

Time to rehospitalization in involuntarily hospitalized individuals suffering from schizophrenia discharged on long-acting injectable antipsychotics or oral antipsychotics

Ching-Hua Lin , Hung-Yu Chan , Fu-Chiang Wang  and Chun-Chi Hsu 

Abstract

Background: Involuntarily hospitalized individuals suffering from schizophrenia often have a poorer prognosis after discharge.

Objective: This study aimed to analyze time to rehospitalization within 6 months of discharge in involuntarily hospitalized individuals suffering from schizophrenia discharged on long-acting injectable antipsychotics (LAIs) or oral antipsychotics (OAPs). In addition, temporal trends in LAI use at discharge were explored.

Methods: Involuntarily hospitalized individuals suffering from schizophrenia discharged from the study hospital between 2006 and 2019 ($n = 806$) were included in the analysis. Survival analysis was used to compare time to rehospitalization within 6 months of discharge between individuals discharged on LAIs and OAPs, and between first-generation antipsychotic (FGA) LAIs and second-generation antipsychotic (SGA) LAIs. The Cochran–Armitage trend test was used to test whether a temporal trend existed for LAIs use at discharge during the study period.

Results: The LAIs group ($n = 231$) had a significantly lower rate of rehospitalization and a significantly longer time to rehospitalization than the OAPs group ($n = 575$). Rehospitalization rate and time to rehospitalization were not significantly different between individuals discharged on FGA-LAIs and SGA-LAIs. LAIs use at discharge grew significantly from 16.77% in 2006 to 50.00% in 2019 ($Z = 6.81$, $p < 0.0001$). Among all LAIs, only use of SGA-LAIs at discharge increased significantly ($Z = 5.74$, $p < 0.0001$), but not FGA-LAIs.

Conclusions: LAIs were superior to OAPs in preventing rehospitalization. However, SGA-LAIs were comparable with FGA-LAIs in reducing rehospitalization risk. Use of LAIs increased significantly in discharged involuntarily hospitalized individuals during the study period, especially SGA-LAIs.

Keywords: involuntary admission, long-acting injectable antipsychotics, rehospitalization, schizophrenia, second-generation antipsychotics

Received: 23 October 2021; revised manuscript accepted: 14 January 2022.

Introduction

Schizophrenia is a chronic mental illness characterized by severe and often persistent symptoms and recurrent relapses. Antipsychotic medications are a cornerstone of effective treatment for schizophrenia; however, the individuals' lack of insight, comorbidities of schizophrenia, and side

effects of antipsychotic medications often make long-term medication adherence challenging.^{1–5} If an individual presents with severe psychosis, a serious risk of harm to self or others, or an inability to provide self-care, thus making outpatient treatment unsafe or ineffective, hospitalization is required.^{6,7} If said individual does not agree to

Ther Adv Psychopharmacol

2022, Vol. 12: 1–12

DOI: 10.1177/
20451253221079165

© The Author(s), 2022.
Article reuse guidelines:
sagepub.com/journals-
permissions

Correspondence to:
Hung-Yu Chan
Department of General
Psychiatry, Taoyuan
Psychiatric Center, No.
71, Long-Show Street,
Taoyuan City 33058.

Department of Psychiatry,
National Taiwan University
Hospital, College of
Medicine, National Taiwan
University, Taipei
jan30@seed.net.tw

Ching-Hua Lin
Kaohsiung Municipal Kai-
Sryan Psychiatric Hospital,
Kaohsiung

Department of Psychiatry,
School of Medicine,
College of Medicine,
Kaohsiung Medical
University, Kaohsiung

Fu-Chiang Wang
Kaohsiung Municipal Kai-
Sryan Psychiatric Hospital,
Kaohsiung

Chun-Chi Hsu
Department of General
Psychiatry, Taoyuan
Psychiatric Center,
Taoyuan City

hospitalization, involuntary hospitalization will be ordered to prevent suicidal or violent behavior.

Prior to hospitalization, involuntarily hospitalized individuals typically have little insight into their mental illness and lack adherence to treatment.^{8,9} Insight into illness and positive attitudes toward treatment have been regarded as strong influences for a positive long-term outcome in individuals suffering from schizophrenia.¹⁰ After discharge, involuntarily hospitalized individuals often continue to have lower levels of medication adherence. They are also likely to feel coerced into accepting outpatient treatment and are prone to skipping postdischarge outpatient appointments.^{11,12} Another factor to take into consideration is the adaption to daily life after a recent hospital discharge. After an extended stay within the protected environment of the hospital, returning to family and the community can be especially difficult for an individual. As it is anticipated that many prehospitalization stressors, for example, securing a job, housing, and treatment providers, still remain and reexposure is eminent.¹³ Consequently, involuntarily hospitalized individuals have a higher risk of subsequent psychiatric rehospitalizations.¹⁴⁻¹⁷

Long-acting injectable antipsychotics (LAIs) were originally developed to maintain relatively stable blood levels while eliminating the need for daily dosing through biweekly, monthly, or 3-month injections in individuals suffering from schizophrenia, thus useful in individuals suffering from frequent relapses or a history of nonadherence to oral antipsychotics (OAPs).^{6,18-23} Awareness of adherence is also enhanced, as lack of adherence to treatment will be immediately noticed by the clinician if the individuals missed a scheduled injection.⁶ Therefore, LAIs can reduce symptom severity, lengthen the time to discontinuation, and consequently reduce the risk of further hospitalizations.²⁴⁻²⁷ A recent meta-analysis²⁸ concludes that LAIs are significantly and consistently more efficacious than OAPs in preventing hospitalization of individuals suffering from schizophrenia in randomized trials, mirror image studies, and cohort studies. However, LAIs also have certain disadvantages, such as requiring a longer time to reach a steady-state plasma concentration, less flexibility of dose adjustment, delayed disappearance of side effects, pain at the injection site, and perception of stigma and coercive intervention.¹⁹

We hypothesized that use of LAIs during postdischarge treatment may facilitate continuity of

treatment and avoid deterioration of symptoms for involuntarily hospitalized individuals. In keeping with this assumption, LAIs would be superior to OAPs in reducing the risk of rehospitalization in these individuals. To test this hypothesis, we conducted a hospital-based study under real-world clinical conditions to investigate the effectiveness of LAIs. The primary goal of our study was to examine the risk of rehospitalization within 6 months of discharge from a large public psychiatric hospital in involuntarily hospitalized individuals suffering from schizophrenia discharged on LAIs *versus* OAPs. Covariates that may impact time to rehospitalization were adjusted for. LAIs used include both the first-generation LAIs (FGA-LAIs) and the second-generation LAIs (SGA-LAIs). As SGA-LAIs have been available in Taiwan since 2004, the secondary goal of this study was to explore whether SGA-LAIs were superior to FGA-LAIs in lowering the risk of rehospitalization. The final goal was to test whether a temporal trend existed for LAI use at discharge during the study period.

