Latency to Long-Acting Injectable Antipsychotic Initiation and Psychiatric Hospitalization in First-Episode Schizophrenia

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Abstract

Objective: Long-acting injectable (LAI) antipsychotics are increasingly recommended for patients in the early phase of schizophrenia. We examined how the timing of LAI initiation affects treatment discontinuation and hospitalization duration in first-episode schizophrenia.

Methods: Using the Korean Health Insurance Review and Assessment Service claims database, we identified 6,380 patients with first-episode schizophrenia receiving continuous LAI treatment. The interval from diagnosis to LAI initiation was categorized into 6 groups (<1, 1–2, 2–3, 3–4, 4–5, and >5 years). Treatment discontinuation and the proportion of psychiatric hospitalization days during continuous LAI use were analyzed using Cox and linear regression models.

Results: Earlier LAI use increased over time, but the duration of continuous treatment declined. Patients who started LAIs >2 years after diagnosis had lower risks of discontinuation than those within the first year (2–3 years: hazard ratio [HR] = 0.77 [0.69–0.87]; 3–4 years: HR = 0.77 [0.68–0.86]; 4–5 years: HR = 0.70 [0.61–0.79]; >5 years: HR = 0.66 [0.59–0.74]). Later initiation was associated with greater psychiatric hospitalization burden, particularly among patients with prior hospitalizations (1–2 years: $\beta = 0.039$, $P = .039$; 3–4 years: $\beta = 0.057$, $P = .010$; >5 years: $\beta = 0.162$, $P < .001$), and within the >5-year group, longer delays further increased hospitalization days ($\beta = 1.87 \times 10^{-4}$, $P < .001$).

Conclusion: Although delayed initiation was linked to better treatment adherence, early LAI use reduced hospitalization burden, supporting guidelines advocating earlier LAI treatment in schizophrenia.

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Antipsychotic medications are central to schizophrenia treatment. However, adherence to antipsychotic treatment remains suboptimal,[1] with poor adherence associated with increased risks of relapse, psychiatric rehospitalization, and suicide.[2] Long-acting injectable (LAI) antipsychotics were developed to address these challenges and have been increasingly adopted in clinical practice.[3] A meta-analysis reported that LAIs are associated with lower rates of treatment discontinuation and psychiatric hospitalization compared to oral antipsychotics,[4] even when matched by compound and dose.[5]

Although LAI antipsychotics were initially developed for patients with chronic illness and poor adherence, clinical guidelines are increasingly endorsing their use in the early phases of schizophrenia.[6] Early and sustained treatment during the initial stage of illness is believed to prevent chronicity and support functional recovery,[7] including vocational and social outcomes.[8] Emerging evidence supports the benefits of early LAI initiation, showing associations with reduced risks of treatment discontinuation, psychiatric hospitalization, and decreased healthcare costs compared to oral antipsychotics.[9–12] The first 5 years following illness onset are widely recognized as a critical period for long-term prognosis.[13,14] However, it remains unclear which specific time point within the first 5 years may be most critical for LAI initiation. Previous studies have variably defined early LAI use as initiation within 1, 3, or 5 years of diagnosis or illness onset, reflecting the absence of a consensus regarding the optimal timing.[10,12,15,16] Additionally, the extent to which the effectiveness of LAIs diminishes when initiated beyond the 5-year mark remains poorly understood.

Although evidence continues to grow in favor of both the use and early introduction of LAI antipsychotics, their

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Clinical Points

- Despite growing evidence supporting the use of long-acting injectable (LAI) antipsychotics, the optimal timing of initiation in first-episode schizophrenia has not been well established.
- Early LAI initiation (within 1 year) was associated with fewer hospitalization days than delayed initiation (>5 years), and longer delays beyond 5 years were linked to progressively greater hospitalization burden.

uptake in clinical practice worldwide remains limited.[17,18] The relatively low incidence and prevalence of schizophrenia[19] pose substantial challenges to conducting large-scale randomized controlled trials on LAI use in this population. In South Korea, however, the universal single-payer national health insurance system captures comprehensive healthcare utilization data across the entire population. Researchers are granted access to this administrative claims database for research purposes, which enables the identification and analysis of large patient cohorts with rare conditions or infrequently used treatments.[20] This infrastructure provides unique opportunities to examine real-world prescribing patterns and treatment outcomes with sufficient statistical power, even for low-prevalence disorders like schizophrenia.[21]

Using a nationwide claims database, we aimed to examine how the timing of LAI antipsychotic initiation affects hospitalization duration in first-episode schizophrenia. We analyzed trends in initiation timing and treatment duration by year of diagnosis and evaluated whether initiating LAI antipsychotics within the first 5 years, categorized in 1-year intervals, was associated with fewer psychiatric hospitalization days.

