Comparison of Long-Acting Injectable and Oral Antipsychotics in Bipolar Disorder

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Objective: Long-acting injectable antipsychotics (LAIAs) can improve adherence, but their optimal use in bipolar disorder needs to be further explored. This study compared LAIAs and oral antipsychotics with respect to health care utilization, illness relapse, and safety in individuals with bipolar disorder.

Methods: A self-controlled case series study was conducted using data from Hong Kong's electronic health records on individuals with bipolar disorder who received prescriptions for both LAIAs and oral antipsychotics during the period of January 1, 2004, through December 31, 2023. Outcomes included measures of health care utilization, illness relapse, and safety. Adjusted incidence rate ratios (aIRRs) for LAIA versus oral antipsychotic treatment periods were estimated using conditional Poisson regression.

Results: Among 17,841 people with bipolar disorder, 2,086 (11.7%) received prescriptions for both LAIAs and oral antipsychotics. Compared with oral antipsychotics, LAIAs were associated with statistically significantly lower risks of all-cause emergency department visits (aIRR=0.85, 95% CI=0.81, 0.89), all-cause hospitalizations (aIRR=0.79, 95% CI=0.73, 0.85), psychiatric hospitalizations (aIRR=0.67, 95% CI=0.61, 0.74), hospitalizations for manic episodes (aIRR=0.51, 95% CI=0.44, 0.59), and hospitalizations for mixed episodes (aIRR=0.31, 95% CI=0.14, 0.66). No statistically significant difference was found for hospitalizations for depressive episodes (aIRR=1.34, 95% CI=0.94, 1.93), nonpsychiatric hospitalizations (aIRR=0.97, 95% CI=0.87, 1.08), or cardiovascular hospitalizations (aIRR=0.84, 95% CI=0.62, 1.14). LAIAs were initially associated with an increased risk of extrapyramidal symptoms (aIRR=2.95, 95% CI=1.40, 6.22), but this difference was not statistically significant beyond 90 days of treatment.

Conclusions: LAIAs were associated with substantially less health care utilization and fewer relapses of manic and mixed episodes, and they were not associated with increased risk of nonpsychiatric hospitalizations, notably for cardiovascular disease. These findings support the use of LAIAs for bipolar disorder, with close monitoring for extrapyramidal symptoms during initiation.

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Bipolar disorder is a severe psychiatric illness affecting approximately 40 million individuals worldwide (1). Bipolar I disorder is characterized by at least one manic episode, with or without a major depressive episode, and bipolar II disorder requires at least one hypomanic and one depressive episode; bipolar I and II disorders have distinct clinical features, outcomes, and treatment responses (2, 3). The recurrent mood episodes significantly contribute to unemployment, suicide attempts, poor quality of life, and markedly reduced life expectancy (1, 2, 4). To reduce the severity of mood episodes and prevent recurrences, treatments for bipolar disorder include mood stabilizers, antipsychotics, and psychotherapy; most patients require combination therapy and lifelong treatment to maintain remission (1, 2, 4–6).

Over the past two decades, antipsychotics have been increasingly prescribed for people with bipolar disorder, gradually supplanting mood stabilizers (7). However, medication nonadherence remains a critical challenge, affecting approximately 60% of this population (8) and leading to higher relapse rates, increased health care utilization, and greater societal burden (9, 10). Long-acting injectable antipsychotics (LAIAs), with dosing intervals ranging from 2 weeks to 6 months (11), are a promising option to address these issues and are recommended in major guidelines for bipolar disorder (5, 6, 12). These agents primarily act by modulating neurotransmission in dopaminergic pathways (e.g., antagonizing dopamine D_2 receptors) and serotoninergic (5-HT) pathways (13), providing therapeutic effects for both manic and depressive episodes. Their

pharmacokinetic profile, with fewer peak-trough fluctuations, may reduce side effects to enhance tolerability (14) and ensure more stable therapeutic effects, helping with symptoms that may persist because of the variable plasma levels of oral antipsychotics (OAs).

Although several studies have pointed to the benefits of LAIAs in bipolar disorder, few have examined outcomes other than emergency department visits and hospitalizations (15–18) or compared their safety to that of OAs. This gap is particularly important given that antipsychotics are well known to be associated with increased cardiovascular mortality arising from direct adverse effects such as arrhythmias and QTc prolongation (1) as well as indirect risks such as obesity and metabolic dysfunction (19). They are also related to increased risk of movement disorders, particularly extrapyramidal symptoms (EPS), due to their antagonizing effects on dopamine D_2 receptors (13, 20). Given these risks, it is crucial to develop a better understanding of how safety profiles compare between LAIAs and OAs.

Moreover, previous studies have primarily focused on aripiprazole and risperidone, despite the common off-label use of other LAIAs. Randomized controlled trials often have strict inclusion and exclusion criteria (21), and mirror-image studies comparing equal periods of time before and after the use of LAIAs (16–18, 22) have frequently been unable to account for concomitant medications commonly used in bipolar disorder. Additionally, most studies have been single-center studies and had limited sample sizes and short follow-up periods, limiting the generalizability of their findings and their ability to capture long-term effects.

LAIAs have demonstrated benefits in treating schizophrenia (23, 24) and are typically reserved for the most nonadherent patients or those with the most severe bipolar disorder illness. Evidence of LAIA use in some patient groups is particularly scarce. Specifically, elderly individuals who experience significant pharmacokinetic, pharmacodynamic, and comorbidity-related changes remain underrepresented in studies. Substance use, a common psychiatric comorbidity in bipolar disorder (25), often leads to poorer adherence and poor outcomes (26), raising uncertainties about LAIA use for those with this comorbidity. Although studies in schizophrenia highlight the benefits of early initiation of LAIAs in improving outcomes (23), comparable guidance for bipolar disorder is lacking. These concerns highlight the need for more robust evidence in order to understand their optimal use across the full spectrum of people with bipolar disorder.

To address these knowledge gaps, we investigated the health care utilization, illness relapse, and safety associated with the use of LAIAs versus OAs among people with bipolar disorder in Hong Kong, including special patient groups such as older adults and individuals with comorbid substance use disorder. Our aim in this study was to enhance understanding and inform clinical practice regarding the use of LAIAs in managing bipolar disorder.

