Long-term Outcomes of Early Use of Long-Acting Injectable Antipsychotics in Schizophrenia

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ABSTRACT

Background: Long-acting injectable antipsychotics (LAIs) may potentially benefit patients requiring psychiatric hospitalization during the early stages of schizophrenia. However, few studies have compared the long-term effectiveness between patients who switched to LAIs and those who remained on oral antipsychotics (OAPs).

Methods: Using the Taiwan National Health Insurance Research Database, we constructed a population-based cohort with 19,813 new OAP users with *ICD-9-CM*–defined schizophrenia who were hospitalized from 2002 to 2005. Within this cohort, 678 patients who switched to LAIs during their hospitalization were identified. The LAI group was matched to patients who remained on OAPs (n = 678). The LAI cohort was further subdivided for analysis into patients who switched to LAIs within 3 years of OAP initiation ("an early stage") and those who switched after 3 years ("a late stage"). Conditional Cox regressions and conditional negative binomial regressions were used to estimate the risk of death and the number of hospital visits between the two groups.

Results: During the 13-year study period, 312 patients switched to LAIs within the first 3 years of OAP initiation. All- and natural-cause mortalities in these patients were significantly lower than in those who remained on OAPs. The hazard ratios (HRs) for all- and natural-cause mortalities were 0.49 (95% confidence interval [CI], 0.27–0.87) and 0.30 (95% CI, 0.15–0.60), respectively. No significant decrease associated with LAIs was observed in unnatural-cause mortality. Patients receiving LAIs had lower risks of rehospitalization (incidence rate ratio [IRR] = 0.56, 95% CI, 0.45–0.69), psychiatric hospitalization (IRR = 0.63, 95% CI, 0.50–0.81), and psychiatric emergency room visits (IRR = 0.58, 95% CI, 0.45–0.75) compared to patients who remained on OAPs. Use of LAIs in the late stage of treatment did not decrease the risk of relapse or mortality.

Conclusions: Switching to LAIs during the first 3 years of treatment improved antipsychotic adherence, decreased relapses, and reduced long-term mortality. Our results provide evidence to support the benefits of early LAI treatment in schizophrenia.

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Schizophrenia is a chronic and severe mental illness that affects more than 21 million people worldwide. Patients with schizophrenia generally have poor outcomes, and their lifespan is shortened by 10–25 years compared to the general population, which is the worst among all mental disorders.[1] Early medical intervention generally yields the best outcomes in patients.[2] However, treatment discontinuation due to nonadherence remains a major challenge for effective schizophrenia therapies, because a long duration of untreated psychosis results in poor long-term outcomes.[3]

Long-acting injectable antipsychotics (LAIs) were developed to improve treatment adherence in patients with schizophrenia, thereby reducing the incidences of relapse and rehospitalization due to treatment discontinuation.[4,5] Despite the high efficacy and tolerability of LAIs, they are not widely used in clinical practice.[6] Instead, LAIs are primarily used in patients who are in the late stages of schizophrenia.[7] These patients generally have poor outcomes, as they exhibit the most severe symptoms, have poor scores of therapy adherence, and are most likely to experience a relapse.[7] However, increasing evidence suggests that during the early stages of schizophrenia, a critical time when the disease is most treatable, patients may experience more beneficial effects of LAI treatment.[8] Successful prevention of disease relapse at this stage may determine the disease trajectory, which would lead to the greatest benefits.[9] Recent evidence suggested that LAI treatment during the first disease episode was associated with a lower risk of hospitalization or rehospitalization compared to oral antipsychotics (OAPs).[10,11] Our previous study showed that patients who switched to LAIs during the early stages of treatment generally had decreased risks of suicide attempts and mortality.[12] Those results spurred further investigation into whether patients with severe schizophrenia who required psychiatric hospitalization would benefit from the early adoption of LAIs. Hospitalized patients represent patients with exacerbated symptoms for many reasons, and hospitalization is also a predictor of treatment resistance and long-term underlying cognitive and functional declines, which could become large health care burdens.[13]

The aim of this study was to examine a psychiatric hospitalized schizophrenia patient cohort that reflects patients with an active psychotic episode or severe symptoms, where LAIs are usually used as the second-line treatment for those who were initially prescribed OAPs. The objective of this study was to assess whether OAP-treated

Clinical Points

- Long-acting injectable antipsychotics (LAIs) were found to generally decrease all-cause mortality compared to oral antipsychotics (OAPs). However, the effectiveness of LAIs in patients with acute psychosis events requiring hospitalizations is not clear.
- This study further demonstrated that early use of LAIs in patients requiring psychiatric hospitalization was associated with decreased rehospitalizations, emergency room use, and mortality.

patients who switched to LAIs during hospitalization in the early stages of treatment showed a decreased risk of psychiatric rehospitalizations and emergency room (ER) visits and improved mortality compared to patients who remained on OAPs.