METHODS

Data Source

We used the Health Insurance Review and Assessment Service (HIRA) claims database, which contains reimbursed records of diagnoses, prescriptions, and hospitalizations for almost the entire population of South Korea. The database covers the general population, excluding certain groups such as military personnel, prisoners, and individuals supported by specific public aid programs. Further details on the HIRA database have been described previously.[20] The present study was approved by the Institutional Review Board (IRB) of Asan Medical Center (IRB No. 2022-0104). As the HIRA database is anonymous and de-identified, informed consents were exempted by the IRB.

Study Population

We identified patients with incident schizophrenia using the HIRA database from August 1, 2010, to August 31, 2021. Patients were considered newly diagnosed with schizophrenia if they met the following criteria: First, the main diagnostic code F20 had to be recorded at least twice for outpatient visits or at least once for an inpatient admission during the observation period. Second, schizophrenia diagnosis was defined as the first registration of a main diagnostic code within the F20 to F29 range, with the patient aged between 18 and 65 years at the time of diagnosis. Third, there had to be no record of any F20 to F29 code during the 2 years prior to the initial diagnosis. Fourth, an F20 to F29 code had to be present at the last psychiatric visit within the observation period, with psychiatric visits identified by a main diagnostic code within the F00 to F99 range. Fifth, the patient had to receive >30 days of antipsychotic prescriptions during the observation period. Lastly, the observation period, starting from the date of diagnosis, had to exceed 1 year.

Among patients with incident schizophrenia identified by the above criteria, we included those who received continuous LAI antipsychotic treatment. Continuous use was defined as having at least 7 consecutive LAI prescriptions, with no gap longer than the expected interval between injections plus a 28-day grace period. Additionally, patients were required to have at least 90 days of follow-up after initiating LAI treatment.

Timing of LAI Antipsychotic Initiation

The interval between the date of schizophrenia diagnosis and the initiation of LAI treatment was used as the main analytic variable. Drawing on prior studies emphasizing the prognostic importance of the early course of illness,[13,14] this interval was categorized into 6 groups: ≤1 year, 1–2 years, 2–3 years, 3–4 years, 4–5 years, and >5 years. In addition, this categorization was guided by established clinical guidelines for maintenance treatment in schizophrenia,[22] which generally recommend treatment continuation and reassessment at annual intervals. Accordingly, the 1-year interval grouping was designed to reflect clinically meaningful timeframes and to facilitate evaluation of the period of LAI initiation most relevant for clinical decision-making.

Outcome Measures

We evaluated 2 outcome measures. The first was treatment discontinuation, defined as a lapse of >28 days after the expected end date of the previous LAI antipsychotic injection. The observation period began on the date of LAI initiation and ended at the earliest occurrence of treatment discontinuation or August 31, 2021. Discontinuation was solely based on LAI administration and did not account for concurrent oral antipsychotic medications. The second outcome was the proportion of psychiatric hospitalization days during the

continuous LAI treatment period. Since hospitalization claims are recorded monthly and may not correspond to individual episodes, we reconstructed hospitalization episodes using the episode-of-care approach described by Ha et al.[23] A clean period of 1 day was applied to define the boundary between consecutive inpatient stays. Following our previous studies,[24–26] any psychiatric readmission occurring within 30 days was considered a continuation of the previous hospitalization episode. Hospitalizations were classified as psychiatric if the admission type was general medical or psychiatric and the main diagnostic code fell within the F00–F99 range. The total number of psychiatric hospitalization days was divided by the duration of the LAI treatment period to calculate the hospitalization-day ratio.