METHODS

Data Source

This population-based study used data from the Clinical Data Analysis and Reporting System (CDARS), an electronic health records database managed by the Hong Kong Hospital Authority. This database is representative of the general population in Hong Kong and contains data for over 7.5 million people in the public sector (27). CDARS contains anonymized patient data, including demographic characteristics, diagnoses, procedures, prescriptions, laboratory tests, and admission records since 1993, and it has been widely used in high-quality pharmacoepidemiology studies (23, 24, 28).

Self-Controlled Case Series Design

We employed the self-controlled case series (SCCS) design, which compares the incidence of the event of interest during exposed and unexposed periods within the same individual (29, 30). Patients served as their own controls, and only the patients who had the exposure and outcome of interest within a prespecified period were included. This approach implicitly controls for both measured and unmeasured time-invariant confounders, such as genetics and historical factors, which vary between individuals. This method has been extensively used to evaluate the association between treatment outcomes and psychotropic medications in high-quality studies (23, 24, 31).

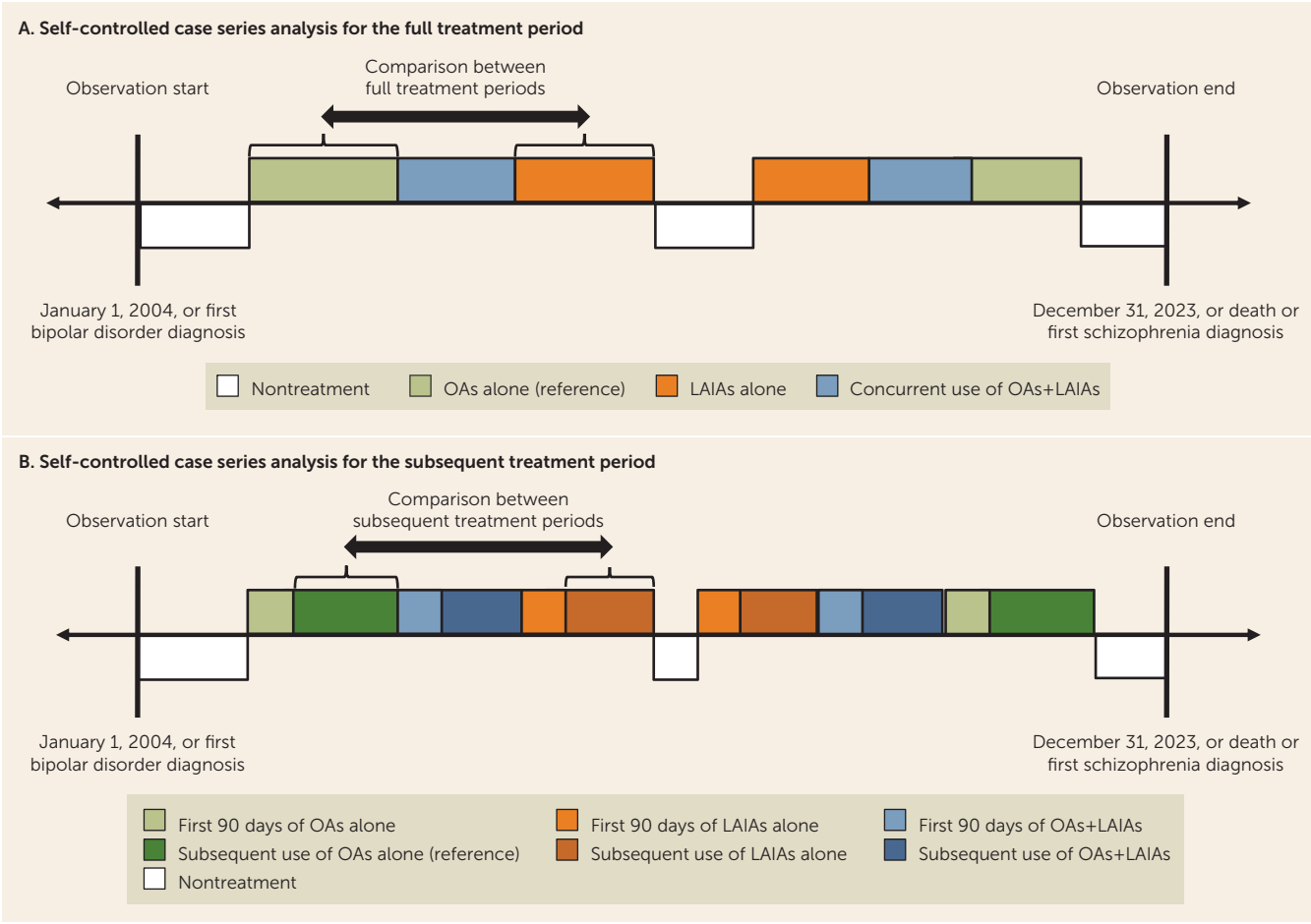
Participants

The initial cohort included people diagnosed with bipolar disorder (identified by *ICD-9-CM* codes 296.0, 296.1, and 296.4–296.8) on or before December 31, 2023, without any preceding diagnosis of schizophrenia spectrum disorder (*ICD-9-CM* code 295). The individual observation period began on January 1, 2004, or the date of the first bipolar disorder diagnosis, whichever was later. Follow-up was censored at death, at diagnosis of schizophrenia spectrum disorder, or on December 31, 2023, whichever occurred first. Case subjects were defined as individuals with bipolar disorder who had received at least one prescription of an OA (identified by British National Formulary [BNF] code 4.2.1, excluding short-acting injectable antipsychotics), had received at least one prescription of an LAIA (BNF code 4.2.2), and had at least one record of the outcome of interest within the observation period. Because the SCCS analysis includes only cases, the number of patients included in the comparison varied for each outcome.

Exposures and Outcomes

The observation period for individuals was divided into four mutually exclusive categories: nontreatment, use of OAs alone, use of LAIAs alone, and concurrent use of OAs and LAIAs (i.e., at least one OA and one LAIA used on the same day) (Figure 1A). The nontreatment period reflects the absence of OA and LAIA use but not of other pharmacological treatments. For periods classified as OAs alone or LAIAs

FIGURE 1. Self-controlled case series study of the use of long-acting injectable antipsychotics versus oral antipsychotics in bipolar disorder[a]



[a] LAIA, long-acting injectable antipsychotic; OA, oral antipsychotic.

alone, only the formulation was considered, without differentiating between specific antipsychotic agents. The exposure dates were derived from the start and end dates of each prescription. A washout period equivalent to five half-lives of each antipsychotic (see Table S1 in the online supplement) was added to the prescription end date to account for any residual treatment effects.