METHODS

Study Design

We designed a prevalent new-user study in a cohort consisting of patients who switched from OAPs to LAIs matched with patients based on propensity scores who remained on OAPs during a psychiatric hospitalization.[14]

Data Source

We conducted a population-based cohort study using the Taiwan National Health Insurance (NHI) Research Data (NHIRD) and the Taiwan National Death Registry database. The NHIRD is derived from Taiwan's single-payer compulsory NHI program, covering up to 99% of the 23 million people in Taiwan. The NHIRD includes all medical claims data on disease diagnoses, procedures, drug prescriptions, demographics, and enrollment profiles of all NHI beneficiaries.[15] The National Death Registry of Taiwan database contains the ascertained vital status, date of death, and cause of death for each individual. The accuracy of cause-of-death coding in the Taiwan National Death Registry database was previously validated.[16] The database used in this study covered the period from January 1, 2002, to December 31, 2015.

Study Population

Base cohort. We created a base cohort consisting of patients 16–65 years of age with newly diagnosed schizophrenia (*International Classification of Diseases, Ninth Revision, Clinical Modification* [*ICD-9-CM*] code: 295) who received OAP therapy during the period of 2002–2005. Patients with missing information regarding sex or age (n = 382) were excluded. We included a total of 19,183 patients who were hospitalized for schizophrenia at least once in the base cohort.

Study cohort. From the base cohort, we identified a study cohort of patients who switched to LAIs during hospitalization and were further prescribed LAIs at least 6 times within 1 year postdischarge. Evidence indicated that patients adherent to antipsychotics after 6 months showed a good adherence rate.[17] We did not require LAIs to be the same compound as the OAPs. Using a prevalent new-user study design,[14] we had 2 matching steps. First, each patient who added LAIs was matched with those receiving OAPs based on sex, age, time since first antipsychotic prescription, and time of the first prescription of LAIs. We selected only patients who received OAPs at least 6 times after the index date to ensure comparability of the LAI and OAP groups. Furthermore, we used a propensity score matching method to balance baseline psychotic diseases diagnosed (for 1 year prior to the index date) between the LAI and OAP groups. Psychotic diseases included mood disorders (*ICD-9-CM*: 296.2, 296.3, 300.4, and 311.x), anxiety disorders (*ICD-9-CM*: 300.x except 300.4), alcohol abuse (*ICD-9-CM*: 291.x, 303.x, 305.0, 357.5, 425.5, 535.3, 571.0, 571.1, 571.2, and 571.3), and substance abuse (*ICD-9-CM*: 292.x, 304.x, and 305.2–305.9). LAI- and OAP-treated patients were matched within their respective risk groups at a 1:1 ratio based on nearest-neighbor matching. The cohort index date was defined as the issue date of the first prescription of LAIs.

All patients were followed up from the index date to until either the end of the study (December 31, 2015) or death before the designated endpoint of the study, whichever came first. OAP group patients switching to LAIs during the follow-up were censored on the date of the LAI prescription (Figure 1).