Statistical Analyses

As described above, the timing of LAI antipsychotic initiation was categorized into 6 groups (<1 year, 1–2 years, 2–3 years, 3–4 years, 4–5 years, and >5 years) and was included as a categorical variable in subsequent models. To examine the association between LAI timing and treatment discontinuation, Kaplan-Meier survival curves and Cox proportional hazards models were used. For the hospitalization-day ratio, 2 linear regression models were applied. Model 1 included LAI timing as a categorical variable, using the <1 year group as the reference. Model 2 assessed the linear association between time to LAI initiation, treated as a continuous variable, and the hospitalization-day ratio within each timing group. All models were adjusted for age at diagnosis, sex, and calendar year of diagnosis. Subgroup analyses of the linear regression models were performed among patients who experienced psychiatric hospitalization during the LAI treatment period. All statistical analyses were conducted using R version 3.5.1 (R Development Core Team, Vienna, Austria). Two-sided *P* values <.05 were considered statistically significant.

RESULTS

Demographic and Clinical Characteristics of the Study Population

Table 1 presents the demographic and clinical characteristics of patients with incident schizophrenia who received continuous LAI treatment (N = 6,380). The mean age at diagnosis was 30.9 years (SD = 12.0), and 40.8% of patients were male. The average interval between diagnosis and LAI antipsychotic initiation was 1,090.6 days (SD = 941.8), and the mean duration of continuous LAI treatment was 547.7 days (SD = 545.7). During the treatment period, patients experienced a mean number of 1.13 psychiatric hospitalizations per patient-year (SD = 7.73), with an average of 23.4 hospitalization days per patient-year (SD = 79.6).

Table 1.

Demographic and Clinical Characteristics of the Study Population

Variable	Patients with continuous LAI treatment (N = 6,380)
Age of onset, mean (SD), y	30.9 (12.0)
Age of onset, n (%), y	
18–19	692 (10.8)
20–29	2,304 (36.1)
30–39	1,604 (25.1)
40–49	1,002 (15.7)
50–59	627 (9.8)
60–65	151 (2.4)
Male sex, n (%)	2,603 (40.8)
Calendar year of diagnosis, n (%)	
2011	815 (12.8)
2012	765 (12)
2013	676 (10.6)
2014	665 (10.4)
2015	701 (11)
2016	664 (10.4)
2017	672 (10.5)
2018	624 (9.8)
2019	497 (7.8)
2020	301 (4.7)
Time from diagnosis to LAI antipsychotic initiation, mean (SD), days	1,090.6 (941.8)
Time from LAI antipsychotic initiation to discontinuation, mean (SD), days	547.7 (545.7)
Number of hospitalizations per patient-year, mean (SD)	1.13 (7.73)
Duration of hospitalizations per patient-year, days, mean (SD)	23.43 (79.63)

Abbreviation: LAI = long-acting injectable.

Temporal Trends in LAI Treatment Initiation and Duration by Year of Schizophrenia Diagnosis

Table 2 summarizes treatment patterns and clinical characteristics stratified by calendar year of schizophrenia diagnosis. The mean interval from diagnosis to LAI antipsychotic initiation decreased steadily, from 1,980.8 days (SD = 1,095.4) in 2011 to 133.4 days (SD = 127.6) in 2020. This reflects a clear trend toward earlier initiation. The average duration of LAI treatment before discontinuation also declined, from 646.1 days (SD = 736.9) to 246.4 days (SD = 140.0). The mean proportion of cumulative psychiatric hospitalization days per patient-year remained relatively stable, ranging from 0.095 (SD = 0.220) in 2013 to 0.054 (SD = 0.177) in 2020. Paliperidone palmitate 1-month formulation (PP1M) was the most commonly prescribed LAI throughout the study period. It accounted for 76.9% of initial prescriptions in 2011 and 65.2% in 2020. Use of aripiprazole monohydrate increased from 19.8% in 2011 to a peak of 43.5% in 2017, followed by a gradual

Table 2.
Temporal Trends in LAI Treatment Initiation and Duration by Year of Schizophrenia Diagnosis

