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Association Between Paliperidone Long-Acting Injectable Coverage and Hospitalization Burden in Patients With Schizophrenia: A Real-World Cohort Study

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Abstract

Background： Long-acting injectable antipsychotics can substantially improve effective medication coverage and are widely used in the treatment of schizophrenia. However, real-world evidence on the dose–response relationship between sustained long-acting injectable antipsychotic treatment and hospitalization burden remains limited. This study aimed to examine the association between paliperidone long-acting injectable (LAI) coverage days and hospitalization outcomes among patients with schizophrenia in routine clinical practice.

Methods： This retrospective cohort study used data from community mental health centers and psychiatric specialty hospitals across Guangdong Province, China. The study included 9,605 patients with schizophrenia who initiated paliperidone LAI treatment between April 15, 2020, and April 15, 2024, and who had experienced at least one hospitalization in the year prior to the first injection. The analysis calculated the number of paliperidone LAI coverage days during the 1-year follow-up period after the index injection and the total number of hospitalization days during the same period. Nonparametric locally weighted scatterplot smoothing (LOESS) examined the potential nonlinear association between LAI coverage and hospitalization days. The study also conducted covariate-adjusted path analyses and prespecified subgroup analyses.

Results： Among the 9,605 patients (mean [SD] age, 38.0 [10.9] years; 39.8% female), higher paliperidone LAI coverage was associated with fewer hospitalization days during follow-up. Patients with the highest coverage experienced approximately 60 fewer hospital days than those with the lowest coverage. LOESS-smoothed analyses

showed a graded inverse association between medication coverage and hospitalization days during the first year after treatment initiation, whereas no comparable gradient appeared during the year before treatment initiation. In covariate-adjusted path analyses, higher coverage remained independently associated with fewer hospitalization days (standardized $\beta = -0.347$), primarily through a direct effect. Subgroup analyses indicated that the association was particularly pronounced among male patients, younger patients, and those with a longer duration of illness.

Conclusions： Greater continuity of paliperidone long-acting injectable treatment was associated with a lower hospitalization burden among patients with schizophrenia, with stronger associations observed among men, younger patients, and those with longer illness duration. These findings support the clinical value of sustained long-acting injectable antipsychotic treatment in reducing hospitalization burden.

Key words: Schizophrenia; Long-acting injectable antipsychotics; Paliperidone; Hospitalization burden; Real-world evidence

Introduction

Schizophrenia is a chronic and severe mental disorder characterized by substantial functional impairment, recurrent relapse, and extensive use of health care resources. According to the Global Burden of Disease 2021 estimates, schizophrenia affected approximately 23 million individuals worldwide and accounted for more than 14 million disability-adjusted life years, underscoring its considerable contribution to the global burden of disease[1, 2]. In the United States, schizophrenia has been associated with substantial excess health care expenditures and with inpatient care representing a major component of overall costs. Reducing psychiatric hospital days therefore remains a central goal of both clinical management and public health strategies for schizophrenia[3].

Nonadherence to oral antipsychotic medications is common among individuals with schizophrenia and has been consistently linked to relapse and rehospitalization[4, 5]. Long-acting injectable (LAI) antipsychotics, including paliperidone palmitate, are designed to provide sustained medication delivery and reduce the need for daily oral dosing[6], and have been associated with improved treatment continuity and lower risks of psychiatric hospitalization in real-world studies[7]. Long-term mirror-image studies have also suggested marked reductions in hospitalization frequency and duration following initiation of paliperidone palmitate[8]. However, much of the existing evidence has been derived from heterogeneous patient populations, often without explicitly accounting for baseline hospitalization burden. Because patients with prior hospitalization are at substantially higher risk of subsequent rehospitalization[9, 10], the magnitude and generalizability of these associations among patients with

established hospitalization burden remain uncertain.

Moreover, the mechanisms through which LAI antipsychotics may influence hospitalization outcomes are not well understood. Although symptom improvement is commonly assumed to play a central role[11, 12], it remains unclear whether potential reductions in psychiatric hospital days is mediated by improved adherence to concomitant oral antipsychotic medications, changes in social risk profiles, or other pathways. In addition, potential heterogeneity in these associations across clinically relevant subgroups—such as stage of illness, age, and sex—has not been well characterized, limiting the ability to individualize treatment decisions in routine clinical practice.

Using population-based real-world data from multiple prefecture-level cities in Guangdong Province, China, we conducted a retrospective cohort study to examine the association between paliperidone palmitate coverage and psychiatric hospitalization among patients diagnosed with schizophrenia with prior hospitalization. We further evaluated the potential mediating roles of concurrent oral medication adherence and social risk, and assessed whether these associations varied across clinically relevant subgroups.