Antipsychotic Exposure

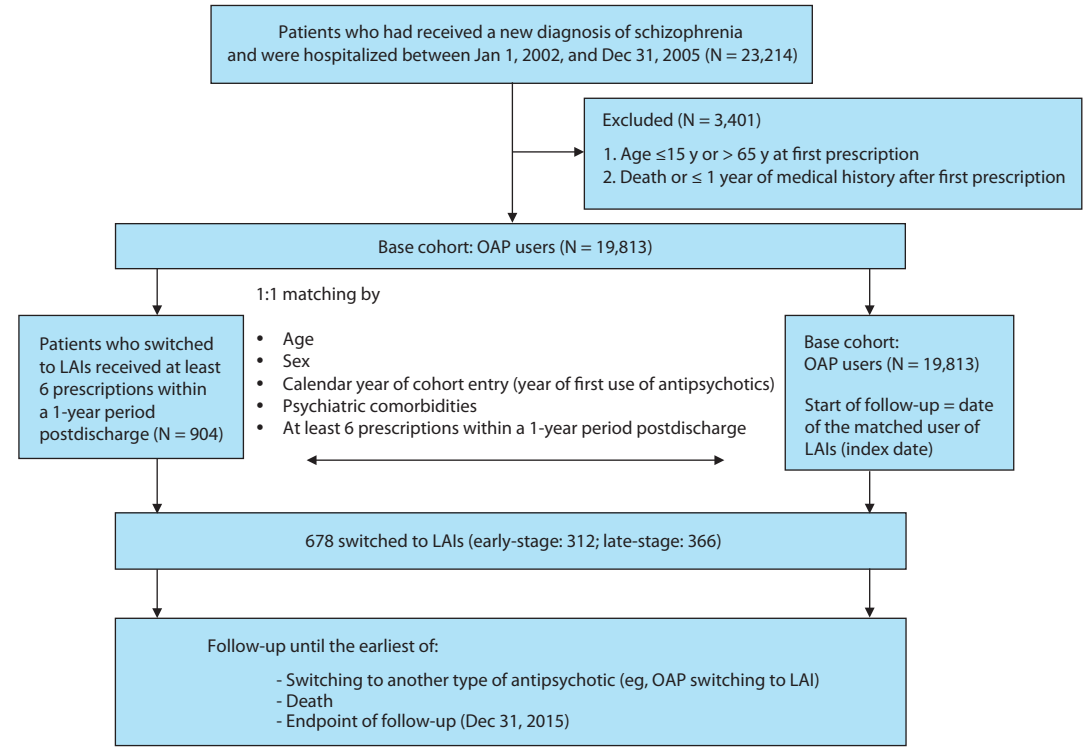
Evidence of antipsychotic exposure was obtained from ambulatory and inpatient prescription claims data using the Anatomic Therapeutic Chemical (ATC) Classification System code N05A (antipsychotics) while excluding N05AN (lithium).[18] We also estimated the time from OAP initiation to either adding or switching to LAIs and grouped patients into early-stage switching (≤ 3 years) and late-stage switching (> 3 years) according to the literature.[8,19]

Outcomes of Interest

Primary outcomes were all-cause, natural-cause (*ICD-10* codes: A00–R99), and unnatural-cause mortality (*ICD-10* codes: V01–Y89). Occurrences of all, natural, and unnatural causes of deaths were determined from cause-of-death data in the death registry from the base cohort entry date (OAP initiation) to either death or the end of the study (December 31, 2015).

Secondary outcomes were occurrences of rehospitalizations, psychiatric rehospitalizations, and psychiatric ER visits during the follow-up period, within 1 year and during 1–2 years after the index date. We also examined antipsychotic adherence as assessed by the modified medication possession ratio (MPR).[20] The MPR calculates the cumulative days of antipsychotic prescriptions divided by the summation of days from the index date to the date of rehospitalization. Hospitalization was defined as admission for both medical and psychiatric reasons. Psychiatric hospitalization was defined as any admission to a psychiatric hospital or department of psychiatry in a general

Figure 1. Flowchart Showing the Study Cohorts



hospital. A psychiatric ER visit was defined as any ER visit at a psychiatric hospital or at a general hospital where a definite diagnosis of schizophrenia was made.

Other Covariates

We included Charlson Comorbidity Index (CCI) within 1 year before the index date as a covariate because these conditions are associated with survival.[21] The CCI was abstracted from NHIRD claims during 1 year prior to the index date to assess the burden of comorbidities, and it was grouped into scores of 0, 1, 2, and ≥ 3.

Statistical Analysis

Descriptive statistics were used to summarize characteristics of patients in the matched LAI and OAP groups. Potential imbalances after matching among covariates were assessed using standardized mean differences (SMDs). All-, natural-, and unnatural-cause mortalities per 100,000 were independently estimated for the LAI and OAP groups. Conditional Cox regressions were used to estimate the risk of death in patients receiving LAIs compared to those receiving OAPs. Survival was estimated from the time of switching to LAIs for the LAI group and the corresponding date for the matched OAP group. Survival curves for patients in the LAI and OAP groups were derived using the Kaplan-Meier method. Moreover, conditional negative binomial regressions were used to examine the number of events per month of hospitalizations, psychiatric hospitalizations, and psychiatric ER visits between the LAI and OAP groups. Incidence rate ratios (IRRs) with 95% confidence intervals (CIs) were determined to measure the effects of the independent variable on the dependent variables. We initially explored the data using the Poisson model, but likelihood ratio tests indicated that our data were significantly overdispersed. Therefore, a negative binomial model was utilized. All statistical analyses were performed using SAS v. 9.4 (SAS Institute, Cary, NC). No adjustments were made for multiple comparisons. This study was reviewed and approved by the Institutional Review Board of Taipei Medical University (TMU-JIRB no. 201610013).