Variable	Calendar year of diagnosis									
	2011	2012	2013	2014	2015	2016	2017	2018	2019	2020
Number of patients	815	765	676	665	701	664	672	624	497	301
Time from diagnosis to LAI antipsychotic initiation, mean (SD), days	1,980.8 (1,095.4)	1,787.9 (984.4)	1,534.8 (843.9)	1,363.2 (718)	1,029.6 (638.8)	833.7 (552)	546.8 (424.5)	378.7 (337.4)	226.4 (220.6)	133.4 (127.6)
Time from LAI antipsychotic initiation to discontinuation, mean (SD), days	646.1 (736.9)	589.6 (644)	620.9 (639.4)	590.4 (542.4)	588.6 (534.1)	551.9 (487)	555.6 (448.9)	463.5 (354.9)	378.8 (253.8)	246.4 (140)
Proportion of cumulative duration of hospitalizations per patient-year, mean (SD)	0.083 (0.216)	0.087 (0.213)	0.095 (0.22)	0.058 (0.157)	0.064 (0.168)	0.073 (0.188)	0.063 (0.172)	0.069 (0.194)	0.076 (0.192)	0.054 (0.177)
Type of antipsychotic at LAI antipsychotic initiation, n (%)										
Haloperidol decanoate	16 (2.0)	12 (1.6)	15 (2.2)	7 (1.1)	7 (1.0)	10 (1.5)	6 (0.9)	4 (0.6)	3 (0.6)	1 (0.3)
Aripiprazole monohydrate	161 (19.8)	181 (23.7)	180 (26.6)	206 (31.0)	201 (28.6)	266 (39.9)	292 (43.5)	251 (40.0)	181 (36.4)	102 (33.8)
PP1M	627 (76.9)	566 (74.0)	479 (70.8)	451 (67.8)	493 (70.2)	390 (58.5)	371 (55.2)	371 (59.2)	313 (63.0)	197 (65.2)
PP3M	2 (0.2)	0 (0.0)	1 (0.1)	0 (0.0)	1 (0.1)	1 (0.1)	2 (0.3)	0 (0.0)	0 (0.0)	1 (0.3)
Risperidone microspheres	9 (1.1)	6 (0.8)	2 (0.3)	1 (0.2)	0 (0.0)	0 (0.0)	1 (0.1)	1 (0.2)	0 (0.0)	1 (0.3)

Abbreviations: LAI = long-acting injectable, PP1M = paliperidone palmitate 1-month formulation, PP3M = paliperidone palmitate 3-month formulation.

decline to 33.8% in 2020. Other LAI antipsychotics, including haloperidol decanoate, risperidone microspheres, and the 3-month formulation of paliperidone (PP3M), were prescribed infrequently.

Treatment Discontinuation According to Time of LAI Antipsychotic Initiation

Table 3 and Figure 1 present the risk of LAI treatment discontinuation according to the interval between schizophrenia diagnosis and LAI initiation. Among 6,380 patients, 30.5% were initiated on LAI treatment within the first year after diagnosis. The risk of discontinuation declined progressively with later initiation. Compared to those who commenced LAI antipsychotics within 1 year, the hazard ratios (HRs) for treatment discontinuation were significantly lower among patients who were initiated at 2–3 years (HR = 0.774; 95% confidence interval [CI], 0.692–0.866; $P < .001$), 3–4 years (HR = 0.768; 95% CI, 0.682–0.864; $P < .001$), 4–5 years (HR = 0.698; 95% CI, 0.613–0.794; $P < .001$), and >5 years (HR = 0.657; 95% CI, 0.586–0.736; $P < .001$) after diagnosis.

Psychiatric Hospitalization Days According to Time of LAI Antipsychotic Initiation

Table 4 presents the association between the timing of LAI antipsychotic initiation and the proportion of cumulative psychiatric hospitalization days during the treatment period. In the full cohort (N = 6,380), patients who were initiated on LAIs >5 years after diagnosis had significantly higher hospitalization-day ratios compared to those initiated within 1 year (model 1: $\beta = 0.024$, $t = 2.87$, $P = .004$). Within the >5-year group, a longer delay to LAI initiation was also associated with increased hospitalization burden (model 2: $\beta = 3.69 \times 10^{-5}$, $t = 2.53$, $P = .011$).

In the subgroup of patients with a history of psychiatric hospitalization during the LAI treatment period (N = 2,109), additional significant associations were observed. Compared to the <1-year group, patients who were initiated on LAIs at 1–2 years ($\beta = 0.039$, $t = 2.06$, $P = .039$), 3–4 years ($\beta = 0.057$, $t = 2.57$, $P = .010$), and >5 years ($\beta = 0.162$, $t = 7.71$, $P < .001$) had significantly higher hospitalization-day ratios. Within-group analyses (model 2) showed a significant positive association between time to LAI initiation and hospitalization burden in the <1-year ($\beta = 2.02 \times 10^{-4}$, $t = 2.12$, $P = .034$), 4–5-year ($\beta = 3.45 \times 10^{-4}$, $t = 2.22$, $P = .028$), and >5-year ($\beta = 1.87 \times 10^{-4}$, $t = 4.96$, $P < .001$) groups.