Methods

Study Design and Data Source

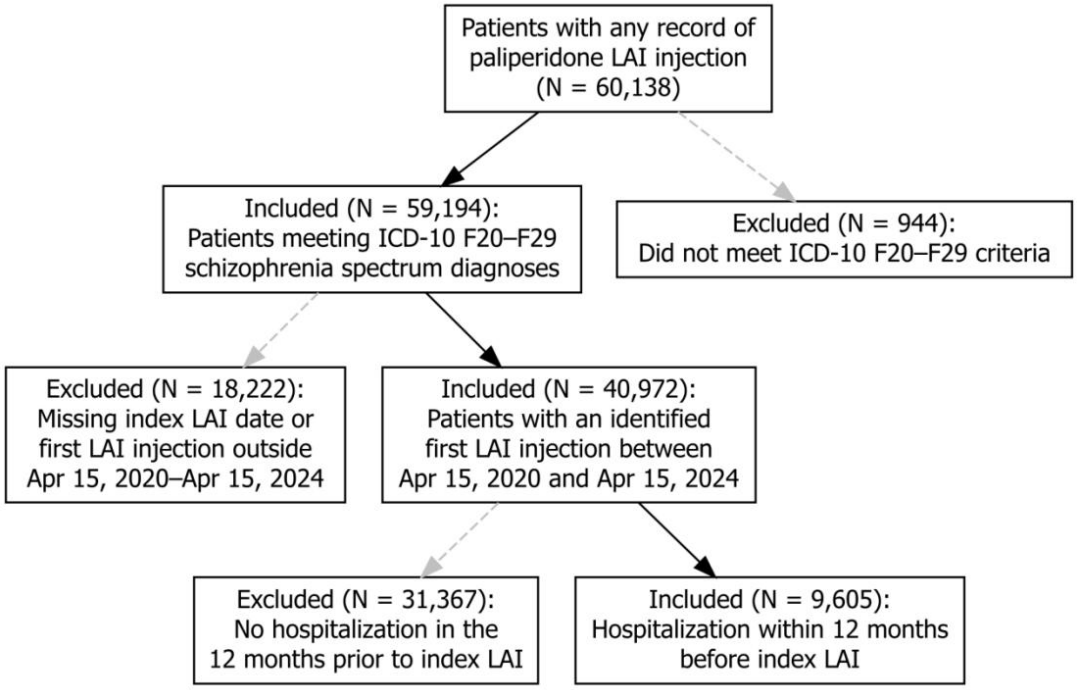
This retrospective real-world cohort study examined routinely administrative data from patients who received paliperidone LAI treatment across multiple prefecture-level cities in Guangdong Province between April 15, 2020, and April 15, 2024. The study

aimed to evaluate the association between paliperidone LAI medication coverage and hospitalization outcomes among patients with schizophrenia. We defined the observation window as 1 year before and 1 year after initiation of paliperidone LAI treatment.

Study Population

We identified eligible patients as those with a diagnosis of schizophrenia who received at least 1 paliperidone LAI injection during the study period. We defined the index date as the date of the first paliperidone LAI administration. We excluded patients with incomplete follow-up during the observation window, missing key exposure or outcome variables, or no hospitalization records during the year preceding the index date. The final analytic cohort consisted of 9,605 patients (Figure 1).

Figure 1. Flowchart of Participant Inclusion and Exclusion



Exposure Assessment

We quantified medication exposure as the number of days covered by paliperidone

LAI during the year following treatment initiation. Medication coverage was primarily analyzed as a continuous variable (coverage days). For descriptive purposes, patients were additionally classified as having full coverage (≥80% of days covered) or partial coverage (<80%)[13, 14].

We calculated coverage days based on injection formulation. A 1-month formulation was assumed to provide coverage for 30 days[15] following injection, and a 3-month formulation for 90 days[16]. To account for overlapping injections, we calculated coverage as the total number of unique days covered during the observation year rather than as the sum of nominal coverage durations.

Outcome Measures

The outcome of interest was the total number of hospitalization days during the year after initiation of LAI treatment. Using each patient's unique hospitalization identifier, we retrieved all inpatient records occurring within the predefined observation window following the index injection date. For each hospitalization episode, admission and discharge dates were used to define the hospitalization interval. Hospitalization days were calculated by summing the number of days overlapping with the specified time window (i.e., 1 year after the index injection date). For patients with multiple admissions, hospitalization days were aggregated across all qualifying inpatient episodes within the follow-up period to derive the total hospitalization burden after paliperidone LAI initiation. All hospitalization data were obtained from hospital discharge records.