RESULTS

Patient Characteristics

During the follow-up period (median = 88.5 months), 678 hospitalized patients switched to LAI treatment. Among these patients, 312 received LAIs within the first 3 years of OAP initiation, and 366 received LAIs 3 or more years after OPA initiation. We failed to find a match for 226 patients in the OAP group. Table 1 presents the baseline characteristics of LAI patients and their 678 matched OAP hospitalized counterparts. The CCI score did not significantly differ between the LAI and OAP groups in either stage.

All-, Natural-, and Unnatural-Cause Mortalities

Our results suggested that in patients switching to LAIs within the first 3 years of OAP initiation, all- and natural-cause mortalities were significantly lower than those in OAP patients (Table 2). Hazard ratios (HRs) for all- and natural-cause mortalities were 0.49 (95% CI = 0.27–0.87) and 0.30 (95% CI = 0.15–0.60), respectively. In contrast, LAIs did

Table 1. Characteristics of Patients Hospitalized With Schizophrenia Who Switched to Long-Acting Injectable Antipsychotics (LAIs) During the Early or Late Stage of Treatment Compared to Their Hospitalized Counterparts Treated With Oral Antipsychotics (OAPs)

	Early stage[a] (N = 624)			Late stage[a] (N = 732)		
	LAIs (n = 312)	OAPs (n = 312)	SMD[b]	LAIs (n = 366)	OAPs (n = 366)	SMD[b]
Age at first antipsychotics, mean (SD), y	35.2 (9.2)	35.1(9.3)	0.02	32.5 (10.1)	32.6 (10.1)	0.01
Age group, n (%)						
15–39 y	214 (68.6)	216 (69.2)	0.04	273 (74.6)	272 (74.3)	0.02
40–65 y	98 (31.4)	96 (30.8)	0.04	93 (25.4)	94 (25.7)	0.02
Sex, n (%)						
Male	172 (55.1)	172 (55.1)	0.00	176 (48.1)	176 (48.1)	0.00
Female	140 (44.9)	140 (44.9)	0.00	190 (51.9)	190 (51.9)	0.00
Duration from first antipsychotics to index date in months, mean (SD)	10.4 (11.4)	10.4 (11.4)	0.00	83.5 (29.9)	83.5 (29.9)	0.00
Psychiatric comorbidities, n (%)						
Mood disorder	42 (13.5)	42 (13.5)	0.00	52 (14.2)	52 (14.2)	0.00
Anxiety disorder	18 (5.8)	18 (5.8)	0.00	31 (8.5)	31 (8.5)	0.00
Bipolar disorder	34 (10.9)	34 (10.9)	0.00	33 (9.0)	33 (9.0)	0.00
Alcohol use disorder	16 (5.1)	16 (5.1)	0.00	9 (2.5)	8 (2.2)	0.19
Substance use disorder	21 (6.7)	21 (6.7)	0.00	10 (2.7)	10 (2.7)	0.00
Calendar year, n (%)						
2002	86 (27.6)	55 (17.6)	0.83	108 (29.5)	101 (27.6)	0.13
2003	77 (24.7)	113 (36.2)	0.78	97 (26.5)	109 (29.8)	0.23
2004	74 (23.7)	83 (26.6)	0.22	94 (25.7)	86 (23.5)	0.17
2005	75 (24.0)	61 (19.6)	0.37	67 (18.31)	60 (19.1)	0.07
			P value[c]			*P* value[c]
Charlson Comorbidity Index, n (%)			.05			.36
0	292 (93.6)	274 (87.4)		325 (88.8)	323 (88.3)	
1	14 (4.5)	23 (7.4)		25 (6.8)	19 (5.2)	
2	4 (1)	6 (1.9)		9 (2.5)	11 (3.0)	
≥ 3	2 (0.9)	9 (2.8)		7 (1.9)	13 (3.6)	

[a]Early stage was defined as LAI initiation at ≤ 3 years after OAP initiation. Late stage was defined as LAI initiation at > 3 years after OAP initiation.
[b]Standardized mean difference (SMD) = |P1 – P2|/square root of [P1(1 – P1) + P2(1 – P2)/2]. They are the same for all categorical variables with 2 levels.
[c]*P* value was generated by χ^2 test.