Each treatment period was further divided into the first 90 days and the subsequent treatment period beyond the first 90 days, to account for the delayed onset of full therapeutic effects, event-driven treatment changes (e.g., medication changes due to symptom worsening or initiation of OAs or LAIAs following hospitalizations), and residual effects from the previous treatment modality (Figure 1B).

The primary outcomes were health care utilization (all-cause emergency department visits and hospitalizations) and illness relapse (psychiatric hospitalizations, hospitalizations for depressive episodes, hospitalizations for manic episodes, and hospitalizations for mixed episodes). Secondary outcomes included nonpsychiatric hospitalizations, cardiovascular hospitalizations, and EPS to assess the safety profiles of the antipsychotics. Detailed definitions of each outcome are provided in Table S2 in the online supplement.

Statistical Analysis

Conditional Poisson regression models were used to calculate the adjusted incidence rate ratios and the corresponding 95% confidence intervals, adjusted for time-varying covariates: age, season, COVID-19 stringency index (32), and concomitant medications, including mood stabilizers, antidepressants, hypnotics and anxiolytics, and antiparkinsonian drugs (see Table S3 in the online supplement). To ensure accuracy for hospitalization-related outcomes (i.e., for all the outcomes except EPS), we excluded periods of inpatient stay (except the day of admission), as patients cannot be rehospitalized or visit at the emergency department while they are inpatients.

In the main analysis, we compared the risk of outcome events during the full treatment period of LAIAs alone and OAs alone. Next, we evaluated the maintenance phase (beyond 90 days) by comparing the subsequent treatment period of LAIAs alone and OAs alone. In addition to the overall comparison, we directly compared the oral and

TABLE 1. Characteristics of patients in a study comparing long-acting injectable antipsychotics and oral antipsychotics in bipolar disorder[a]

Characteristic	Received prescriptions for both OA and LAIA during observation period (N=2,086)		Received prescriptions for OA and LAIA, with at least one outcome event during observation period																	
			Primary outcomes												Secondary outcomes					
			All-cause ED visits (N=1,912)		All-cause hospitalizations (N=1,881)		Psychiatric hospitalizations (N=1,723)		Hospitalizations for depressive episodes (N=320)		Hospitalizations for manic episodes (N=1,244)		Hospitalizations for mixed episodes (N=164)		Nonpsychiatric hospitalizations (N=1,252)		Cardiovascular hospitalizations (N=346)		Extrapyramidal symptoms (N=100)	
	N	%	N	%	N	%	N	%	N	%	N	%	N	%	N	%	N	%	N	%
Sex																				
Female	1,155	55.4	1,060	55.4	1,053	56	963	55.9	225	70.3	683	54.9	127	77.4	708	56.5	187	54	56	56
Male	931	44.6	852	44.6	828	44	760	44.1	95	29.7	561	45.1	37	22.6	544	43.5	159	46	44	44
	Mean	SD	Mean	SD	Mean	SD	Mean	SD	Mean	SD	Mean	SD	Mean	SD	Mean	SD	Mean	SD	Mean	SD
Age (years)																				
At first bipolar diagnosis	36.3	13.2	35.1	12.8	36.2	13.7	33.8	12.8	35.0	13.4	34.1	12.3	34.4	13.0	39.8	14.3	43.9	13.9	41	15.4
At cohort entry	37.8	13.3	37.3	12.8	38.5	13.8	36.1	13.2	36.8	13.7	36.6	12.7	37.1	13.5	42.2	14.1	46.9	13.2	43.5	14.6
At time of event			45.4	13.8	46.7	15.1	43.2	14.2	43.3	13.5	43.4	13.8	43.0	14.3	51.9	14.8	57.4	12.7	51.1	15.6
	N	%	N	%	N	%	N	%	N	%	N	%	N	%	N	%	N	%	N	%
Comorbidities throughout observation period																				
Anxiety	127	6.1	118	6.2	123	6.5	112	6.5	28	8.8	78	6.3	12	7.3	88	7.0	32	9.3	32	9.3
Personality disorders	237	11.4	227	11.9	228	12.1	220	12.8	53	16.6	147	11.8	26	15.9	166	13.3	40	11.6	40	11.6
Substance use disorders	333	16.0	316	16.5	314	16.7	300	17.4	71	22.2	201	16.2	36	22.0	221	17.7	46	13.3	46	13.3

[a] The observation period for each individual began on January 1, 2004, or the date of the first bipolar disorder diagnosis, whichever was later. Follow-up was censored at death, diagnosis of schizophrenia spectrum disorder, or December 31, 2023, whichever occurred first. ED, emergency department; LAIA, long-acting injectable antipsychotic; OA, oral antipsychotic.

long-acting formulations for all antipsychotics available for both delivery forms in our database, including aripiprazole, flupenthixol, haloperidol, paliperidone, risperidone, and zuclopenthixol. To evaluate the effects of individual antipsychotics, we also compared each antipsychotic treatment period against its pre-exposure period (i.e., 30 days before antipsychotic use), which is often a time of clinical instability. This approach helps address the SCCS assumption of event-dependent exposure by accounting for the heightened risk prior to treatment initiation and allows for evaluating the profiles of individual antipsychotics.

We also performed subgroup analyses based on sex, age, timing of LAIA initiation, age at onset of bipolar disorder, substance use, timing of bipolar disorder diagnosis, and follow-up duration. We performed 10 sensitivity analyses to test the robustness of the main results, accounting for potential exposure and/or outcome misclassification and the possible violation of key assumptions of SCCS design, specifically event-dependent exposure, independent event, and event-dependent observation. Upper respiratory tract infection was used as a negative control for validation. We calculated E-value (33) to assess the potential impact on the conclusion of any unmeasured confounding. Detailed descriptions of the analyses are presented in the online supplement.

The reporting of this study followed the Strengthening the Reporting of Observational Studies in Epidemiology (STROBE) guideline (34). All p values were from two-sided tests, and results were deemed statistically significant at $p<0.05$. All analyses were performed using R, version 4.4.2.