Oral Medication Adherence

We assessed oral medication adherence at each follow-up visit based on physician reports and classified it into four categories: no oral medication prescribed; oral medication prescribed and taken as prescribed; oral medication presecribed but taken irregularly; and oral medication prescribed but t refused. For analysis, we dichotomized adherence as no adherence problem (categories 0–1) versus presence of nonadherence (categories 2–3). Oral medication adherence data were collected for both the year preceding and the year following paliperidone LAI initiation.

Social Dangerousness Rating

Social dangerousness ratings we recorded at each follow-up visit using physician-reported evaluations based on the Chinese National Risk Assessment Scale for Patients with Severe Mental Disorders, which categorizes social dangerousness from 0 (no risk) to 5 (severe violence). For analysis, we categorized ratings as no social dangerousness (0), low social dangerousness (1–2), and high social dangerousness (3–5). Social dangerousness ratings were collected for both the year preceding and the year following paliperidone LAI initiation.

Covariates

Baseline covariates included age, sex, duration of illness from schizophrenia diagnosis to paliperidone LAI initiation, days of psychiatric hospitalization, social dangerousness rating, and oral medication adherence status during the year preceding injection initiation, as well as concomitant oral psychiatric medications at the index date, including antipsychotics, antidepressants, mood stabilizers, and benzodiazepines.

Statistical Analysis

Continuous variables were summarized as mean (SD), and categorical variables as number (percentage). Group comparisons were performed using t tests for continuous variables and χ^2 tests for categorical variables. Standardized mean differences (SMDs) were calculated to assess baseline covariate balance.

To explore potential nonlinear associations between paliperidone LAI coverage days and hospitalization days during the year following injection initiation, nonparametric LOESS[17] smoothing was used for descriptive visualization. For comparison, analogous analyses were conducted for hospitalization days during the year preceding injection initiation.

To examine potential mechanisms underlying the observed associations, we constructed path models to estimate direct and indirect associations between paliperidone LAI coverage days and hospitalization outcomes[18]. The models incorporated post-initiation social dangerousness rating and post-initiation oral medication adherence as intermediate variables, allowing for both parallel and sequential mediation pathways. We estimated both unadjusted models and adjusted models controlling for prespecified patient characteristics and clinical factors measured prior to paliperidone LAI initiation. Indirect effects were decomposed into pathway-specific components, and total effects were calculated as the sum of direct and indirect effects. Model parameters were estimated using bootstrap resampling with 2000 replications to derive confidence intervals.

Prespecified subgroup analyses were conducted by sex, age group, illness duration, use of the 3-month paliperidone formulation, and concomitant psychotropic medication

use. Within each subgroup, separate linear regression models were fitted to estimate the association between paliperidone LAI coverage days and hospitalization outcomes, adjusting for hospitalization burden during the year preceding injection initiation. To formally assess effect modification, interaction terms between paliperidone LAI coverage days and each subgroup variable were additionally introduced into models fitted in the overall cohort. Interaction effects were evaluated using the P value of the corresponding interaction term.

Results

Baseline Characteristics

The final analytic cohort includeded 9,605 patients with schizophrenia who had at least 1 hospitalization during the year preceding paliperidone LAI initiation. The mean age of the cohort was 38.0 years, and 39.8% of patients were female (Table 1).

Table 1. Baseline demographic and clinical characteristics.

Variables	Partial exposure (n=4021)	Full exposure (n=5584)	P	SMD
Demographic characteristics				
Age, years, mean (SD)	37.83 (10.90)	37.78 (10.71)	0.838	0.004
Gender (female), n (%)	1580 (39.3)	2242 (40.2)	0.409	0.018
Residence, n (%)			0.021	0.048
Urban	1360 (33.8)	2017 (36.1)		
Rural	2661 (66.2)	3567 (63.9)		
Education background, n (%)			<0.001	0.100
Basic education	3044 (75.7)	4084 (73.1)		
Secondary education	593 (14.7)	978 (17.5)		
Higher education	275 (6.8)	421 (7.5)		