Table 2. All-Cause, Natural-Cause, and Unnatural-Cause Mortality and Hazard Ratios (HRs) in Patients Hospitalized With Schizophrenia Who Switched to Long-Acting Injectable Antipsychotics (LAIs) During the Early or Late Stage of Treatment Compared With Their Hospitalized Counterparts Treated With Oral Antipsychotics (OAPs)

	Early stage (N = 624)				Late stage (N = 732)			
Mortality	No. of deaths	PY	Mortality rate per 100,000 PY (95% CI)	HR (95% CI)	No. of deaths	PY	Mortality rate per 100,000 PY (95% CI)	HR (95% CI)
All-cause mortality								
LAIs	25	3,354	7 (5–11)	0.49 (0.27–0.87)*	26	1,870	14 (9–20)	1.50 (0.80–2.82)
OAPs	37	3,197	11 (8–16)	Ref	19	1,866	10 (6–15)	Ref
Natural mortality								
LAIs	10	3,269	3 (2–6)	0.30 (0.15–0.60)*	12	1,833	6 (4–12)	1.38 (0.72–2.64)
OAPs	23	3,110	7 (5–11)	Ref	10	1,832	5 (3–10)	Ref
Unnatural mortality								
LAIs	15	3,292	5 (3–8)	0.71 (0.40–1.28)	14	1,828	8 (5–9)	1.63 (0.86–3.08)
OAPs	14	3,022	5 (3–8)	Ref	9	1,836	5 (3–9)	Ref

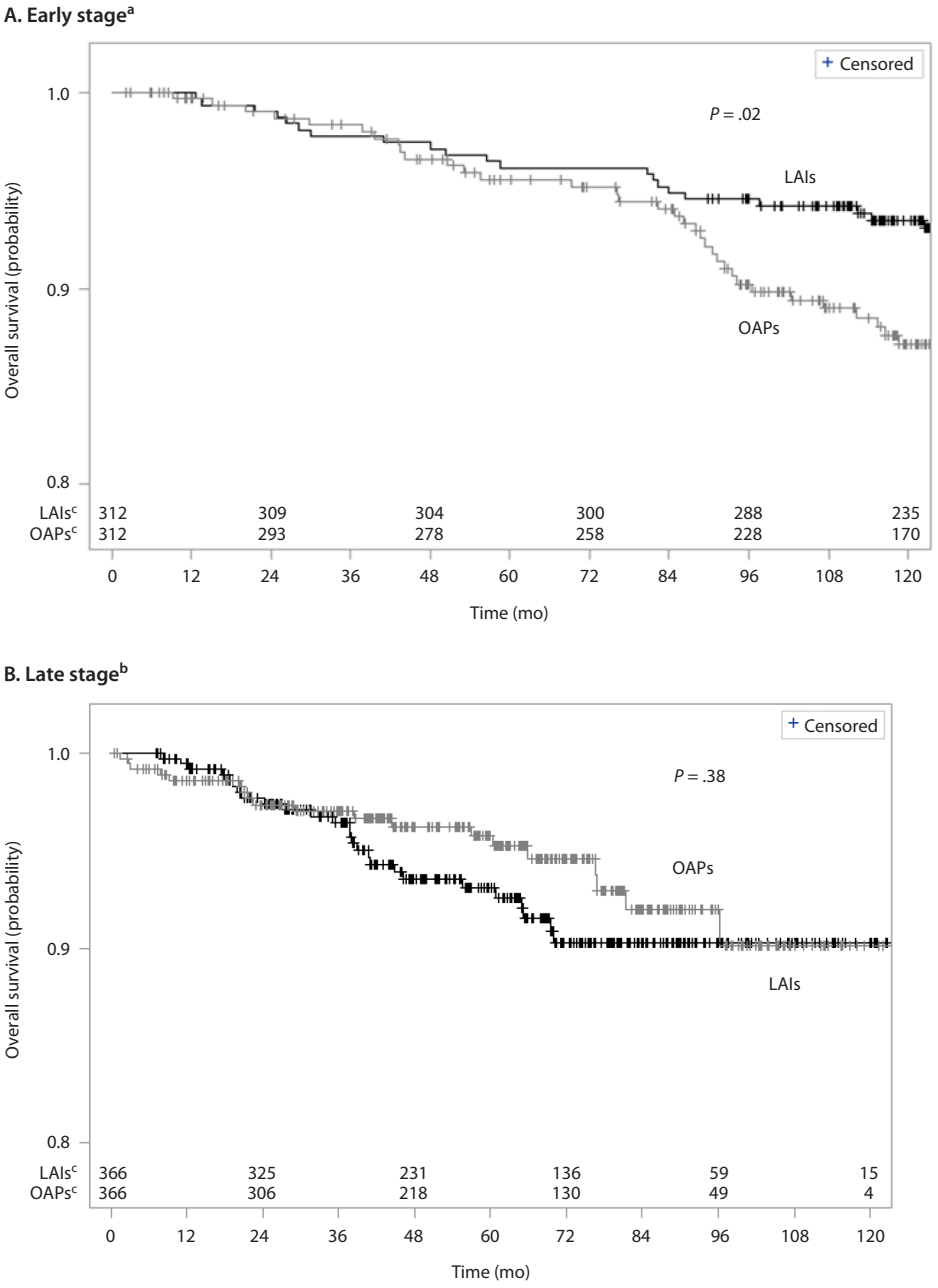
[a]Early stage was defined as LAI initiation at ≤ 3 years after OAP initiation. Late stage was defined as LAI initiation at > 3 years after OAP initiation.
*$P < .05$.
Abbreviations: CI = confidence interval, PY = person-years, Ref = reference.