Ethics

The study was approved by the Institutional Review Board of the University of Hong Kong/Hospital Authority Hong Kong West Cluster (reference number UW 20-113).

RESULTS

The database contained data for 17,841 individuals diagnosed with bipolar disorder on or before December 31, 2023 (mean age=39.7 years [SD=16.5]; 38.8% male). Of these, 12,780 (71.6%) received prescriptions for OAs alone and 2,086 (11.7%) received prescriptions for both OAs and LAIAs during the observation period (Table 1; see also Table S4 Figure S1 in the online supplement). The mean age at the beginning of the observation period was 37.8 years (SD=13.3), and the mean follow-up duration was 11.6 years (SD=6.8). The mean durations of exposure to OAs alone, LAIAs alone, and concurrent OAs and LAIAs were 5.93 years (SD=5.65), 2.11 years (SD=3.55), and 2.21 years (SD=3.68), respectively. Among the incident cohort (N = 1,288; i.e., those with first diagnosis of bipolar disorder on or after January 1, 2004), the first treatment modality was OAs alone for 724 (56.2%), concurrent OAs and LAIAs for 243 (18.9%), and LAIAs alone for 49 (3.8%); initially, no antipsychotic treatment was administered for 272 (21.1%).

During the observation period for those who received prescriptions for both OAs and LAIAs, 1,912 (91.7%) had at least one emergency department visit, 1,881 (90.2%) had at least one hospitalization, 1,723 (82.6%) had at least one psychiatric hospitalization, 320 (15.3%) had at least one hospitalization for a depressive episode, 1,244 (59.6%) had at least one hospitalization for a manic episode, 164 (7.9%) had at least one hospitalization for a mixed episode, 1,252 (60.0%) had at least one nonpsychiatric hospitalization, 346 (16.6%) had at least one cardiovascular hospitalization, and 100 (4.8%) had EPS (Table 1). During the observation period, 1,812 (86.9%) individuals used mood stabilizers, 810 (38.8%) used antidepressants, 1,958 (93.9%) used hypnotics and anxiolytics, and 1,784 (85.5%) used antiparkinsonian drugs.

During the full treatment periods (Table 2), the use of LAIAs was associated with a statistically significant lower risk of all-cause emergency department visits (adjusted incidence rate ratio [aIRR]=0.85, 95% CI=0.81, 0.89) and all-cause hospitalizations (aIRR=0.79, 95% CI=0.73, 0.85) compared to the use of OAs. Additionally, there was a statistically significant lower risk of psychiatric hospitalizations (aIRR=0.67, 95% CI=0.61, 0.74), hospitalizations for manic episodes (aIRR=0.51, 95% CI=0.44, 0.59), and hospitalizations for mixed episodes (aIRR=0.31, 95% CI=0.14, 0.66). No statistically significant difference was observed in the risk of hospitalizations for depressive episodes (N=320, aIRR=1.34, 95% CI=0.94, 1.93). Regarding the safety of LAIAs, no statistically significant differences were found in the risk of nonpsychiatric hospitalizations (aIRR=0.97, 95% CI=0.87, 1.08) or cardiovascular hospitalizations (aIRR=0.84, 95% CI=0.62, 1.14). However, an increased risk of EPS (aIRR=2.95, 95% CI=1.40, 6.22) was observed for LAIAs compared to OAs. After excluding the first 90 days of each treatment period, the results for all the outcomes during the subsequent treatment period were consistent with those during the full treatment period, except for EPS, where the increased risk was no longer statistically significant (Table 3).

In the comparison of both formulations of the same antipsychotic (Figure 2), aripiprazole long-acting injectable (LAI) (aIRR=0.61, 95% CI=0.50, 0.75) and flupenthixol LAI (aIRR=0.64, 95% CI=0.52, 0.79) were associated with a statistically significant lower risk of all-cause emergency department visits when compared to their oral counterparts, whereas haloperidol LAI (aIRR=1.49, 95% CI=1.33, 1.67) and zuclopenthixol LAI (aIRR=3.08, 95% CI=1.48, 6.41) were associated with an increased risk of all-cause emergency department visits. For all-cause hospitalizations, aripiprazole LAI (aIRR=0.63, 95% CI=0.48, 0.81), paliperidone LAI (aIRR=0.59, 95% CI=0.44, 0.80), and risperidone LAI (aIRR=0.37, 95% CI=0.17, 0.79) were associated with a statistically significant lower risk, whereas flupenthixol LAI (aIRR=1.49, 95% CI=1.05, 2.13) was associated with an increased risk. Aripiprazole LAI (aIRR=0.37, 95% CI=0.25, 0.56), paliperidone LAI (aIRR=0.42, 95% CI=0.28, 0.62), and risperidone LAI (aIRR=0.31, 95% CI=0.13, 0.75) were associated with a statistically significant lower risk of psychiatric hospitalizations. Aripiprazole LAI (aIRR=0.20, 95% CI=0.04, 0.95) was the only LAIA associated with decreased risk of hospitalizations for depressive episodes compared to its oral counterpart. Aripiprazole LAI (aIRR=0.43, 95% CI=0.23, 0.80), flupenthixol LAI (aIRR=0.64, 95% CI=0.42, 0.98), paliperidone LAI (aIRR=0.32, 95% CI=0.23, 0.43), and zuclopenthixol LAI (aIRR=0.61, 95% CI=0.47, 0.80) were associated with a statistically significant lower risk of hospitalizations for manic episodes. For nonpsychiatric hospitalizations, only flupenthixol LAI (aIRR=1.83, 95% CI=1.06, 3.16) was associated with an increased risk. For hospitalizations for mixed episodes, cardiovascular hospitalizations, and EPS, no statistically significant difference was found for any LAIA compared to its oral counterpart.

Subgroup analyses were generally consistent with the main findings (Figure 3; see also Figures S2 and S3 in the online supplement). Similar associations were observed when cases were stratified by age at onset of bipolar disorder, substance use, bipolar disorder cohort (incident versus prevalent), and follow-up duration. Stratification by sex revealed an increased risk of hospitalizations for depressive episodes among female patients. Age-stratified subgroup analyses showed consistent results among individuals ages 18–44 and 45–65 years. Among those over age 65, LAIAs were not associated with statistically significant reduced risks in all-cause emergency department visits and any hospitalization outcomes compared with OAs. Notably, early initiation of LAIAs was associated with lower health care utilization than late initiation, with 47% fewer all-cause emergency department visits and 48% fewer all-cause hospitalizations, compared to 13% and 22% lower risks among late initiators, respectively.