Unknown	109 (2.7)	101 (1.8)		
Clinical features				
Illness duration, n (%)			0.117	0.043
<1 year	1271 (31.6)	1776 (31.8)		
1-5 years	1224 (30.4)	1793 (32.1)		
>5 years	1525 (37.9)	2014 (36.1)		
Physical comorbidity, n (%)	3243 (80.7)	4557 (81.6)	0.247	0.024
Social dangerousness rating[a], n (%)			0.002	0.073
None	2577 (66.7)	3733 (69.0)		
Low	778 (20.1)	934 (17.3)		
High	510 (13.2)	740 (13.7)		
Social dangerousness rating[b], n (%)			<0.001	0.279
None	2979 (75.9)	4794 (86.5)		
Low	619 (15.8)	534 (9.6)		
High	326 (8.3)	213 (3.8)		
Oral medication nonadherence[a], n (%)	501 (12.5)	671 (12.0)	0.533	0.014
Oral medication nonadherence[b], n (%)	288 (7.2)	51 (0.9)	<0.001	0.322
Antipsychotic, n (%)	2935 (73.0)	4173 (74.7)	0.058	0.040
Antidepressant, n (%)	210 (5.2)	296 (5.3)	0.902	0.004
Mood stabilizer, n (%)	1058 (26.3)	1474 (26.4)	0.944	0.002
Benzodiazepine, n (%)	698 (17.4)	1060 (19.0)	0.045	0.042
Prior use of paliperidone /risperidone, n (%)	569 (14.2)	2129 (38.1)	<0.001	0.567
Number of injections, mean (SD)	4.94 (3.01)	11.44 (1.89)	<0.001	2.59
Three-month LAI initiators	183 (4.6)	1758 (31.5)	<0.001	0.748
Medication coverage days, mean (SD)	130.60 (85.32)	342.96 (17.61)	<0.001	3.447
Hospitalization days[a]	114.37 (94.35)	105.82 (88.94)	<0.001	0.093

Hospitalization days[b]	52.48 (86.82)	9.11 (37.81)	<0.001	0.648

Note. a. within 1 year before index injection; b. within 1 year after index injection.

Among these patients, 5,584 (58.1%) had full paliperidone LAI coverage and 4,021 (41.9%) had partial coverage during the year following injection initiation. Patients with full coverage received more injections and had substantially longer cumulative coverage durations than those with partial coverage (mean [SD] coverage, 342.96 [17.61] days vs 130.60 [85.32] days). Patients with full coverage were more likely to have used oral paliperidone or risperidone prior to LAI initiation and less likely to exhibit high post-injection social risk or poor medication adherence. Most other baseline demographic and clinical characteristics were well balanced between groups, with standardized mean differences generally below 0.1.

Hospitalization Outcomes

During the year following paliperidone LAI initiation, patients with full coverage experienced substantially fewer hospitalization days than those with partial coverage (mean [SD], 9.11 [37.81] days vs 52.48 [86.82] days). The number of hospitalizations during follow-up was also lower among patients with full coverage (Table 1).

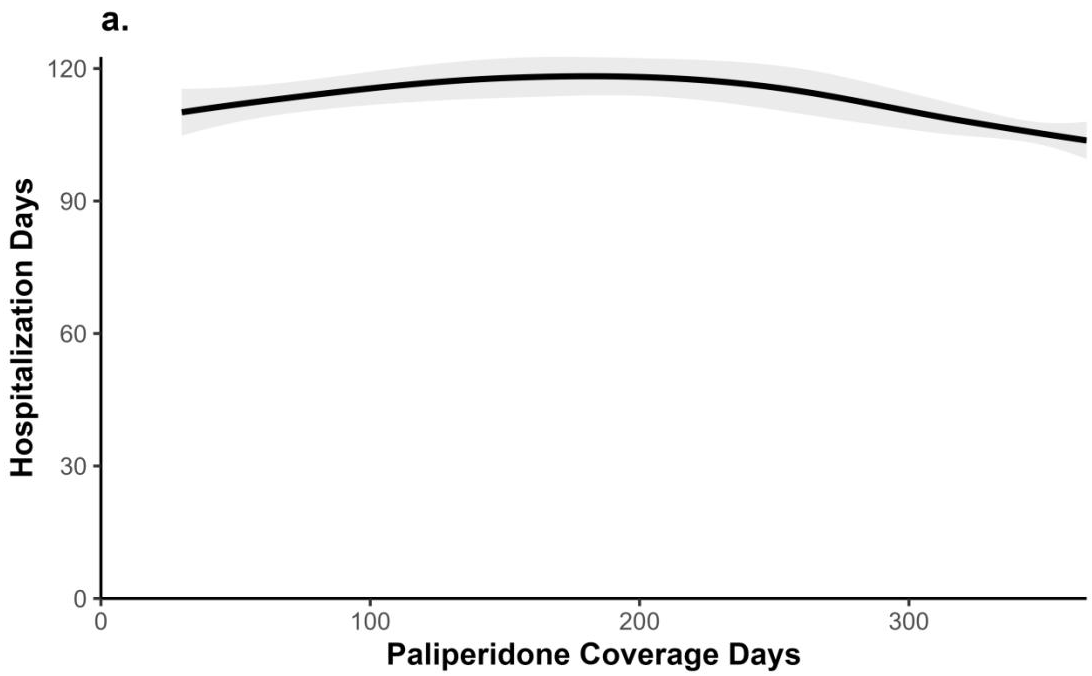
In contrast, hospitalization burden during the year preceding injection initiation was similar between groups, with only small differences in hospitalization days (mean [SD], 105.82 [88.94] days vs 114.37 [94.35] days), supporting comparability of baseline hospitalization burden.