Methods

Ethics statement

The current study was approved by the Kai-Syuan Psychiatric Hospital Institutional Review Board (IRB number: KSPH-2020-08) and carried out in accordance with both the Declaration of Helsinki (2013) and Taiwan's national legislation (the Human Subjects Research Act). Informed consent was not required, as this was a register-based study using anonymized data.

Subjects

This observational study with a retrospective cohort design was conducted at Kaohsiung Municipal Kai-Syuan Psychiatric Hospital, an 820-bed public psychiatric hospital located in southern Taiwan, providing comprehensive inpatient and outpatient psychiatric services. Catchment area of the hospital includes both urban and rural regions, with a total population of about 2.7 million.

All study participants were inpatients and met the *Diagnostic and Statistical Manual of Mental Disorders, Fourth Edition, Text Revision (DSM-IV-TR)* or *Fifth Edition (DSM-5)* criteria for either schizophrenia or schizoaffective disorder.^{29,30} Only individuals who were involuntarily admitted and discharged on LAIs or OAPs between 1 January 2006 and 31 December 2019 were

included in the analysis. Every episode of involuntary hospitalization involved individual refusing inpatient treatment and meeting the legal requirements mandated by Taiwan's Mental Health Act.³¹ The diagnoses were made by board-certified psychiatrists and supported by clinical observations and interviews during hospitalization, past medical records, and information provided by main caregivers. If an individual experienced involuntary hospitalization more than once during the study period, each hospitalization was viewed as an independent event.

Follow-up procedures

After discharge, the individuals attended follow-up at the outpatient clinics at Kai-Syuan Psychiatric Hospital. In addition, the nursing staff made follow-up calls every 2 weeks in the first month after discharge, providing psychoeducation and monitoring clinical condition. For the next 5 months, similar calls were made monthly.

Generally, medications that were found effective for acute phase treatment will be continued after entering the maintenance phase of treatment.⁶ As individuals were usually discharged after a period of stabilization, the medications they were discharged on were continued after discharge. Per Taiwan National Health Insurance Administration policy, refill prescriptions were available for individuals suffering from stable chronic illnesses. These prescriptions were valid for no more than 90 days and could be filled up to 3 times.

The frequency of outpatient follow-up visits was based on the individual's clinical condition and ranged from weekly, biweekly, monthly to tri-monthly. Apart from routine education and counseling, no other specialized care or therapy was provided. Treatment discontinuation was defined as lack of attendance at the outpatient clinic for more than 3 months during the 6-month follow-up period. Date of the last outpatient visit was used as the discontinuation date. For individuals without any outpatient visit after discharge, the date of discharge was used as the discontinuation date. Rehospitalization was used as a proxy for relapse, as it has been widely used across studies.³²

Statistical analyses

Time to rehospitalization within 6 months of discharge was used as the primary outcome measure in this study. Comparisons of LAIs *versus* OAPs

and FGA-LAIs *versus* SGA-LAIs were conducted. All tests were two-tailed and statistical significance was defined as an alpha value of <0.05. Data were analyzed using the SPSS version 27.0 (IBM Corp., Armonk, NY, USA), SAS 9.3 software (SAS Institute Inc., Cary, NC, USA), and MedCalc (MedCalc Software, Belgium).

Pearson's chi-square test, the independent *t* test, and the Mann-Whitney *U* test were used to compare demographic and clinical characteristics between groups. Kaplan-Meier survival analysis was used to determine time to rehospitalization and time to treatment discontinuation, and the statistical significance of between-group differences was analyzed using the log rank test. The Cox proportional hazards multivariate regression model, with treatment (LAIs or OAPs) as a fixed factor, was used to adjust for covariates that may affect time to rehospitalization. Covariates used in the model included gender, age, age at onset, length of hospital stay (days), and number of previous hospitalizations. Results are presented as adjusted hazard ratios (AHRs) with associated 95% confidence intervals (CIs). The Cochran-Armitage trend test was used to evaluate the statistical significance of temporal trends in the rate of involuntary hospitalization among individuals suffering from schizophrenia discharged during study period, as well as rates of LAI, FGA-LAI, and SGA-LAI use at discharge among involuntarily hospitalized individuals.

Sensitivity analysis

A sensitivity analysis was also conducted to validate our primary findings. In the sensitivity analysis, if an individual was involuntarily admitted multiple times during the study period, only the last hospitalization was included. As mentioned above, LAIs are commonly used as a treatment of last resort for individuals suffering from multi-episode schizophrenia or a history of nonadherence to OAPs.^{6,18-23}

Results

Demographic and clinical characteristics

A total of 15,114 individuals suffering from schizophrenia were discharged during the study period. Among the 15,114 individuals, 806 were admitted involuntarily. Among the 806 involuntarily hospitalized individuals, 231 (28.7%) were discharged on LAIs and 575 (71.3%) were discharged on OAPs. Among the 231 individuals treated with

Table 1. Characteristics and demographic data of the cohort.