DISCUSSION

Using the HIRA claims database, we examined the impact of the timing of LAI antipsychotic initiation on treatment discontinuation and psychiatric hospitalization in patients with first-episode

Table 3.

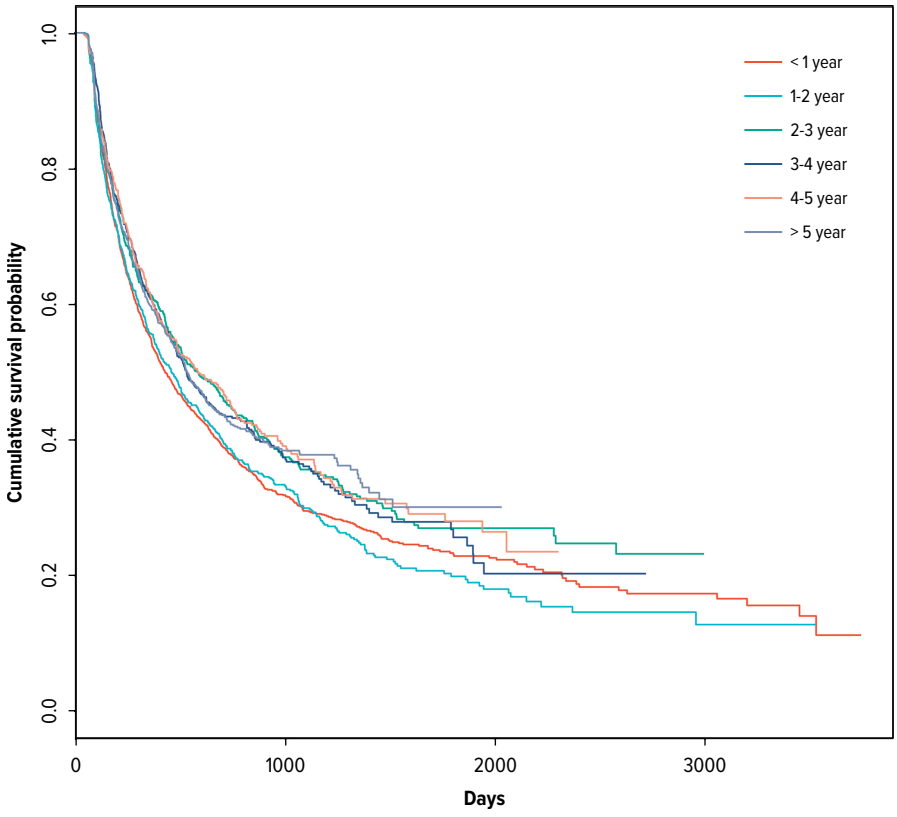
Treatment Discontinuation According to Timing of LAI Initiation

Time from diagnosis to LAI antipsychotic initiation, years	Number of patients, n (%)	Time from LAI antipsychotic initiation to discontinuation, mean (SD), days	HR	95% CI	*P*
<1	1,948 (30.5)	581.9 (609.2)		Ref	
1–2	962 (15.1)	570.7 (587.3)	0.963	0.875–1.061	.450
2–3	745 (11.7)	627.9 (625.5)	0.774	0.692–0.866	<.001
3–4	666 (10.4)	564.6 (501.1)	0.768	0.682–0.864	<.001
4–5	591 (9.3)	563.8 (506.7)	0.698	0.613–0.794	<.001
>5	1,468 (23.0)	432.2 (377.1)	0.657	0.586–0.736	<.001

Abbreviations: HR = hazard ratio, LAI = long-acting injectable, ref = reference group.

Figure 1.

Kaplan-Meier Survival Curves Showing the Probability of Continued Long-Acting Injectable (LAI) Antipsychotic Treatment According to the Time From Schizophrenia Diagnosis to Treatment Initiation



schizophrenia who received continuous LAI treatment. Analysis by calendar year of diagnosis revealed a clear trend toward earlier LAI initiation over time, accompanied by a gradual reduction in treatment duration. When patients were categorized by 1-year intervals from diagnosis to LAI antipsychotic initiation, those who commenced LAIs within the first year had a higher risk of treatment discontinuation than those with delayed initiation. Patients who began LAIs >2 years after diagnosis exhibited a stepwise increase in treatment duration and a lower risk of discontinuation. Regarding psychiatric hospitalization, initiation >5 years after diagnosis was associated with a significantly higher number of hospitalization days compared to initiation within the first year. Within the >5-year group, longer delays to LAI antipsychotic initiation were linearly

Table 4.