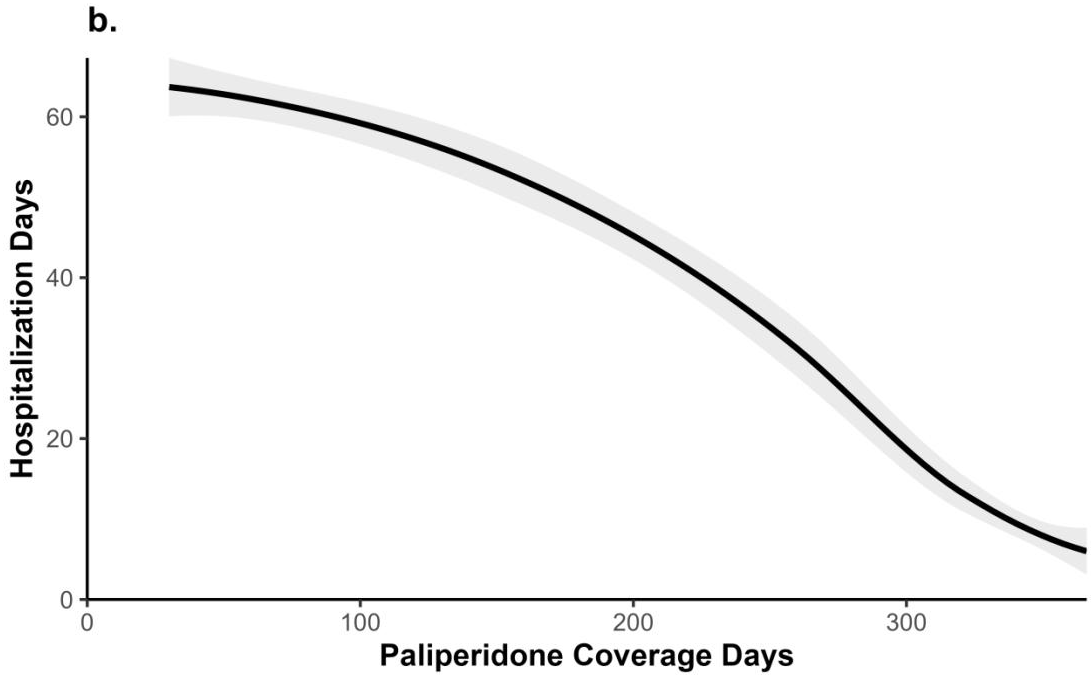
Nonlinear Association Between Coverage and Hospitalization

Descriptive LOESS-smoothed curves illustrated no clear association between

paliperidone LAI coverage days and hospitalization days during the year preceding injection initiation (Figure 2a). In contrast, during the year following treatment initiation, higher levels of coverage were associated with progressively fewer hospitalization days (Figure 2b). The inverse association was evident only after treatment initiation, with an approximate difference of 60 hospital days between the lowest and highest coverage levels.

Figure 2. Nonlinear association between hospitalization days and paliperidone LAI coverage days.





Panels:

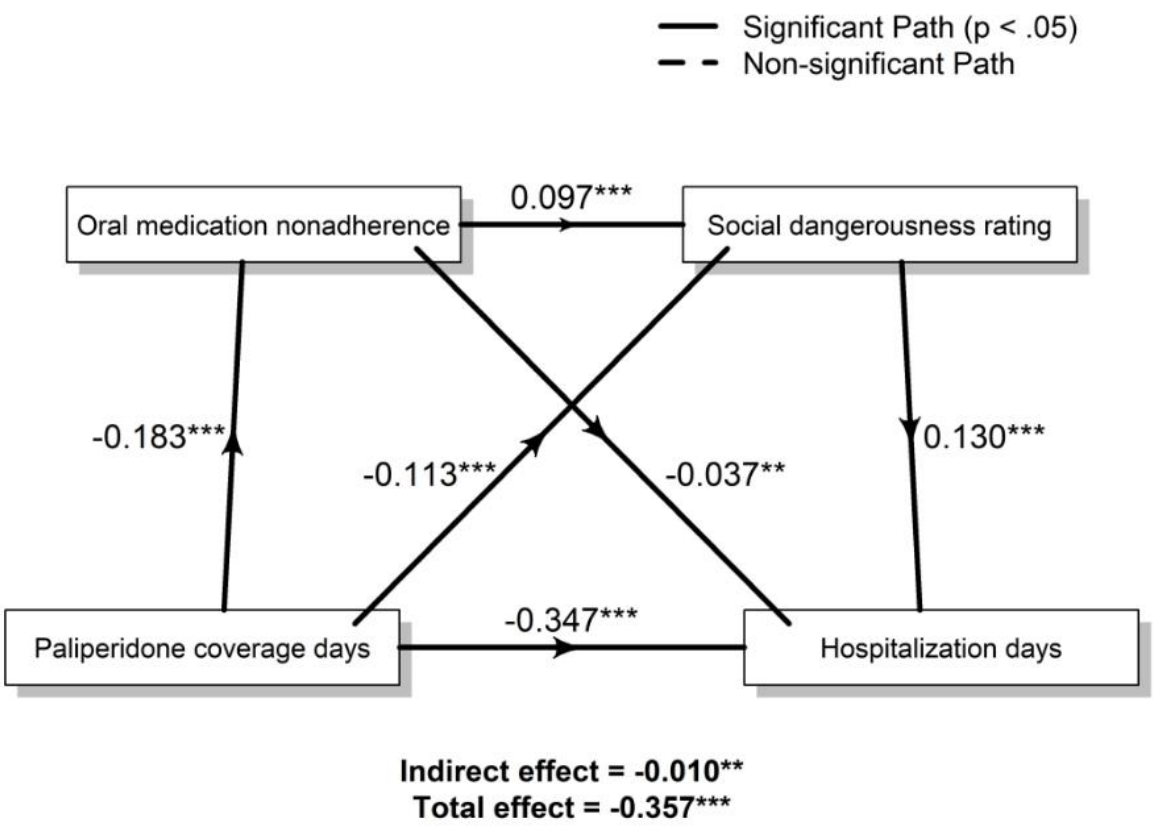
a. Hospitalizations within 1 year before the first injection

b. Hospitalizations within 1 year after the first injection

Path Models

In covariate-adjusted path analyses (Figure 3), higher paliperidone long-acting injectable (LAI) coverage was significantly associated with fewer hospitalization days during the year following treatment initiation.

Figure 3. Covariate-Adjusted Path Models of Paliperidone Coverage and Hospitalization Days.



Note. Adjusted for psychotropic medications (antipsychotics, antidepressants, mood stabilizers, and benzodiazepines), baseline risk stratification in the year before injection, illness duration from schizophrenia diagnosis to the index injection, and hospitalization days in the year before injection, as well as age and sex.

Specifically, each additional day of paliperidone LAI coverage was associated with an estimated 0.18-day reduction in hospitalization over 1 year (direct effect, −0.178 days; P < .001), indicating a strong and independent association between medication coverage and hospitalization burden.

Higher paliperidone LAI coverage was also significantly associated with lower post-injection social dangerousness ratings (−0.001 per day; P < .001) and reduced oral medication nonadherence (P < .001). Oral medication nonadherence was positively

associated with social dangerousness (0.097; P < .001), and both higher social dangerousness (14.53 days per unit increase; P < .001) and poorer oral medication adherence (−12.25 days; P = .002) were associated with greater hospitalization days.

These associations supported statistically significant indirect pathways linking paliperidone LAI coverage to hospitalization outcomes through improvements in oral medication adherence and reductions in social dangerousness. However, the magnitude of the indirect effect was small (total indirect effect, −0.005 days; P = .001) compared with the direct effect.