	Total (N = 806)	LAI ^a (n = 231)	OAP ^b (n = 575)	<i>p</i>
Sex				0.011^c
Male, <i>n</i> (%)	345 (42.8)	115 (49.8)	230 (40.0)	
Female, <i>n</i> (%)	461 (57.2)	116 (50.2)	345 (60.0)	
Age (year), mean (SD)	42.4 (11.1)	45.3 (10.3)	41.2 (11.2)	<0.001^d
Age at onset (year), mean (SD)	35.9 (11.8)	37.4 (11.8)	35.2 (11.8)	0.018^d
No. of previous hospitalizations, mean (SD)	1.4 (2.3)	1.7 (2.5)	1.3 (2.2)	0.024^d
Length of hospital stay (days)	112.4 (239.6)	86.8 (120.1)	122.7 (272.7)	0.002^e
SD, standard deviation. Statistically significant values are in bold. ^a LAI _s = long-acting injectable antipsychotics. ^b OAP _s = oral antipsychotics. ^c Pearson's χ^2 test. ^d Independent <i>t</i> test. ^e Mann-Whitney <i>U</i> test.				

LAI_s, 186 (80.5%) received FGA-LAI_s [flupenthixol decanoate = 13.4% (*n* = 25), haloperidol decanoate = 86.6% (*n* = 161)] and 45 (19.5%) received SGA-LAI_s [risperidone LAI = 88.9% (*n* = 40), 1-month formulation of paliperidone LAI = 11.1% (*n* = 5)]. The most frequently prescribed OAP was haloperidol (*n* = 228), followed by risperidone (*n* = 157). Furthermore, the most frequently prescribed LAI was haloperidol decanoate (*n* = 161), followed by risperidone LAI (*n* = 40). During 6-month follow-up period after discharge, 264 (32.8% = 264/806) individuals were rehospitalized and 145 (18.0% = 145/806) individuals discontinued treatment.

LAI_s Versus OAP_s

Comparisons between the LAI_s group and the OAP_s group are shown in Table 1. Compared with the OAP_s group, individuals in the LAI_s group were more likely to be male, of older age, had a later age of onset, a greater number of previous hospitalizations, and a shorter length of hospital stay.

Sixty (26.0%) individuals in the LAI_s group and 204 (35.5%) in the OAP_s group were rehospitalized within 6 months of discharge. Compared with the OAP_s group, individuals in the LAI_s group had a significantly lower rate of rehospitalization [LAI_s = 26.0% (60/231); OAP_s = 35.5% (204/575); $\chi^2 = 6.758$, *df* = 1, ***p* = 0.009**], a

longer time to rehospitalization (LAI_s, mean time \pm SE = 148.5 \pm 4.0 days; OAP_s, mean time \pm SE = 129.5 \pm 3.1 days; log rank = 12.127, *df* = 1, ***p* < 0.001**; median time to rehospitalization was not reached for two groups) (Figure 1), a lower treatment discontinuation rate [LAI_s = 12.6% (29/231); OAP_s = 20.2% (116/575); $\chi^2 = 6.458$, *df* = 1, ***p* = 0.011**], and a longer time to treatment discontinuation (LAI_s, mean time \pm SE = 160.5 \pm 3.5 days; OAP_s, mean time \pm SE = 146.7 \pm 2.9 days; log rank = 7.907, *df* = 1, ***p* = 0.005**; median time to discontinuation was not reached for two groups) (Figure 2).

After adjusting for covariates (i.e. gender, age, age at onset, number of previous hospitalizations, and length of hospital stay) using the Cox proportional hazards multivariate regression model, LAI use at discharge was still associated with a significantly longer time to rehospitalization [AHR = 0.597; 95% confidence interval (CI) = 0.443–0.804, ***p* = 0.001**] (Table 2) and treatment discontinuation (AHR = 0.570; 95% CI = 0.376–0.863, ***p* = 0.008**) (data not shown in the table). Other factors that were found to be associated with a longer time to rehospitalization included fewer previous hospitalizations and a shorter length of hospital stay (Table 2), whereas a later age at onset (AHR = 1.039; 95% CI = 1.008–1.070, ***p* = 0.012**) and fewer previous hospitalizations (AHR = 0.851; 95% CI = 0.751–0.965, ***p* = 0.012**) were associated with a longer time to treatment discontinuation.

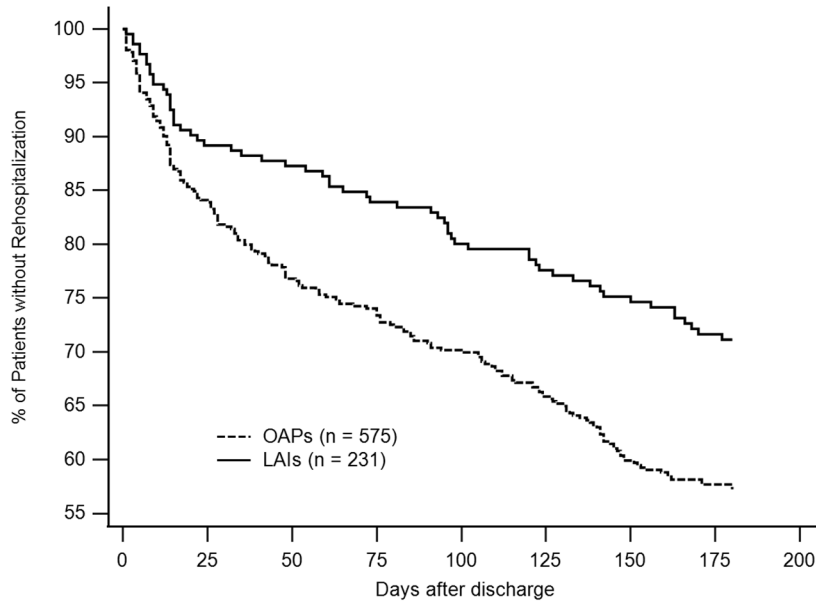


Figure 1. Time to rehospitalization in individuals discharged on LAIs or OAPs (log rank = 2.127, $df = 1$, $p < 0.001$).

LAIs = long-acting injectable antipsychotics, OAPs = oral antipsychotics.