not benefit patients who received LAI antipsychotics after 3 years of OAP initiation. The survival curves of patients who received LAI antipsychotic treatment during early (≤ 3 years) and late (> 3 years) stages of treatment and their matched OAP counterparts are presented in Figure 2. In Figure 2A, patients who switched to LAIs during the early stages of treatment demonstrated significantly better survival than those treated with OAPs alone. In contrast, patients who received LAIs during later stages (> 3 years) did not experience better survival compared to their reference counterparts (Figure 2B).

Antipsychotic Adherence, Rehospitalizations, and ER Visits

We examined antipsychotic adherence from the index date to the date of rehospitalization. Results showed

Figure 2. All-Cause Survival Associated With Adding or Switching to Long-Acting Injectable Antipsychotics (LAIs) and Those Remaining on Oral Antipsychotics (OAPs) in Patients With Schizophrenia by Stage of Treatment



[a]Early stage was defined as LAI initiation at ≤ 3 years after OAP initiation.
[b]Late stage was defined as LAI initiation at > 3 years after OAP initiation.
[c]Number of "at risk" patients at a given time point. The *P* values shown are results from log-rank tests.

that patients who switched to LAIs demonstrated better adherence than those who only received OAPs in both the early and late stages of treatment. Mean MPRs were 0.71 (SD = 0.36) for the LAI group and 0.54 (SD = 0.25) for the OAP groups ($P < .0001$) in the early stage. Mean MPRs were 0.70 (SD = 0.34) for the LAI group and 0.59 (SD = 0.26) for the OAP groups ($P = .01$) in the late stage.

Patients who received LAI antipsychotic treatment during early stages of their disease demonstrated a marked decrease in rehospitalizations, psychiatric rehospitalizations, and psychiatric ER visits compared with their matched OAP counterparts (Table 3). A conditional negative binomial regression analysis showed that patients who switched to LAI therapy during early stages of treatment exhibited a lower risk of rehospitalization (IRR = 0.56, CI = 0.45–0.69), psychiatric hospitalization (IRR = 0.63, CI = 0.50–0.81), and psychiatric ER visits (IRR = 0.58, CI = 0.45–0.75) compared to patients who received OAPs. However, these protective

Table 3. Risk of Rehospitalizations, Psychiatric Rehospitalizations, and Emergency Room (ER) Visits of Patients Hospitalized With Schizophrenia Who Switched to Long-Acting Injectable Antipsychotics (LAIs) During the Early or Late Stage of Treatment Compared to Their Hospitalized Counterparts Treated With Oral Antipsychotics (OAPs)