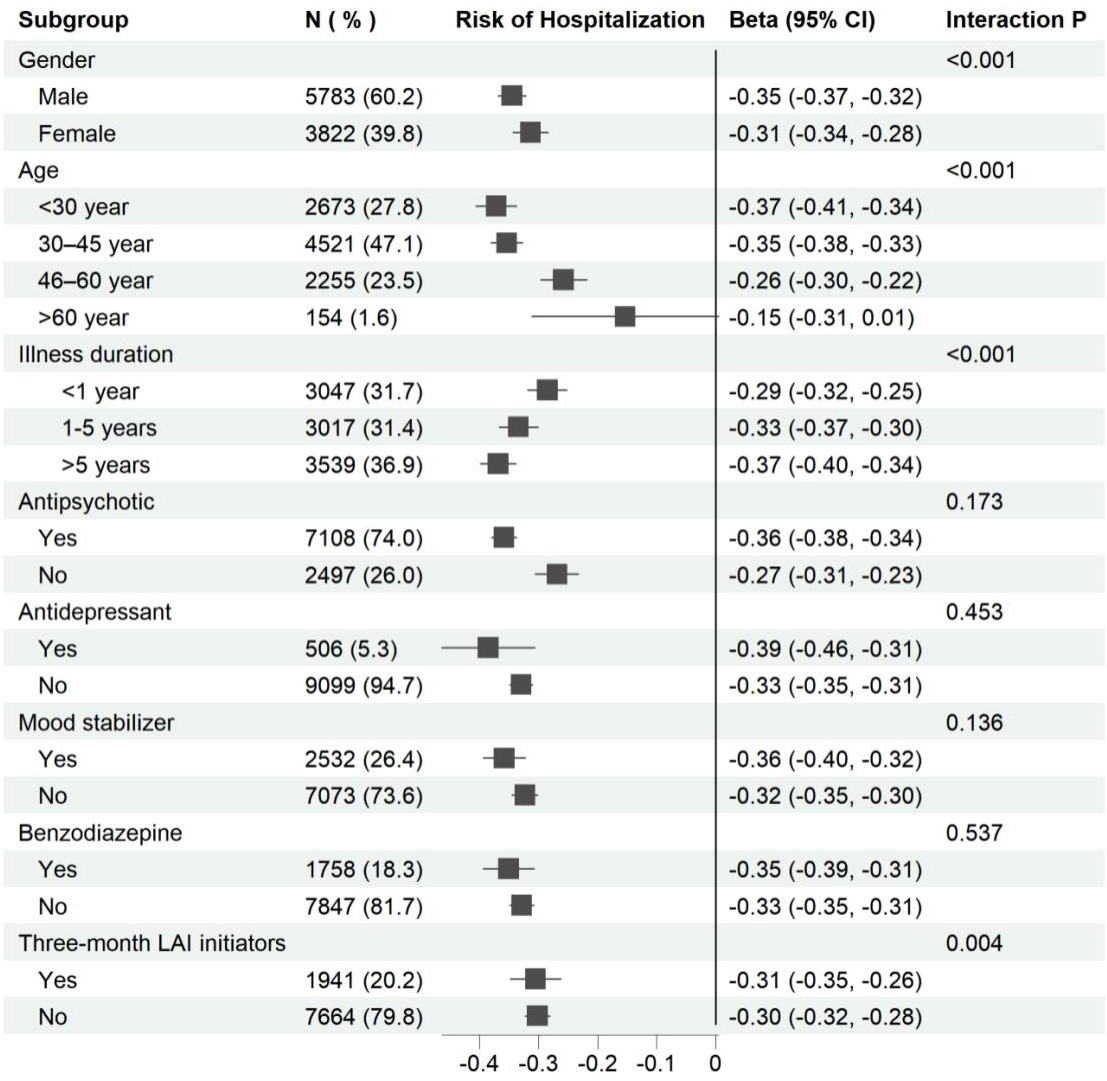
Overall, the total effect of paliperidone LAI coverage on hospitalization burden was −0.184 days per additional coverage day (P < .001), with the majority of this association attributable to the direct pathway rather than mediation through intermediate factors.

Subgroup Analyses

In prespecified subgroup analyses (Figure 4), higher paliperidone LAI coverage days were associated with a lower hospitalization burden in the subsequent year across most subgroups after adjustment for hospitalization burden in the year before treatment initiation. The analysis did not show a statistically significant association among patients aged over 60 years. Sex, age group, illness duration, and initiation of the three-month paliperidone formulation significantly modified the association between paliperidone LAI coverage days and hospitalization burden (interaction P < .01 for all). The analysis showed larger effect estimates in male patients, younger age groups, and patients with longer illness duration. Concomitant psychotropic medication use showed

no evidence of effect modification.

Figure 4. Forest Plot of Standardized Regression Coefficients (β) for the Association Between Paliperidone LAI Coverage and Hospitalization Days Across Subgroups.



Discussion

In this large real-world cohort study of patients with schizophrenia who had been recently hospitalized, we found that higher coverage of paliperidone LAI treatment was associated with a lower hospitalization burden during the year following treatment initiation. Notably, this graded association was evident during the year following

treatment initiation but was not observed during the preceding year, highlighting the temporal specificity of the findings. Path analysis further indicated that LAI coverage was associated with reduced hospitalization burden both indirectly, through improvements in oral medication adherence and reductions in social dangerousness, and more predominantly through a substantial direct effect. In addition, subgroup analyses showed that, after adjusting for hospitalization burden in the year prior to treatment initiation, the association between paliperidone LAI coverage days and reduced hospitalization burden in the subsequent year was generally consistent across most patient subgroups. The association did not reach statistical significance among patients aged ≥60 years. Male patients, younger patients, and those with a longer duration of illness tended to exhibit larger effect estimates. Taken together, these findings highlight the critical importance of achieving and maintaining adequate LAI coverage in reducing hospitalization burden among patients with schizophrenia and provide mechanistic insight into how improvements in treatment continuity may translate into better real-world outcomes.