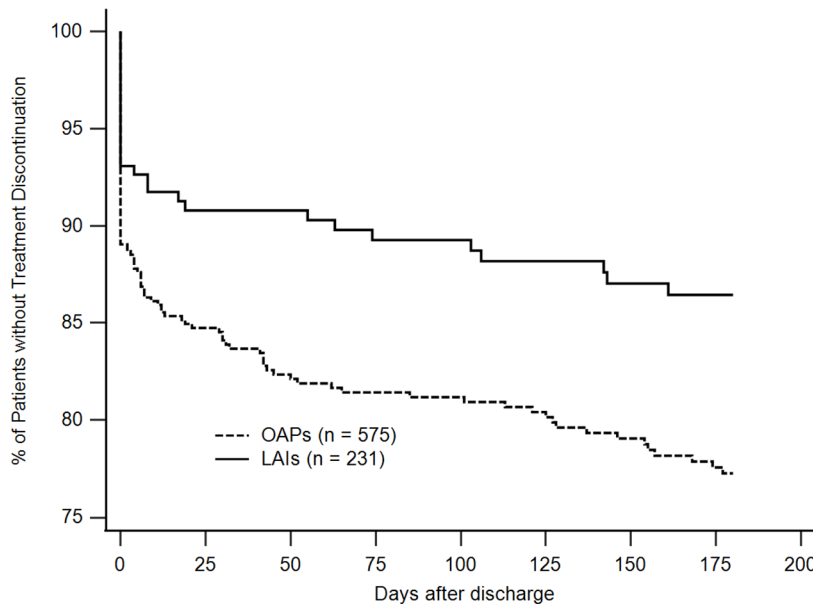


Figure 2. Time to treatment discontinuation in individuals discharged on LAIs or OAPs (log rank = 7.907, $df = 1$, $p = 0.005$).

LAIs = long-acting injectable antipsychotics, OAPs = oral antipsychotics.

FGA-LAIs Versus SGA-LAIs

Rate of rehospitalization [FGA-LAIs = 24.7% (46/186), SGA-LAIs = 31.1% (14/45), $\chi^2 = 0.767$, $df = 1$, $p = 0.381$], time to rehospitalization (FGA-LAIs, mean time \pm SE = 150.4 \pm 4.4 days; SGA-LAIs, mean time \pm SE = 141.2 \pm 9.3

days; log rank test = 0.600, $df = 1$, $p = 0.439$), treatment discontinuation rate [FGA = 12.4% (23/186), SGA = 13.3% (6/45), $\chi^2 = 0.031$, $df = 1$, $p = 0.860$], and time to discontinuation (FGA, mean time \pm SE = 159.4 \pm 4.1 days; SGA, mean time \pm SE = 164.7 \pm 6.6 days; log

rank test = 0.030, $df = 1$, $p = 0.863$) were comparable between individuals discharged on FGA-LAIs and SGA-LAIs. After adjusting for covariates (i.e. gender, age, age at onset, number of previous hospitalizations, and length of hospital stay) using Cox proportional hazards multivariate regression, time to rehospitalization (AHR = 1.186; 95% CI = 0.631–2.232, $p = 0.596$) and time to treatment discontinuation (AHR = 1.157; 95% CI = 0.463–2.893, $p = 0.755$) remain comparable between the two groups (data not shown in the table). A significantly higher proportion of individuals received anticholinergic medications in the FGA-LAIs group (63.4% = 118/186) than the SGA-LAIs group (33.3% = 15/45) ($\chi^2 = 13.447$, $df = 1$, $p < 0.001$).

Trends in rates of involuntary hospitalization and LAI use at discharge among involuntarily hospitalized individuals

Table 3 lists rates of involuntary hospitalization and the LAI use at discharge among involuntarily hospitalized individuals between 2006 and 2019. Results of the Cochran–Armitage trend test revealed a significant decreasing trend in rates of involuntary hospitalization (15.94% in 2006 and 0.78% in 2019, $Z = 5.33$, $p < 0.0001$) and an increasing trend in LAI use at discharge among involuntarily hospitalized individuals (16.77% in 2006 and 50.00% in 2019, $Z = 6.81$, $p < 0.0001$). Individual rates for FGA-LAI and SGA-LAI use at discharge were also collected to determine their respective contribution to the increase in LAI use. The results showed FGA-LAI use at discharge did not significantly change during the study period (16.77% in 2006 and 12.50% in 2019, $Z = 1.54$, $p = 0.20$), whereas SGA-LAI use significantly increased (0.00% in 2006 and 37.50% in 2019, $Z = 5.74$, $p < 0.0001$).

Sensitivity analysis

The results of the sensitivity analysis were in line with the primary analysis.

When only the last episode of involuntary hospitalization of each participant was included in the analysis, the LAIs group ($n = 178$) still had a significantly lower rate of rehospitalization [LAIs = 20.2% (36/178); OAPs = 30.9% (147/475); $p = 0.007$], a longer time to rehospitalization (LAIs, mean time \pm SE = 157.4 \pm 4.0 days; OAPs, mean time \pm SE = 133.9 \pm 3.4 days; log rank = 12.713, $df = 1$, $p < 0.001$), a

lower treatment discontinuation rate [LAIs = 16.3% (29/178); OAPs = 24.2% (115/475), $p = 0.030$], and a longer time to treatment discontinuation (LAIs, mean time \pm SE = 155.1 \pm 4.5 days; OAPs, mean time \pm SE = 140.2 \pm 3.4 days; log rank = 6.244, $df = 1$, $p = 0.012$) than the OAPs group ($n = 475$). After adjusting for covariates using the Cox proportional hazards multivariate regression model, LAI use at discharge was still associated with a significantly longer time to rehospitalization (AHR = 0.502; 95% CI = 0.343–0.734, $p < 0.001$) and treatment discontinuation (AHR = 0.612; 95% CI = 0.403–0.930, $p = 0.021$).