Psychiatric Hospitalization Days According to Timing of LAI Initiation

Time from diagnosis to LAI antipsychotic initiation, years	Number of patients, n (%)	Proportion of cumulative duration of hospitalizations, mean (SD)	Model 1 (between-group)			Model 2 (within-group)		
			β	*t*	*P*	β	*t*	*P*
Total patients (N = 6,380)								
<1	1,948 (30.5)	0.063 (0.173)		Ref		3.37×10^{-5}	0.906	.365
1–2	962 (15.1)	0.073 (0.192)	0.010	1.238	.216	4.78×10^{-5}	0.811	.417
2–3	745 (11.7)	0.072 (0.186)	0.009	1.078	.281	-3.58×10^{-6}	−0.054	.957
3–4	666 (10.4)	0.076 (0.189)	0.013	1.427	.154	-3.06×10^{-6}	−0.044	.965
4–5	591 (9.3)	0.066 (0.172)	0.002	0.177	.859	1.30×10^{-4}	1.969	.049
>5	1,468 (23.0)	0.090 (0.226)	0.024	2.870	.004	3.69×10^{-5}	2.533	.011
Patients with a history of psychiatric hospitalization (N = 2,109)								
<1	642 (30.4)	0.191 (0.258)		Ref		2.02×10^{-4}	2.121	.034
1–2	330 (15.6)	0.211 (0.280)	0.039	2.064	.039	1.74×10^{-4}	1.179	.239
2–3	267 (12.7)	0.201 (0.266)	0.041	1.938	.053	-7.76×10^{-5}	-0.491	.624
3–4	236 (11.2)	0.216 (0.267)	0.057	2.568	.010	3.92×10^{-5}	0.239	.811
4–5	200 (9.5)	0.194 (0.251)	0.041	1.703	.089	3.45×10^{-4}	2.219	.028
>5	434 (20.6)	0.305 (0.328)	0.162	7.710	<.001	1.87×10^{-4}	4.955	<.001

Abbreviations: LAI = long-acting injectable, ref = reference group.

associated with increased hospitalization burden. Among patients with a history of psychiatric hospitalization during LAI antipsychotic treatment, the benefits of earlier initiation were even more pronounced, underscoring its potential role in reducing hospitalization in patients with greater illness severity.

We examined trends in the timing of LAI antipsychotic initiation, treatment duration, and prescribed LAI formulation by calendar year of schizophrenia diagnosis. Over the study period, a clear shift toward earlier initiation of LAIs was observed. This pattern is consistent with some international guidelines that currently recommend LAI use in first-episode schizophrenia[6] and Korean pharmacotherapy guidelines endorsing their use across all stages of illness.[27] These findings suggest that such recommendations are increasingly reflected in routine clinical practice. Among available LAIs, PP1M and aripiprazole monohydrate were most frequently prescribed. In South Korea, PP1M was approved for patients with poor adherence in October 2010 and for acute treatment in November 2015; aripiprazole monohydrate was approved in September 2016. While these approval dates likely influenced prescribing patterns, the trend toward earlier initiation persisted beyond 2017, indicating broader acceptance of early LAI use beyond regulatory changes. Given emerging evidence of different outcomes with different LAI formulations,[28,29] future studies should compare the real-world effectiveness of specific agents on treatment outcomes.

We observed a temporal trend toward earlier initiation of LAI antipsychotics; however, the duration of continuous LAI treatment gradually declined. The overall decline in treatment duration over time may reflect broader systemic and behavioral changes, including evolving reimbursement criteria, increasing patient involvement in treatment decisions, and shifting clinician attitudes toward the long-term use of LAIs. Survival analysis revealed a significantly lower risk of treatment discontinuation among patients who initiated LAIs >2 years after diagnosis, suggesting greater adherence with later initiation. Current clinical guidelines offer inconsistent recommendations on the duration of maintenance therapy for first-episode schizophrenia, with many providing no explicit guidance.[22] Some advocate for 1 to 2 years of maintenance treatment; in contrast, other guidelines support longer treatment durations, emphasizing the heightened risk and potentially severe consequences of relapse during the early course of illness.[30] The relatively short treatment duration observed among patients who were initiated on LAIs early may reflect adherence to shorter maintenance recommendations for early-phase schizophrenia. The higher discontinuation risk in early LAI initiators may reflect limited treatment experience and adherence education, whereas lower discontinuation in later initiators could be related to prior relapse history or selective prescribing in more adherent patients. Existing evidence has reported both the benefits of prolonged antipsychotic use in preventing relapse and the long-term risks, such as weight gain and metabolic syndrome.[31] Early LAI use may impose higher treatment costs[28,32] and should be guided by careful consideration of patient preference and the potential burden of long-term medication exposure. Given this uncertainty, further research is warranted to establish

