to 90% of patients receive oral antipsychotics during the first 3 months of LAIAs treatment, and about 35% of the patients were also prescribed an antidepressant or anxiolytic during an LAIA treatment episode. This study also showed that a substantial proportion of patients were prescribed oral antipsychotics during LAIAs treatment, suggesting a large number of patients still needed oral antipsychotics to control breakthrough psychotic symptoms even during LAIAs treatment. In this study, it was also a notable finding that benzodiazepine use in the LAI risperidone group was decreased, contrary to the relatively constant benzodiazepine use in the other two groups. However, this should be interpreted with consideration that this is a descriptive statistic indicating further statistical analyses are needed to confirm this result.

Several factors were found to be significantly associated with LAIAs treatment discontinuation in this study. However, the hazard ratios of most factors were close to 1.000. Unlike the other factors, type of hospital in the LAI paliperidone group was notable, with a hazard ratio of 1.195 for Hospital and 1.598 for Clinic. Kim et al. (2016) indicated that the type of hospital can be used as a surrogate indicator reflecting early intensive hospitalization treatment, along with a previous report (Suh et al., 2009) that the type of hospital is associated with the extended hospitalization of psychiatric patients in South Korea. These previous studies lead to the interpretation that quality of intensive hospitalization treatment related to the type of hospital may influence LAIAs treatment discontinuation. However, this interpretation should be made with caution, as several confounders regarding the selection of hospital can affect the association of type of hospital with a higher risk of treatment discontinuation. Future studies investigating factors related to hospital selection are needed for a clearer understanding of these results.

This study used register-based data, which allowed for complete coverage of medication use, and there was no missing data. Nationwide coverage of schizophrenia patients in a real clinical practice, which decreased the possibility of selection bias, is a strength of the present study. However, there are some limitations which should be taken into account when interpreting the results. First, we did not obtain information on the date of actual administration of

LAIAs. Although the HIRA database provides reliable information on medication use, the claim data is only a proxy for actual medication use. Second, selection bias should be considered in the interpretation of group comparisons. Pre-treatment group differences among the three groups can affect the outcomes of this study, because this study was performed without random assignment owing to its naturalistic, observational study design. Several factors, including clinical efficacy, medication tolerability, the severity of psychopathology, and familial support which may influence the selection of LAIAs, should be considered in follow-up studies. Third, we did not consider psychopathology, quality of life, and adverse effects of medications in the analyses, because the HIRA database does not have information on these variables. Fourth, there was a large difference in sample size among the three groups, which had an exaggerated tendency to reject null hypotheses with clinically negligible differences. This large difference may be due to that the LAI paliperidone was commercialized more lately and has relatively better side effects profile than the other LAI antipsychotics. This could affect clinicians' selection for LAI antipsychotics. Also, as we included incident patients as much as possible in order to overcome limitations of RCT, such as selected patients and limited follow up duration, a difference in sample size had become more prominent. However, apart from this samples size issue, most significant group differences in this study seem not to be clinically negligible.

In conclusion, we compared the treatment continuation rates of three LAIAs, and investigated the use of oral medications before and after LAIAs treatment as well as factors associated with treatment discontinuation in each group. The LAI paliperidone group had a higher treatment continuation rate than the LAI haloperidol and LAI risperidone groups, specifically in the treatment continuation proportion of patients after 2 months and 6 months of treatment. A substantial proportion of patients in all three groups received oral antipsychotics during LAIAs treatment, and there was a remarkable decreasing trend in the proportions of patients using oral antipsychotics in the LAI paliperidone and LAI risperidone groups. In the LAI paliperidone group, the type of hospital was a notable variable associated with higher risk for the treatment discontinuation. Although the HIRA database used in this study covers medication use without missing data and also reflects real clinical practice, its observational, naturalistic study design should be noted when interpreting the results, because confounding variables could not be entirely adjusted. Further clinical research is needed to assess the factors contributing to the early discontinuation of LAIAs treatment in medication-related, clinical, and psychosocial aspects. There is also a need for development of intervention strategies to improve LAIAs treatment adherence.

Role of the funding source

This study was supported by Janssen Korea Ltd. The Janssen Korea Ltd. had no influence on data collection, data analyses, writing of the report, and on the decision to submit the study for publication.

Contributors

Seung-Hyun Shon, GumJee Choi, MinJung Koh, and Jungsun Lee designed the study. Jungsun Lee undertook the statistical analysis. Sung Woo Joo, Seung-Hyun Shon, GumJee Choi, MinJung Koh, and Seung Woo Cho participated in the data interpretation. Sung Woo Joo and Seung-Hyun Shon wrote the first draft of the manuscript. All authors contributed to and have approved the final manuscript. The two co-authors affiliated to Janssen laboratory (GumJee Choi and MinJung Koh) have neither any right to access to the HIRA database nor an influence on the statistical analysis.

Conflict of interest

GumJee Choi and MinJung Koh are employed in Janssen Korea Ltd. Other authors declare no conflicts of interest.

Acknowledgments

None.

Supplementary materials

Supplementary material associated with this article can be found, in the online version, at doi:[10.1016/j.euroneuro.2019.07.138](https://doi.org/10.1016/j.euroneuro.2019.07.138).

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