Discussion

The primary finding of this study was, compared with individuals treated with OAPs, individuals treated with LAIs had a significantly lower rate of rehospitalization and a significantly longer time to rehospitalization. The results imply that individuals on LAIs are generally more symptomatically stable and less likely to experience worsening of psychotic symptoms and consequent rehospitalizations. This may be due to the long elimination half-life of LAIs, which contributes to sustained therapeutic plasma medication levels. Discontinuation of LAIs can continue small decrements in antipsychotic levels on plasma and in brain. Such decreasing antipsychotic level so slowly may lessen abrupt increases in dopamine activity. Therefore, time to relapse could be prolonged.³³ In contrast, OAPs are readily eliminated from the body after only several days of missed doses. Furthermore, individuals are often not completely honest about adherence to treatment with OAPs.³⁴ A common scenario is the individual dutifully fills the prescription at the pharmacy without actually taking the medications afterward. As it is widely known, nonadherence is the main reason for treatment discontinuation,³⁵ which is associated with increase in symptom severity and risk of hospitalization. This finding is in keeping with previous studies that compared LAIs with OAPs in involuntarily hospitalized individuals suffering from schizophrenia on outpatient treatment.^{36,37} In those studies, LAIs also resulted in better medication adherence, compared with OAPs.

The second finding was that in addition to OAP use at discharge, a greater number of previous hospitalizations and a longer length of hospital stay were also associated with a higher risk of rehospitalization (Table 2). A systematic review

Table 2. Potential factors associated with time (days) to rehospitalization in the multivariate Cox regression analysis.

Factors	<i>B</i>	Adjusted hazard ratio	95.0% CI	<i>p</i>
LAI use at discharge (yes <i>versus</i> no)	-0.516	0.597	0.443–0.804	0.001
Sex (male <i>versus</i> female)	0.036	1.037	0.804–1.338	0.779
Age	-0.0004	0.9995	0.981–1.018	0.965
Age at onset	-0.006	0.994	0.977–1.013	0.549
No. of previous hospitalizations	0.134	1.144	1.096–1.194	< 0.001
Length of hospital stay (days)	0.001	1.001	1.000–1.001	< 0.001

CI, confidence interval; LAIs, long-acting injectable antipsychotics.

Table 3. Rates of involuntary patients discharged and LAIs prescription, 2006–2019.

Year	2006	2007	2008	2009	2010	2011	2012
A ^a	1010	1049	1111	1127	1034	1068	1145
B ^b	161 (15.94%)	128 (12.2%)	112 (10.08%)	45 (3.99%)	76 (7.35%)	52 (4.87%)	53 (4.63%)
C ^c	27 (16.77%)	34 (26.56%)	29 (25.89%)	13 (28.89%)	19 (25.00%)	11 (21.15%)	20 (37.74%)
C1 ^d	27 (16.77%)	32 (25.00%)	28 (25.00%)	13 (28.89%)	16 (21.05%)	8 (15.38%)	14 (26.42%)
C2 ^e	0 (0.00%)	2 (1.56%)	1 (0.89%)	0 (0.00%)	3 (3.95%)	3 (5.77%)	6 (11.32%)
Year	2013	2014	2015	2016	2017	2018	2019
A ^a	1084	1163	1112	1136	1048	998	1029
B ^b	32 (2.95%)	30 (2.58%)	40 (3.60%)	29 (2.55%)	25 (2.39%)	15 (1.50%)	8 (0.78%)
C ^c	16 (50.00%)	11 (36.67%)	13 (32.5%)	13 (44.83%)	12 (48.00%)	9 (60.00%)	4 (50.00%)
C1 ^d	9 (28.13%)	9 (30.00%)	9 (22.5%)	10 (34.48%)	5 (20.00%)	5 (33.33%)	1 (12.50%)
C2 ^e	7 (21.88%)	2 (6.67%)	4 (10.00%)	3 (10.34%)	7 (28.00%)	4 (26.67%)	3 (37.50%)

LAIs, long-acting antipsychotics.
^aA = Number of patients discharged, *n*.
^bB = Number of involuntary patients discharged, *n* [% = (B/A) × 100].
^cC = Number of involuntary patients discharged on LAIs, *n* [% = (C/B) × 100].
^dC1 = Number of involuntary patients discharged on first-generation antipsychotic-LAIs, *n* [% = (C1/B) × 100].
^eC2 = Number of involuntary patients discharged on second-generation antipsychotic-LAIs, *n* [% = (C2/B) × 100].

study³⁸ has found that the most consistent predictor of rehospitalization was the number of previous hospitalizations. Treatment with LAIs may be a viable choice for these individuals suffering from a high risk of rehospitalization. Another population-based, retrospective cohort study in Taiwan¹⁶ also reported that a longer length of hospital stay foretold an increase in the risk of psychiatric rehospitalization. It is possible that a longer hospital stay simply reflects more

severe symptomatology, lack of effective treatment, or inadequate psychosocial support.¹⁶ Mean length of hospital days in both OAPs group (122.7 ± 272.7) and LAIs group (86.8 ± 120.1) (Table 1) was quite long. One possibility is that chronicity, treatment resistance, poor social support, and comorbid conditions are often more common among individuals in public hospitals.³⁹ In addition, the Taiwan National Health Insurance covers almost all the

hospitalization fee for individuals suffering from schizophrenia.

The third finding was that SGA-LAIs were not superior to FGA-LAIs in reducing the risk of rehospitalization and treatment discontinuation. Previous studies also have yielded similar findings.^{35,40,41} However, compared with individuals receiving FGA-LAIs, fewer individuals in the SGA-LAIs group received concomitant anticholinergic medications. As anticholinergic medications are generally used to reduce extrapyramidal side effects, it indicates that SGA-LAIs are associated with a lower risk for extrapyramidal side effects.⁴²⁻⁴⁴

The final finding was that involuntary hospitalization decreased from 15.94% in 2006 to 0.78% in 2019 (Table 3). Taiwan's Mental Health Act was passed in 1990 and was the first attempt to regulate involuntary hospitalization in the country. A standardized criterion for involuntary hospitalization was set in the Mental Health Act, including presence of severe psychiatric symptoms that are so debilitation as to interfere with rational decision-making, danger to self or others, and recommendation for involuntary treatment by two board-certified psychiatrists. An amendment was implemented in 2008, greatly changing the legal proceedings for involuntary hospitalization. After the amendment, a government reviewing committee was set up, and henceforth all involuntary hospitalizations must be reviewed and approved by the committee within 5 days of admission. As a result, rate of involuntary psychiatric hospitalization has decreased over time in Taiwan.⁴⁵⁻⁴⁷

The increase in LAI use over time seen in this study can probably be attributed to growing familiarity and positive clinical experience with LAIs among clinicians, and improvements in quality and availability of education programs on LAIs. In addition, the increasing body of evidence supporting the efficacy and safety of LAIs may have contributed to their rising popularity.²² Clinicians' attitudes toward LAIs may also have changed from subjective preconceptions to evidence-based decisions.⁴⁸

Furthermore, the increase in LAI use during the study period came mainly from the increase in SGA-LAI use. One possible reason behind this phenomenon is that, effectiveness and safety considerations, SGA-LAIs are more appealing to individuals suffering from schizophrenia and treating clinicians than FGA-LAIs.⁴⁹ There is an

increasing number of studies demonstrating their effectiveness and safety, which may contribute to their continuous rise in popularity.⁵⁰ As a result, clinicians may have held a more positive attitude toward SGA-LAIs over time.