Compared to the pre-exposure period, during the treatment period all antipsychotics were associated with a statistically significant lower risk of all-cause emergency department visits, all-cause hospitalizations, hospitalizations for depressive episodes, hospitalizations for manic episodes, and nonpsychiatric hospitalizations (see Figures S4 and S5 in the online supplement). No antipsychotic was associated with an

TABLE 2. Results for primary outcomes in the self-controlled case series analysis of the use of long-acting injectable antipsychotics alone versus oral antipsychotics alone in bipolar disorder[a]

	Full treatment period								Subsequent treatment period[b]							
Outcome event	Number of events	Person-years	Incidence per 100 person-years	IRR	95% CI	aIRR[c]	95% CI	p	Number of events	Person-years	Incidence per 100 person-years	IRR	95% CI	aIRR[c]	95% CI	p
All-cause ED visits																
OAs alone	15,079	10,400.68	144.98	1 (Ref)		1 (Ref)			11,807	8,966.69	131.68	1 (Ref)		1 (Ref)		
LAIAs alone	4,194	2,721.96	154.08	0.82	0.78, 0.86	0.85	0.81, 0.89	<0.0001	3,183	2,322.62	137.04	0.79	0.75, 0.84	0.80	0.76, 0.85	<0.0001
All-cause hospitalizations																
OAs alone	7,775	10,341.23	75.18	1 (Ref)		1 (Ref)			5,881	8,928.49	65.87	1 (Ref)		1 (Ref)		
LAIAs alone	1,501	2,601.01	57.71	0.73	0.68, 0.79	0.79	0.73, 0.85	<0.0001	1,109	2,213.36	50.10	0.76	0.70, 0.83	0.80	0.73, 0.87	<0.0001
Psychiatric hospitalizations																
OAs alone	4,632	9,686.51	47.82	1 (Ref)		1 (Ref)			3,197	8,355.44	38.26	1 (Ref)		1 (Ref)		
LAIAs alone	813	2,350.00	34.60	0.60	0.54, 0.66	0.67	0.61, 0.74	<0.0001	536	1,992.25	26.90	0.63	0.56, 0.70	0.66	0.59, 0.74	<0.0001
Hospitalizations for depressive episodes																
OAs alone	334	2,266.12	14.74	1 (Ref)		1 (Ref)			213	1,956.12	10.89	1 (Ref)		1 (Ref)		
LAIAs alone	71	347.81	20.41	1.01	0.72, 1.41	1.34	0.94, 1.93	0.11	46	284.70	16.16	1.03	0.70, 1.53	1.22	0.79, 1.88	0.36
Hospitalizations for manic episodes																
OAs alone	2,135	7,830.00	27.27	1 (Ref)		1 (Ref)			1,409	6,798.23	20.73	1 (Ref)		1 (Ref)		
LAIAs alone	306	1,899.50	16.11	0.41	0.36, 0.48	0.51	0.44, 0.59	<0.0001	184	1,618.75	11.37	0.43	0.36, 0.52	0.48	0.40, 0.57	<0.0001
Hospitalizations for mixed episodes																
OAs alone	167	1,245.94	13.40	1 (Ref)		1 (Ref)			118	1,072.74	11.00	1 (Ref)		1 (Ref)		
LAIAs alone	11	232.48	4.73	0.26	0.13, 0.54	0.31	0.14, 0.66	0.0025	8	192.88	4.15	0.30	0.13, 0.69	0.33	0.14, 0.81	0.015

[a] aIRR, adjusted IRR; ED, emergency department; IRR, incidence rate ratio; LAIA, long-acting injectable antipsychotic; OA, oral antipsychotic.
[b] Beyond the first 90 days in each treatment period.
[c] Adjusted for age (1-year bands), season (cut by the first day of March, May, September, and November), COVID-19 stringency index (32), and use of concomitant medications (mood stabilizers, antidepressants, hypnotics and anxiolytics, and antiparkinsonian drugs).

TABLE 3. Results for secondary outcomes in the self-controlled case series analysis of the use of long-acting injectable antipsychotics alone versus oral antipsychotics alone in bipolar disorder[a]

Outcome event	Full treatment period								Subsequent treatment period[b]						
	Number of events	Person-years	Incidence per 100 person-years	IRR	95% CI	aIRR[c]	95% CI	p	Number of events	Person-years	Incidence per 100 person-years	IRR	95% CI	aIRR[c]	95% CI	p
Nonpsychiatric hospitalizations																
OAs alone	3,926	7,971.28	49.25	1 (Ref)		1 (Ref)			3,341	6,938.89	48.15	1 (Ref)		1 (Ref)		
LAIAs alone	826	1,981.37	41.69	0.99	0.89, 1.10	0.97	0.87, 1.08	0.59	675	1,701.81	39.66	0.97	0.87, 1.09	0.95	0.84, 1.07	0.41
Cardiovascular hospitalizations																
OAs alone	537	2,426.16	22.13	1 (Ref)		1 (Ref)			467	2,145.16	21.77	1 (Ref)		1 (Ref)		
LAIAs alone	101	590.64	17.10	0.97	0.73, 1.29	0.84	0.62, 1.14	0.27	78	514.69	15.15	0.83	0.60, 1.14	0.74	0.52, 1.03	0.075
Extrapyramidal symptoms																
OAs alone	63	1,302.72	4.84	1 (Ref)		1 (Ref)			49	1,105.44	4.43	1 (Ref)		1 (Ref)		
LAIAs alone	36	357.18	10.08	3.29	1.73, 6.26	2.95	1.40, 6.22	0.0044	22	294.42	7.47	2.76	1.30, 5.85	2.01	0.85, 4.75	0.11

[a] aIRR, adjusted IRR; IRR, incidence rate ratio; LAIA, long-acting injectable antipsychotic; OA, oral antipsychotic.
[b] Beyond the first 90 days in each treatment period.
[c] Adjusted for age (1-year bands), season (cut by the first day of March, May, September, and November), COVID-19 stringency index (32), and use of concomitant medications (mood stabilizers, antidepressants, hypnotics and anxiolytics, and antiparkinsonian drugs).

increased risk of cardiovascular hospitalizations and EPS relative to the pre-exposure period.