Consistent with existing literature, our results reinforce the association between paliperidone LAI treatment and a reduced hospitalization burden among patients with schizophrenia[19-21]. Importantly, our findings go beyond prior dichotomous comparisons by demonstrating that the magnitude of this association increases with longer durations of effective LAI coverage. This dose–response pattern suggests that the clinical benefits of paliperidone LAI are not confined to treatment initiation but accrue with sustained exposure over time. From a clinical perspective, these results

underscore that discontinuation or intermittent use of LAI treatment may substantially attenuate its potential to reduce hospitalization burden[22].

Consistent with previous studies, our findings support the notion that patients receiving LAI antipsychotics tend to exhibit better treatment adherence[14, 19]. Extending prior evidence, our results further indicate that higher paliperidone LAI coverage was associated not only with improved adherence to concomitant oral medications but also with lower levels of social dangerousness, both of which have been closely linked to hospitalization burden in patients with schizophrenia[23]. At the same time, these pathways accounted for only a small proportion of the overall association between LAI coverage and hospitalization outcomes, suggesting that the association between sustained paliperidone LAI treatment and hospitalization burden is more closely related to the duration of continuous injection itself.

Across patient subgroups, the association between paliperidone LAI coverage and hospitalization burden remained generally consistent; however, larger effect estimates were observed among male patients, younger patients, and those with a longer duration of illness, indicating that the strength of this association varied by patient characteristics. Previous studies have suggested heterogeneity in treatment response to paliperidone LAI according to sex and illness duration[24, 25], and such heterogeneity in treatment response may represent one potential mechanism underlying the observed differences in hospitalization burden across patient subgroups. Overall, these findings indicate a certain degree of heterogeneity in the association between paliperidone LAI coverage and hospitalization burden across different patient characteristics.

These findings suggest that the clinical value of paliperidone LAI treatment lies not only in its initiation but in the duration of continuous use. Higher LAI coverage was associated with lower hospitalization burden and with indicators of broader clinical stability, including better adherence to concomitant oral medications and lower social dangerousness. This underscores the importance of maintaining uninterrupted LAI treatment in routine schizophrenia care[22].

Several limitations should be acknowledged. First, as an observational study, causal inferences cannot be established, and residual confounding from unmeasured factors—such as illness severity, symptom trajectories, family support, or prescribing preferences—cannot be fully excluded. Patients with longer vs shorter paliperidone LAI exposure may also differ systematically in ways related to hospitalization risk. Second, although hospitalization burden is a clinically meaningful and objective outcome, it may be influenced by health system characteristics and local admission practices that were not captured. Social dangerousness was assessed using routine clinical ratings and may be subject to measurement error. Third, adherence to concomitant oral medications was based on clinician reports rather than direct measures, potentially overestimating true adherence. Fourth, reverse causation cannot be entirely ruled out, as clinically stable patients may be more likely to continue LAI treatment. Finally, the study population was drawn from a single province in China, which may limit generalizability to other settings.

Conclusions

In this large real-world cohort of recently hospitalized patients with schizophrenia,

higher paliperidone LAI coverage was associated with a lower subsequent hospitalization burden. The observed dose–response relationship suggests that, beyond treatment initiation, sustained LAI use has additional clinical relevance, with more pronounced associations observed among male patients and those with a longer illness duration. Overall, these findings highlight the importance of maintaining continuous paliperidone LAI treatment in routine care and support treatment strategies that prioritize long-term coverage to reduce hospitalization burden in schizophrenia.

Abbreviations

LAI: Long-acting injectable

LOESS: Locally Weighted Scatterplot Smoothing

SD: Standard deviation

SMDs: Standardized mean differences

Declarations

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Consent for publication

Not applicable.

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Data availability

Data involved in this study are available upon reasonable request.

Ethics Statement:

This study was approved by the Ethics Committee of Guangdong Provincial People's Hospital (approval No. KY2024-402-01).

Author Statement:

Hongbo He provided overall supervision and study oversight. Kunrong Lin performed the statistical analyses and drafted the manuscript. Xuefei Fan assisted with statistical analyses and manuscript preparation. Wenyan Tan and Shibin Wang were responsible for data collection and data management. Robert Rosenheck contributed to study conceptualization, statistical guidance, and critical revision of the manuscript for important intellectual content. Kunrong Lin and Wenyan Tan contributed equally to this work and share first authorship. All authors read and approved the final manuscript.

Competing Interests:

The authors declare no competing interests.

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