This study had several strengths. First of all, observational retrospective studies such as this study often allow for better assessment of real-world effectiveness. One of the main advantages of LAIs is improved adherence; thus, the differences between OAPs and LAIs are better evaluated in naturalistic treatment settings, and even more so in long-term studies.⁵¹ Second, hospitalization is arguably the most costly and policy-relevant clinical outcome measure.⁵² Third, many relevant factors were included in the analyses and adjusted for, thus decreasing confounding. Fourth, LAIs were further grouped into the FGA-LAIs and the SGA-LAIs to investigate whether SGA-LAIs were superior to FGA-LAIs in reducing the risk of rehospitalization and treatment discontinuation. Fifth, given the considerable sample size ($n = 806$), there was enough statistical power, which helped to reduce type II error. Finally, sensitivity analysis was used to validate the primary results.

Several limitations should be considered when interpreting the results of this study. First, this was an observational retrospective study and treatment allocation was not randomized. Consequently, the results may be affected by prescribing bias. Second, LAIs that were not available during the study period, such as olanzapine LAI and aripiprazole LAI, were not included. Third, because not all clinically significant exacerbations in symptoms result in hospitalization, use of rehospitalization as a proxy for relapse may provide only a limited view on differences between LAIs and OAPs.⁵³ Fourth, owing to the retrospective design, data on many factors that could impact rehospitalization or treatment discontinuation were not available because they were not measured or recorded in the first place. Fifth, studies⁵⁴⁻⁵⁶ have reported that not all antipsychotics are equally effective. However, more case numbers are needed to explore the efficacy of different LAIs in preventing rehospitalization. In clinical practice, the choice of LAIs should be carefully discussed with the individuals about the efficacy, tolerability profile, and possible obstacles.⁵⁴ Finally, legislations for involuntary psychiatric treatment differ across countries; therefore, the results of this study may not be generalizable.

Conclusions

LAI were found to be superior to OAPs in reducing the risk of rehospitalization and treatment discontinuation within 6 months of discharge among involuntarily hospitalized individuals suffering from schizophrenia. Fewer individuals in the SGA-LAI group received concomitant anticholinergic medications than the FGA-LAI group. However, SGA-LAI were not superior to FGA-LAI in reducing the risk of rehospitalization and treatment discontinuation. A continuous increase in individuals discharged on LAIs can probably be attributed to growing experiences and success in treating individuals with LAIs among clinicians. Although the nursing staff regularly followed up on the individuals by phone during the 6-month period after discharge, treatment discontinuation rate was as high as 12.6% among individuals receiving LAIs. It reflects the fact that use of LAIs does not guarantee adherence if the individual refuses to take it outright. Furthermore, rehospitalization rate (26.0%) within 6 months of discharge remained high among individuals receiving LAIs. Further research is needed to explore whether other treatment strategies, such as discharge planning, psychoeducation programs, and community-based aftercare services,³⁸ could further reduce the risk of rehospitalization in involuntarily hospitalized individuals suffering from schizophrenia.

Author contributions

Ching-Hua Lin: Conceptualization; Data curation; Formal analysis; Investigation; Methodology; Software; Validation; Visualization; Writing – original draft; Writing – review & editing.

HY Chan: Conceptualization; Data curation; Formal analysis; Funding acquisition; Investigation; Methodology; Project administration; Resources; Software; Supervision; Writing – original draft; Writing – review & editing.

Fu-Chiang Wang: Conceptualization; Data curation; Investigation; Methodology.

Chun-Chi Hsu: Conceptualization; Investigation; Methodology; Writing – review & editing.

Conflict of interest statement

The authors declared no potential conflicts of interest with respect to the research, authorship, and/or publication of this article.

Funding

The authors disclosed receipt of the following financial support for the research, authorship,

and/or publication of this article: This work was supported by the Ministry of Health and Welfare, Taiwan (MOHW-107-47). The funding body played no role in study design, analysis, or interpretation of the study data in this paper.

ORCID iDs

Ching-Hua Lin  <https://orcid.org/0000-0003-2744-0914>

Hung-Yu Chan  <https://orcid.org/0000-0001-8479-5418>

Fu-Chiang Wang  <https://orcid.org/0000-0002-5447-782X>

Chun-Chi Hsu  <https://orcid.org/0000-0002-3891-7768>

References


1. Chan HY, Pan YJ, Chen JJ, *et al.* Time to discontinuation of second-generation antipsychotics versus haloperidol and sulpiride in people with schizophrenia: a naturalistic, comparative study. *J Clin Psychopharmacol* 2017; 37: 13–20.
2. Lin CH, Chan HY, Hsu CC, *et al.* Factors associated with laxative use in schizophrenia patients treated with second-generation antipsychotics. *Eur Neuropsychopharmacol* 2021; 43: 139–146.
3. Lin CH, Chan HY, Hsu CC, *et al.* Temporal trends in clozapine use at time of discharge among people with schizophrenia at two public psychiatric hospitals in Taiwan, 2006–2017. *Sci Rep* 2020; 10: 17984.
4. Chan HY, Chen JJ, Pan YJ, *et al.* Nicotine replacement therapy and healthy lifestyle psychoeducation for smoking reduction in acute psychiatric inpatients: a cluster-randomized parallel study. *J Clin Psychopharmacol* 2020; 40: 149–156.
5. Chan HY, Lai CL, Lin YC, *et al.* Is antipsychotic treatment associated with risk of pneumonia in people with serious mental illness? The roles of severity of psychiatric symptoms and global functioning. *J Clin Psychopharmacol* 2019; 39: 434–440.
6. American Psychiatric Association. *The American Psychiatric Association practice guideline for the treatment of patients with schizophrenia*. 3rd ed. Washington, DC: American Psychiatric Association, 2021.
7. Lehman AF, Kreyenbuhl J, Buchanan RW, *et al.* The Schizophrenia Patient Outcomes