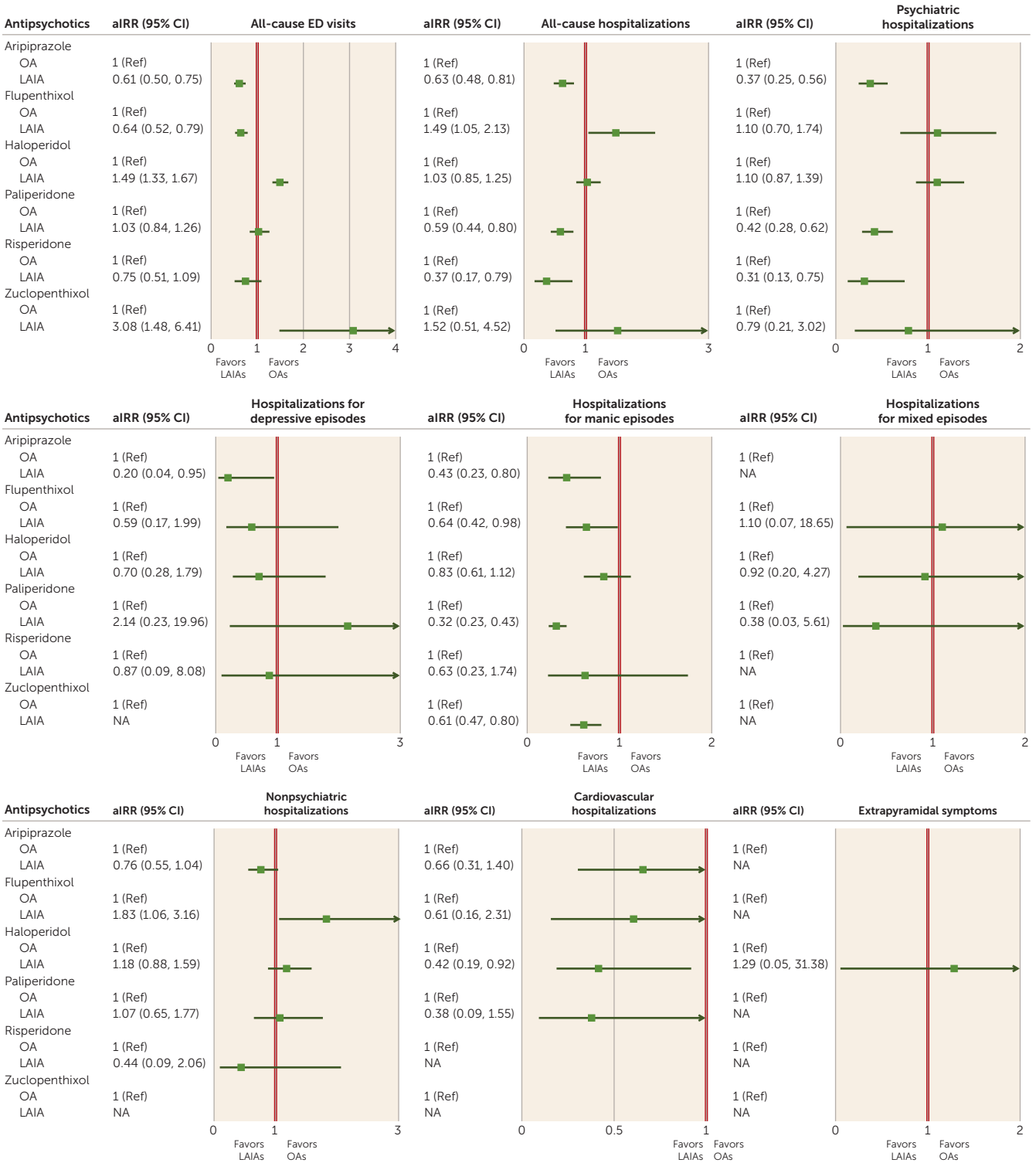
Overall, the sensitivity analyses aligned with the main findings (see Table S5 in the online supplement). In the negative control analysis, no statistically significant difference was observed between LAIAs and OAs for upper respiratory tract infections, supporting the robustness of our findings. For outcomes with significant inverse associations, the E-values for the upper 95% confidence interval ranged from 1.50 to 2.78, quantifying the minimum strength of residual confounding on the rate ratio scale required to explain away the association (see Table S6 in the online supplement).

DISCUSSION

To our knowledge, this is the first study comparing LAIAs and OAs for long-term impact on health care utilization, illness relapse, and safety among people with bipolar disorder. In this SCCS study of 2,086 patients with extended follow-up, LAIAs were associated with substantially less health care utilization and fewer psychiatric hospitalizations and hospitalizations for manic and mixed episodes compared with OAs. Importantly, LAIA use was not associated with an increased risk of nonpsychiatric hospitalizations, notably those for cardiovascular diseases. Although an increased risk of EPS was observed during the full treatment period, it was not statistically significant after the first 90 days of treatment were excluded. These findings highlight the potential of LAIAs to improve clinical outcomes and reduce the health care burden of bipolar disorder.