	Early stage (N = 624)[a]				Late stage (N = 732)[a]			
	No. of patients	No. of events	IRR (95% CI)	*P* value	No. of patients	No. of events	IRR (95% CI)	*P* value
All follow-up periods								
Hospitalizations								
LAIs	268	1,747	0.56 (0.45–0.69)*	< .0001	246	1,063	1.15 (0.93–1.41)	.1978
OAPs	275	1,894	Ref		203	782	Ref	
Psychiatric hospitalizations								
LAIs	244	1,274	0.63 (0.50–0.81)*	.0002	221	858	1.34 (1.04–1.71)*	.0190
OAPs	235	1,449	Ref		146	549	Ref	
Psychiatric ER visits								
LAIs	240	1,168	0.58 (0.45–0.75)*	< .0001	226	584	0.85 (0.69–1.06)	.1590
OAPs	237	1,266	Ref		222	618	Ref	
First year after the index date								
Hospitalizations								
LAIs	98	152	0.54 (0.38–0.75)*	.0003	110	168	1.36 (0.93–1.98)	.1083
OAPs	113	200	Ref		67	109	Ref	
Psychiatric hospitalizations								
LAIs	94	141	0.58 (0.41–0.83)*	.0024	101	147	1.39 (0.94–2.20)	.0921
OAPs	100	170	Ref		63	97	Ref	
Psychiatric ER visits								
LAIs	65	111	0.21 (0.11–0.40)*	< .0001	89	207	1.07 (0.67–1.72)	.7700
OAPs	59	163	Ref		80	168	Ref	
Second year after the index date								
Hospitalizations								
LAIs	94	147	0.71 (0.50–1.00)	.0560	110	180	1.76 (1.24–2.48)*	.0014
OAPs	92	163	Ref		62	95	Ref	
Psychiatric hospitalizations								
LAIs	88	130	0.72 (0.51–1.03)	.0746	106	168	1.96 (1.37–2.80)*	.0002
OAPs	81	136	Ref		54	81	Ref	
Psychiatric ER visits								
LAIs	51	90	0.64 (0.38–1.06)	.0876	94	231	1.36 (0.90–2.05)	.1415
OAPs	63	109	Ref		82	161	Ref	

[a]Early stage was defined as LAI initiation at ≤ 3 years after OAP initiation. Late stage was defined as LAI initiation at > 3 years after OAP initiation.
*$P < .05$.
Abbreviations: CI = confidence interval, IRR = incidence rate ratio, Ref = reference.

effects were not observed in patients who initiated LAI treatment during later stages of schizophrenia (Table 3). In fact, those patients had a higher risk of psychiatric rehospitalization (34%) compared to patients who only received OAPs.

We also found that patients who received LAIs during the early stages of treatment were less likely to become hospitalized and make ER visits within the first year after switching to LAIs (Table 3). However, those effects were not observed in patients who switched to LAIs during the late stages of treatment (Table 3).

DISCUSSION

In this population-based cohort study, we reveal profound impacts of using LAIs on mortality and rehospitalizations during the early stages of treatment for patients hospitalized for schizophrenia. We selected hospitalized schizophrenia patients who were having an active psychotic episode. Within this group, patients who switched to LAIs during hospitalization within the first 3 years of OAP initiation showed significant reductions in all- and natural-cause mortality compared to those who received OAPs. Those patients also demonstrated a decreased risk of rehospitalizations and psychiatric ER visits during the follow-up period. However, these improvements in survival and disease control were not observed in patients who undertook LAI treatment after 3 years of OAP initiation. These real-world data demonstrated that LAIs in the early stage of treatment of hospitalized patients increased disease control and had long-term benefits.

Previous studies showed that patients who received LAIs after their first hospitalization had lower rehospitalization rates than those who received OAPs.[2,22,23] However, those studies did not address the treatment duration or the effectiveness of switching to LAIs in the early stage of schizophrenia. In this study, we adopted a prevalent new-user comparative cohort design. This design enabled us to conduct a head-to-head comparison between LAIs and OAPs by enrolling all patients including those who switched from OAPs and considered the disease duration as a matched covariate. Our previous study showed that LAIs were generally associated with a decrease in all-cause mortality compared to OAPs using this approach.[12] This study further

demonstrated that early use of LAIs in patients requiring psychiatric hospitalization was associated with decreased rehospitalizations, ER use, and mortality.