- Research Team (PORT): updated treatment recommendations 2003. *Schizophr Bull. Schizophr Bull* 2004; 30: 193–217.
8. McEvoy JP, Applebaum PS, Apperson LJ, *et al.* Why must some schizophrenic patients be involuntarily committed? The role of insight. *Compr Psychiatry* 1989; 30: 13–17.
 9. Walker S, Mackay E, Barnett P, *et al.* Clinical and social factors associated with increased risk for involuntary psychiatric hospitalisation: a systematic review, meta-analysis, and narrative synthesis. *Lancet Psychiatry* 2019; 6: 1039–1053.
 10. Mohamed S, Rosenheck R, McEvoy J, *et al.* Cross-sectional and longitudinal relationships between insight and attitudes toward medication and clinical outcomes in chronic schizophrenia. *Schizophr Bull* 2009; 35: 336–346.
 11. Balıkcı A, Erdem M, Zıncır S, *et al.* Adherence with outpatient appointments and medication: a two-year prospective study of patients with schizophrenia. *Bull Clin Psychopharmacol* 2013; 23: 57–64.
 12. Jaeger S, Pfiffner C, Weiser P, *et al.* Long-term effects of involuntary hospitalization on medication adherence, treatment engagement and perception of coercion. *Soc Psychiatry Psychiatr Epidemiol* 2013; 48: 1787–1796.
 13. Bell Lynum KS, Henderson DC, Wright HJ, *et al.* Treatment effect with paliperidone palmitate compared with oral antipsychotics in Black/African American patients with schizophrenia and a history of criminal justice system involvement: a post hoc analysis of the PRIDE study. *J Clin Psychiatry* 2021; 82: 20m13356.
 14. Rosca P, Bauer A, Grinshpoon A, *et al.* Rehospitalizations among psychiatric patients whose first admission was involuntary: a 10-year follow-up. *Isr J Psychiatry Relat Sci* 2006; 43: 57–64.
 15. Hung YY, Chan HY and Pan YJ. Risk factors for readmission in schizophrenia patients following involuntary admission. *PLoS ONE* 2017; 12: e0186768.
 16. Lin CE, Chung CH, Chen LF, *et al.* Compulsory admission is associated with an increased risk of readmission in patients with schizophrenia: a 7-year, population-based, retrospective cohort study. *Soc Psychiatry Psychiatr Epidemiol* 2019; 54: 243–253.
 17. Silva M, Antunes A, Loureiro A, *et al.* Factors associated with length of stay and readmission in acute psychiatric inpatient services in Portugal. *Psychiatry Res* 2020; 293: 113420.
 18. Narasimhan M, Un Pae C, Masand N, *et al.* Partial compliance with antipsychotics and its impact on patient outcomes. *Int J Psychiatry Clin Pract* 2007; 11: 102–111.
 19. Brissos S, Veguilla MR, Taylor D, *et al.* The role of long-acting injectable antipsychotics in schizophrenia: a critical appraisal. *Ther Adv Psychopharmacol* 2014; 4: 198–219.
 20. Tohen M, Goldberg JF, Hassoun Y, *et al.* Identifying profiles of patients with bipolar I disorder who would benefit from maintenance therapy with a long-acting injectable antipsychotic. *J Clin Psychiatry* 2020; 81: OT19046AH1.
 21. Simpson GM. A brief history of depot neuroleptics. *J Clin Psychiatry* 1984; 45: 3–4.
 22. Correll CU, Citrome L, Haddad PM, *et al.* The use of long-acting injectable antipsychotics in schizophrenia: evaluating the evidence. *J Clin Psychiatry* 2016; 77: 1–24.
 23. Weiden PJ, Kim E, Bermak J, *et al.* Does half-life matter after antipsychotic discontinuation? A relapse comparison in schizophrenia with 3 different formulations of paliperidone. *J Clin Psychiatry* 2017; 78: e813–e820.
 24. Taylor M, Dangelo-Kemp D, Liu D, *et al.* Antipsychotic utilisation and persistence in Australia: a nationwide 5-year study. *Aust NZ J Psychiatry*. Epub ahead of print 16 October 2021. DOI: 10.1177/00048674211051618.
 25. Lin CH, Chen FC, Chan HY, *et al.* Time to rehospitalization in patients with schizophrenia receiving long-acting injectable antipsychotics or oral antipsychotics. *Int J Neuropsychopharmacol* 2019; 22: 541–547.
 26. Tiihonen J, Mittendorfer-Rutz E, Majak M, *et al.* Real-world effectiveness of antipsychotic treatments in a nationwide cohort of 29823 patients with schizophrenia. *JAMA Psychiatry* 2017; 74: 686–693.
 27. Subotnik KL, Casaus LR, Ventura J, *et al.* Long-acting injectable risperidone for relapse prevention and control of breakthrough symptoms after a recent first episode of schizophrenia. a randomized clinical trial. *JAMA Psychiatry* 2015; 72: 822–829.
 28. Kishimoto T, Hagi K, Kurokawa S, *et al.* Long-acting injectable versus oral antipsychotics for the maintenance treatment of schizophrenia: a systematic review and comparative meta-analysis of randomised, cohort, and pre-post studies. *Lancet Psychiatry* 2021; 8: 387–404.
 29. APA. *Diagnostic and statistical manual of mental disorders: DSM-IV-TR*. 4th ed., text revision.