Previous studies have focused primarily on effectiveness outcomes limited to all-cause hospitalizations and emergency department visits (15–18, 22, 35–37). Our study provides additional insights into hospitalizations for various causes and EPS by evaluating all seven LAIAs available in Hong Kong public hospitals, including aripiprazole, flupenthixol, fluphenazine, haloperidol, paliperidone, risperidone, and zuclopenthixol, both collectively and individually. Our study aligns with previous work showing that LAIAs are associated with lower risks of all-cause emergency department visits (16, 22, 35, 37), all-cause hospitalizations (15–18, 22, 35, 36), and psychiatric hospitalizations (15, 38). Moreover, our results show that LAIAs were particularly effective in reducing manic and mixed episodes, whereas their impact on depressive episodes was generally limited, which is consistent with the previous studies (18, 22, 35, 39, 40). Notably, aripiprazole LAI was the only agent associated with a reduced risk of hospitalizations for depressive episodes compared to its oral formulation. Second-generation LAIAs, including aripiprazole, paliperidone, and risperidone, were associated with lower risks of all-cause and psychiatric hospitalizations than their oral counterparts, whereas this difference was not observed for first-generation LAIAs, such as flupenthixol and haloperidol. This may be partly due to the pharmacological properties of second-generation antipsychotics, such as 5-HT_{2A} antagonism and 5-HT_{1A} partial agonism, which enhance

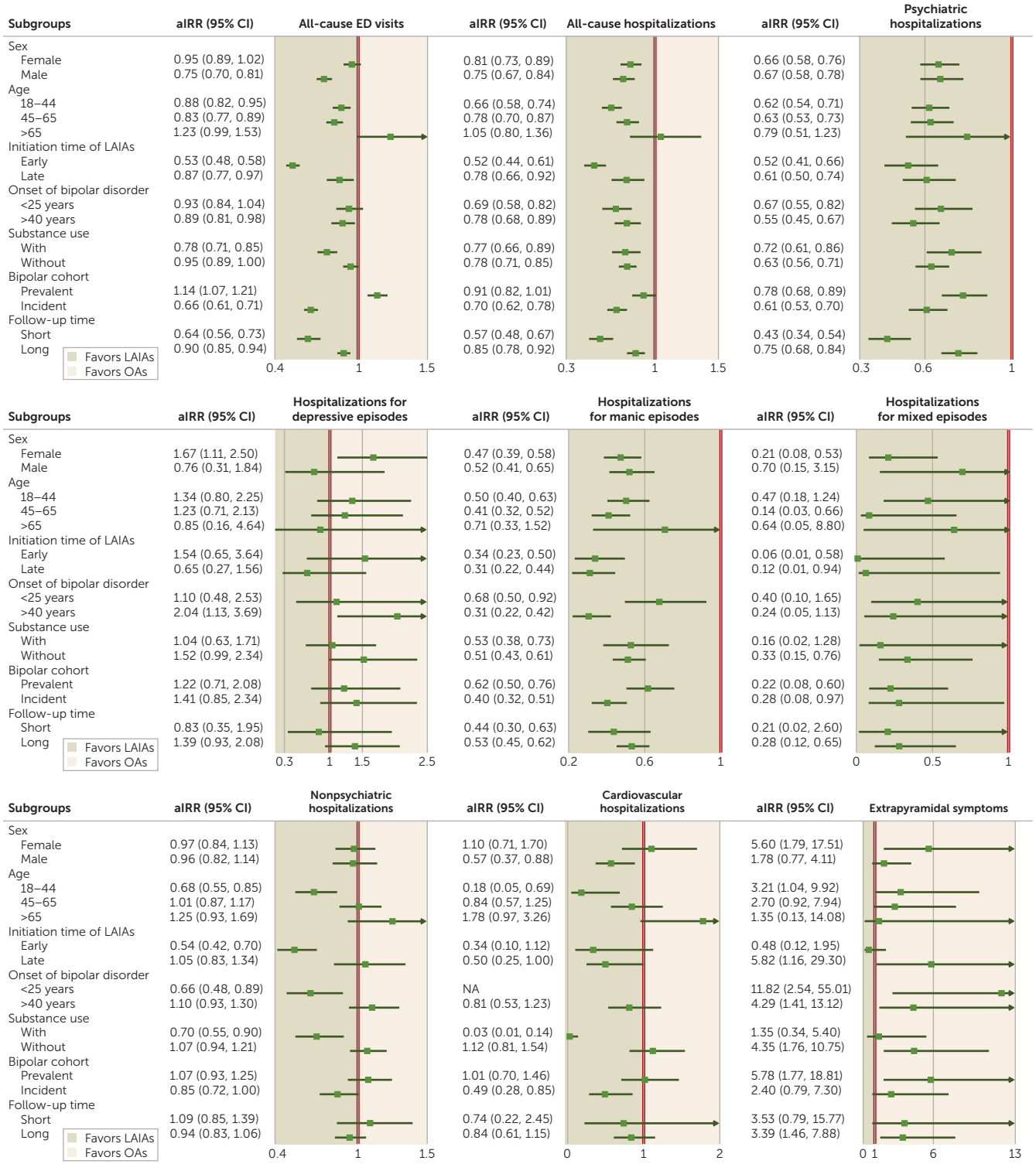
FIGURE 2. Direct comparison between the oral and long-acting injectable formulations of the same antipsychotic in bipolar disorder[a]



[a] The aIRR estimation was adjusted for age (1-year bands), season (cut by the first day of March, May, September, and November), COVID-19 stringency index (32), and use of concomitant medications (mood stabilizers, antidepressants, hypnotics and anxiolytics, and antiparkinsonian drugs). ED, emergency department; aIRR, adjusted incidence rate ratio; LAIA, long-acting injectable antipsychotic; OA, oral antipsychotic.

their efficacy and tolerability when they are administered as LAIAs. The superior effects of LAIAs on manic relapses may be attributed to the antipsychotics' mechanism; they work primarily on dopamine receptors instead of serotonin receptors related to depressive episodes. Although five antipsychotics (cariprazine, lumateperone, lurasidone, olanzapine,

FIGURE 3. Subgroup analyses for the use of long-acting injectable antipsychotics versus oral antipsychotics during the full treatment period in bipolar disorder[a]



[a] The aIRR estimation was adjusted for age (1-year bands), season (cut by the first day of March, May, September, and November), COVID-19 stringency index (32), and the use of concomitant medications (mood stabilizers, antidepressants, hypnotics and anxiolytics, and antiparkinsonian drugs). Subgroups were categorized by sex, age, timing of LAIA initiation (early, within 2 years of the first bipolar disorder diagnosis; or late, after 2 years), age at onset of bipolar disorder (early onset, first episode before age 25; or late onset, first episode after age 40), substance use, timing of the first bipolar disorder diagnosis (prevalent cohort, first diagnosis before January 1, 2004; or incident cohort, first diagnosis on or after January 1, 2004), and duration of follow-up (short, ≤10 years; or long, >10 years). aIRR, adjusted incidence rate ratio; ED, emergency department; LAIA, long-acting injectable antipsychotic; OA, oral antipsychotic.