Our findings suggest that patients who switched to LAIs during an early stage of treatment had decreased mortality compared with those who did not. These findings are built upon the "critical period" hypothesis[24] that patients in first 2–3 years of schizophrenia exert strong biological and psychosocial influences on long-term consequences. Consistent antipsychotic treatment during this period was found to be associated with decreased risks of rehospitalizations and death.[8,25,26] The superiority of LAIs in benefiting symptom control, enhancing treatment responses, and preventing relapses during the critical period can partly be explained by better medication adherence during early schizophrenia, as previously reported.[27,28] Consistently, our data indicated that LAI-treated patients showed better adherence and had lower risks of inpatient and ER visits in the first and second years after switching to LAIs. Better early-stage medication adherence in LAI-treated patients may have long-term impacts. We observed improved antipsychotic adherence in patients who switched to LAIs in the late stage of treatment. However, the risks of relapse and mortality did not decrease in those patients. Psychosis is believed to have neurotoxic effects, and the duration of untreated schizophrenic psychosis may directly affect neurocognitive functioning or the brain structure.[29] Patients in the later stages of schizophrenia, especially those who require hospitalization, may represent a group of patients whose condition is unstable. Our results are in line with previous literature showing that patients with a longer duration of illness are less likely to achieve remission compared to patients experiencing a first episode.[30,31] This may partly explain the lack of LAI-mediated protective effects in patients who adopted LAIs in the late stage. Additional studies exploring the association of LAIs and the improvement of patients with schizophrenia in terms of the brain structure between early and late stages are required to fully address these questions. In addition, the survival benefit of LAIs in the early stage appeared mostly after 24–48 months, and one possible reason is that we required patients to have received at least 6 prescriptions of LAIs or OAPs after the index date to be included in the study. Therefore, both groups had good treatment adherence at the beginning of follow-up. Our results may reflect the level of adherence after the first year between LAIs and OAPs.

Strengths and Limitations

The major strength of this study is its population-based design. The prevalent new-user cohort design, including patients with previous events, allowed data collection from most patients exposed to LAIs. Hospitalization was considered a reasonable indication of disease severity. In this study, we constructed our cohort from patients who were hospitalized for schizophrenia to ensure the comparability of disease severity. By adopting this approach in hospitalized patients, we increased the comparability of these two groups to avoid selection bias.

Additionally, our follow-up data allowed us to examine long-term mortality as our primary outcome. In this study, we considered the disease duration and psychiatric comorbidities at the baseline, which provided a relatively fair indication of the comparative effectiveness between LAIs and OAPs. Lastly, we evaluated psychiatric inpatient and ER visits. All results indicated improvements in patients who switched to LAIs in the first 3 years of a schizophrenia diagnosis (OAP initiation).

Several limitations need to be addressed. First, due to the nature of observational studies, there is potential for residual confounding in our study. However, we made great efforts to minimize this potential bias by stringently selecting a matched cohort using the duration of OAP treatment, year of the first antipsychotic treatment, and baseline psychotic comorbidities. Second, lifestyle factors, socioeconomic status, patients' social support, and psychiatrists' personal preferences were not included in our study. We cannot completely rule out the possibility that those factors may have influenced the outcomes of patients. In addition, only 5% of our base cohort were prescribed LAIs at least 6 times within 1 year after discharge, which was lower than the rate in other countries.[25] Our study cohort was composed with patients in 2002–2005, and LAIs had not been widely adopted during that period in Taiwan. We cannot totally avoid the possibility that those early adaptors of LAIs may also experience a better treatment environment that resulted in better patient outcomes. Third, we required patients to have received at least 6 prescriptions of either LAIs or OAPs. A potential immortal time bias may have affected the results of both mortality and adherence in this initial period. However, mortality, hospitalizations, and psychiatric ER visits did not significantly differ between the LAI and OAP groups. Thus, the likelihood of an immortal time bias in our study was deemed to be low. Fourth, because of the limited event number of suicides, we were unable to individually examine this underlying cause. Instead, we examined heterogeneous outcomes of unnatural-cause mortality which included accidents, suicides, and homicides. Also, the risk of suicide is usually low during hospitalization and in patients requiring enhanced medical attention. Fifth, we did not match the type of antipsychotics and were unable to match them based on the medical illness (eg, using the CCI) in the final analysis.

CONCLUSIONS

Using LAIs in the early stage of schizophrenia profoundly increased treatment adherence and decreased rehospitalizations and psychotic ER visits, leading to improved long-term outcomes, including all-cause mortality. Thus, more active consideration of LAIs in this stage should be encouraged.

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