- ed. Washington, DC: American Psychiatric Association, 2000.
30. APA. *Diagnostic and statistical manual of mental disorders: DSM-5*. Washington, DC: American Psychiatric Pub, 2013.
 31. Act TMH, 2020, <https://lawmojgovtw/ENG/LawClass/LawAllaspx?pcode=L0020030>
 32. Olivares JM, Sermon J, Hemels M, *et al.* Definitions and drivers of relapse in patients with schizophrenia: a systematic literature review. *Ann Gen Psychiatry* 2013; 12: 32.
 33. Schoretsanitis G, Kane JM, Correll CU, *et al.* Predictors of lack of relapse after random discontinuation of oral and long-acting injectable antipsychotics in clinically stabilized patients with schizophrenia: a re-analysis of individual participant data. *Schizophr Bull* 2022; 48: 296–306.
 34. Agid O, Foussias G and Remington G. Long-acting injectable antipsychotics in the treatment of schizophrenia: their role in relapse prevention. *Expert Opin Pharmacother* 2010; 11: 2301–2317.
 35. Nielsen J, Jensen SO, Friis RB, *et al.* Comparative effectiveness of risperidone long-acting injectable vs first-generation antipsychotic long-acting injectables in schizophrenia: results from a nationwide, retrospective inception cohort study. *Schizophr Bull* 2015; 41: 627–636.
 36. Swartz MS, Swanson JW, Wagner HR, *et al.* Effects of involuntary outpatient commitment and depot antipsychotics on treatment adherence in persons with severe mental illness. *J Nerv Ment Dis* 2001; 189: 583–592.
 37. Muirhead D, Harvey C and Ingram G. Effectiveness of community treatment orders for treatment of schizophrenia with oral or depot antipsychotic medication: clinical outcomes. *Aust NZ J Psychiatry* 2006; 40: 596–605.
 38. Donisi V, Tedeschi F, Wahlbeck K, *et al.* Pre-discharge factors predicting readmissions of psychiatric patients: a systematic review of the literature. *BMC Psychiatry* 2016; 16: 449.
 39. Patrick V, Schleifer SJ, Nurenberg JR, *et al.* Best practices: an initiative to curtail the use of antipsychotic polypharmacy in a state psychiatric hospital. *Psychiatr Serv* 2006; 57: 21–23.
 40. Lammers L, Zehm B and Williams R. Risperidone long-acting injection in Schizophrenia Spectrum Illnesses compared to first generation depot antipsychotics in an outpatient setting in Canada. *BMC Psychiatry* 2013; 13: 155.
 41. Yu HY, Hsiao CY, Chen KC, *et al.* A comparison of the effectiveness of risperidone, haloperidol and flupentixol long-acting injections in patients with schizophrenia—A nationwide study. *Schizophr Res* 2015; 169: 400–405.
 42. Miyamoto S, Duncan GE, Goff DC, *et al.* Therapeutics of schizophrenia. In: Davis KL, Charney D, Coyle JT, *et al.* (eds) *Neuropsychopharmacology: The fifth generation of progress*. Philadelphia, PA: Lippincott Williams & Wilkins, 2002, pp. 775–807.
 43. Chan HY, Chiang SC, Chang CJ, *et al.* A randomized controlled trial of risperidone and olanzapine for schizophrenic patients with neuroleptic-induced tardive dyskinesia. *J Clin Psychiatry* 2010; 71: 1226–1233.
 44. Chan HY, Chang CJ, Chiang SC, *et al.* A randomised controlled study of risperidone and olanzapine for schizophrenic patients with neuroleptic-induced acute dystonia or parkinsonism. *J Psychopharmacol* 2010; 24: 91–98.
 45. Wang JP, Chiu CC, Yang TH, *et al.* The low proportion and associated factors of involuntary admission in the psychiatric emergency service in Taiwan. *PLoS ONE* 2015; 10: e0129204.
 46. Hsu W-T, Wu H-C and Chou F. A history of mental health laws in Taiwan. *Taiwan J Psychiatry* 2017; 31: 195–203.
 47. Lee S-M and Liao D-L. Involuntary hospitalization review mechanism in Taiwan: lessons learned from a 12-Year experience. *Taiwan J Psychiatry* 2021; 35: 3.
 48. Liu CH, Tsai PH and Chen CY. Discrepancy in Taiwanese psychiatrists' preferences for long-acting injectable antipsychotics across facilities: a nationwide questionnaire survey. *Neuropsychiatr Dis Treat* 2018; 14: 429–433.
 49. Chan CH, Chan HY and Chen YC. Switching antipsychotic treatment to aripiprazole in psychotic patients with neuroleptic-induced tardive dyskinesia: a 24-week follow-up study. *Int Clin Psychopharmacol* 2018; 33: 155–162.
 50. Olivares JM, Pinal B and Cinos C. Comparison of long-acting antipsychotic injection and oral antipsychotics in schizophrenia. *Neuropsychiatry* 2011; 1: 275.
 51. Schooler NR. Relapse and rehospitalization: comparing oral and depot antipsychotics. *J Clin Psychiatry* 2003; 64: 14–17.
 52. Ascher-Svanum H, Zhu B, Faries DE, *et al.* The cost of relapse and the predictors of relapse in the treatment of schizophrenia. *BMC Psychiatry* 2010; 10: 2.

53. Marcus SC, Zummo J, Pettit AR, *et al.* Antipsychotic adherence and rehospitalization in schizophrenia patients receiving oral versus long-acting injectable antipsychotics following hospital discharge. *J Manag Care Spec Pharm* 2015; 21: 754–768.
54. Bertolini F, Ostuzzi G, Pievani M, *et al.* Comparing long-acting antipsychotic discontinuation rates under ordinary clinical circumstances: a survival analysis from an observational, pragmatic study. *CNS Drugs* 2021; 35: 655–665.
55. Ostuzzi G, Bertolini F, Del Giovane C, *et al.* Maintenance treatment with long-acting injectable antipsychotics for people with nonaffective psychoses: a network meta-analysis. *Am J Psychiatry* 2021; 178: 424–436.
56. Kane JM, McEvoy JP, Correll CU, *et al.* Controversies surrounding the use of long-acting injectable antipsychotic medications for the treatment of patients with schizophrenia. *CNS Drugs* 2021; 35: 1189–1205.

Visit SAGE journals online
[journals.sagepub.com/
home/tpp](https://journals.sagepub.com/home/tpp)

 SAGE journals