and quetiapine) are approved for bipolar depression by the U.S. Food and Drug Administration (2), long-acting formulations are not available for most of these medications, and olanzapine LAI is not available in Hong Kong. The lack of concomitant mood stabilizer treatment may further reduce protection against depressive episodes, suggesting adjunctive treatments alongside LAIAs may be required. Moreover, a statistically significant increase in risk of hospitalizations for depressive episodes associated with LAIAs was observed among female patients. This may be due to the prolonged dopamine blockade by LAIAs, particularly prolactin-raising agents like risperidone, which elevate prolactin and suppress gonadotropin-releasing hormone, thereby reducing estradiol levels (41). Women may be especially vulnerable during periods such as menses, perimenopause, and the postpartum, when estradiol fluctuations exacerbate bipolar depression (42). This emphasizes the need to consider sex-specific factors when selecting and initiating antipsychotic agents and highlights the importance of closely monitoring female patients on LAIAs for signs of depressive relapses.

Our findings provide evidence regarding the safety profiles of LAIAs in bipolar disorder. Specifically, we found no increased risk of nonpsychiatric hospitalizations associated with LAIAs compared to OAs, which is consistent with a previous study (38). Despite the well-known risk of elevated cardiovascular mortality associated with antipsychotics (1, 13), this is the first study to compare cardiovascular risk between LAIAs and OAs. The evaluation of cardiovascular hospitalizations revealed no increased risk with LAIAs, suggesting their longer-term safety among people with bipolar disorder. However, our findings showed that LAIAs were initially associated with an elevated risk of EPS compared to OAs, but this association was no longer statistically significant after the first 90 days were excluded. This early increased risk may be attributable to several factors. First, the loading doses and sustained-release formulations of LAIAs can elevate peak drug levels and block dopamine D_2 receptors for a prolonged period, which can abruptly heighten the risk of EPS (43). Additionally, milder EPS symptoms often resolve within days to weeks and can be effectively managed with anticholinergic agents (44). Patients are also typically more closely monitored during treatment initiation, which may lead to higher detection rates of EPS, and undercoding for EPS in observational studies might bias these findings. Additional prospective studies with validated EPS assessments are needed to better define the safety profile of LAIAs and to inform guidelines for EPS monitoring. To enhance safety and tolerability, clinicians may consider strategies such as slow titration, close monitoring, and judicious use of "as-needed" anticholinergic medications when initiating LAIAs in individuals with bipolar disorder.

In the age-stratified analysis, the benefits of LAIAs compared to OAs were not observed among individuals age 65 and older. This lack of observed benefit may be attributable to age-related changes in pharmacokinetics and pharmacodynamics, as well as the high prevalence of comorbidities, which might diminish the relative effectiveness of LAIAs. Conversely, our results support the use of LAIAs as a valuable treatment option for individuals with substance use disorders, who are more vulnerable to nonadherence and frequent relapse (25, 26). We observed that early initiation of LAIAs is associated with reduced risk of health care utilization, suggesting potential benefits of timely intervention. While current guidelines generally recommend reserving LAIAs for severe cases or individuals with established nonadherence (5, 6, 12), our findings support reassessment of this conservative approach to optimize care for individuals with bipolar disorder.

This study has several strengths. First, we used an intra-individual comparison approach that controlled for both unknown and unmeasured time-invariant confounders by having participants function as their own controls. In addition, we adjusted for critical time-varying confounders, including age, season, COVID-19 stringency index, and concomitant medications, which further strengthened the robustness of our results. Furthermore, our analyses extended beyond an overall comparison of LAIAs and OAs, which includes the head-to-head comparisons between oral and depot formulations of the same antipsychotic and comparisons between individual antipsychotic treatments between treatment periods and the corresponding pre-exposure periods. Unlike most previous studies, which were restricted to 12 months, the long-term follow-up in this study (a mean of 11.6 years) enabled exploration of the long-term effectiveness and safety of LAIAs in people with bipolar disorder, who often require lifelong treatment. Additionally, as far as we are aware, this is the first investigation of LAIAs analyzing periods after the first 90 days of treatment among people with bipolar disorder. The design minimized bias by accounting for the delayed onset of full treatment effects, event-driven treatment changes, and residual effects from previous treatments.

This study has several limitations. First, our database included only Hong Kong public hospitals and excluded private health care users and individuals who moved out of Hong Kong during the study period. Since the Hospital Authority accounts for over 80% of hospital admissions and most patients with chronic diseases (27), the impact of missing data is limited. Nonetheless, the results of the study may not generalize to other regions, owing to variations in health care access and socioeconomic and cultural factors. Second, key variables such as illness severity, medication adherence, bipolar disorder subtype, psychosocial interventions, and patient preferences for medications were unavailable, and doses for OAs and LAIAs were recorded differently in CDARS. The sequence and duration of the treatment modalities were not adjusted, owing to the inherent challenge of using the SCCS design. These gaps may result in exposure and outcome misclassification and hinder dose-specific and bipolar disorder subtype–specific analyses, leading to residual confounding. However, for the significant inverse associations, the E-values for the upper 95% confidence interval ranged from 1.50 to

2.78, quantifying the minimum strength of residual confounding on the rate ratio scale required to explain away the association. Third, the SCCS design selected individuals who had received prescriptions for both OAs and LAIAs and experienced at least one outcome event, potentially biasing the sample toward more severe cases. Although milder relapses without hospital visits were not captured in our analysis, the included patients may represent those most likely to experience nonadherence and to be in need of LAIAs in clinical practice. Moreover, the requirement for exposure and outcomes further limits the analyses of individual LAIAs and the combinations of antipsychotics with concurrent medications (e.g., mood stabilizers). Future studies could explore potential synergistic effects of adjunctive treatments and assess individual LAIAs more comprehensively.

In summary, among people with bipolar disorder, LAIAs were associated with less health care utilization and fewer relapses of manic and mixed episodes compared to OAs, without increased risk of nonpsychiatric hospitalizations, including cardiovascular hospitalizations. While the use of LAIAs was associated with an elevated risk of EPS, this association was not statistically significant when the first 90 days of treatment were excluded. Our findings support the implementation of long-term LAIA use among people with bipolar disorder, along with close monitoring for EPS, particularly during the initiation phase.

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