evidence-based recommendations regarding the optimal duration of maintenance therapy in early schizophrenia, particularly to inform LAI prescribing in routine clinical practice.

We found that earlier initiation of LAI antipsychotics was associated with a reduction in psychiatric hospitalization days during the treatment period. This association was more pronounced among patients who experienced psychiatric hospitalization while on LAI treatment. Compared to those initiated on LAIs within 1 year of diagnosis, patients with later initiation exhibited a stepwise increase in hospitalization duration. Notably, even among those who began LAIs >5 years after diagnosis, longer delays to initiation were linearly associated with greater hospitalization burden. These findings are consistent with prior studies advocating the clinical benefits of early LAI use.[10,12,16] Correll et al. further reported that initiating LAIs not just early, but specifically before the occurrence of emergency department visits or hospitalizations, was associated with improved outcomes and reduced healthcare costs.[32] Our results support the early use of LAI antipsychotics within the first 5 years after diagnosis, especially in patients with more severe illness. However, these findings have limitations in establishing a definitive conclusion. Importantly, the observed benefit of earlier LAI antipsychotic initiation extended even to patients with chronic illness, indicating that delayed initiation does not preclude meaningful reductions in hospitalization burden. Future research should focus on identifying predictors of treatment response and long-term outcomes to guide individualized decision-making around LAI antipsychotic use in routine clinical care.

This nationwide, population-based study investigated the impact of the timing of LAI antipsychotic initiation on treatment outcomes in patients with first-episode schizophrenia. Leveraging large-scale claims data, we captured real-world trends in LAI antipsychotic utilization and demonstrated the potential benefits of early initiation, findings that would be difficult to obtain through conventional clinical trials. However, several limitations should be considered. First, although the use of nationwide administrative claims data allowed inclusion of a large and representative cohort, it also limited access to important clinical variables such as symptom severity, functional status, and patient insight, which may influence treatment adherence and outcomes. These constraints should be considered when interpreting the results. Second, continuous LAI antipsychotic treatment was defined based on prescription refill patterns, which may not accurately reflect actual adherence. Third, although we adjusted for age, sex, and year of diagnosis, unmeasured confounding may remain. For instance, concurrent use of oral psychotropic medications during LAI treatment could have influenced outcomes.[33,34] Fourth, we could not conduct stratified analyses by LAI antipsychotic type due to the relatively recent approval of aripiprazole monohydrate in Korea, limiting statistical power to detect differential effects across formulations. Future research should evaluate whether adherence and effectiveness vary by specific LAI antipsychotic agents. Fifth, our analysis focused on hospitalization during continuous LAI antipsychotic use and did not account for intermittent use or prolonged efficacy after discontinuation. Sixth, although our inclusion criteria were designed to identify patients with first-episode schizophrenia, some individuals may have experienced prior psychotic episodes or hospitalizations before study registration. Thus, the cohort should be regarded as representing newly diagnosed rather than strictly first-episode schizophrenia.

In conclusion, this nationwide study using real-world claims data provides evidence that earlier initiation of LAI antipsychotics in patients with first-episode schizophrenia is associated with fewer psychiatric hospitalization days, particularly among those with greater illness severity. Patients initiated on LAI antipsychotics within 1 year of diagnosis experienced significantly fewer hospitalization days than those who began treatment after 5 years. Even among patients who started LAIs >5 years after diagnosis, a longer delay to initiation was associated with an increased proportion of hospitalization days. Although the use of LAI antipsychotics has shifted earlier over the past decade, the duration of continuous treatment has declined. Patients who were initiated on LAIs >2 years after diagnosis had lower treatment discontinuation rates than those who started within the first year. Given the uncertainty surrounding the optimal duration of maintenance treatment in first-episode schizophrenia, future research is needed to support individualized treatment planning using LAI antipsychotics and to strengthen the evidence base for early initiation.

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