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Predictors of Long-Acting Injectable Antipsychotic Medication Use in Patients with Schizophrenia Spectrum, Bipolar, and Other Psychotic Disorders in a US Community-based, Integrated Health System

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Background and Hypothesis. **Long-acting injectable (LAI) antipsychotics improve patient outcomes and are recommended by treatment guidelines for patients with limited medication adherence in schizophrenia spectrum, bipolar, and other psychotic disorders. Reports of LAI antipsychotic use in these disorders and if use aligns with treatment guidelines are lacking. This study aimed to report patient characteristics associated with LAI antipsychotic use in these disorders.** ***Study Design.*** **Retrospective observational study of patients ≥18-years-old with bipolar or psychotic disorders at a large, integrated, community-based health system. Patient demographic and clinical characteristics served as exposures for the main outcome of adjusted odds ratio (aOR) for LAI versus oral antipsychotic medication use from January 1, 2017 to December 31, 2023.** ***Study Results.*** **There were $N = 2685$ LAI and $N = 31\ 531$ oral antipsychotic users. Being non-white (aOR = 1.3-2.0; $P < .0001$), non-female (aOR = 1.5; $P < .0001$), from a high deprivation neighborhood (NDI, aOR = 1.3; $P < .0007$), having a higher body mass index (BMI, aOR = 1.3-1.7; $P < .0009$), having a schizophrenia/schizoaffective (aOR = 5.8-6.8; $P < .0001$), psychotic (aOR = 1.6, $P < .0001$), or substance use disorder (aOR = 1.4; $P < .0001$), and outpatient psychiatry (aOR = 2.3-7.5; $P < .0001$) or inpatient hospitalization (aOR = 2.4; $P < .0001$) utilization in the prior year with higher odds and age ≥40 (aOR = 0.4-0.7; $P < .0001$) or bipolar disorder (aOR = 0.9; $P < .05$) were associated with lower odds of LAI use. Non-white, non-female, age 18-39, and high NDI patients had higher LAI use regardless of treatment adherence markers. Smoking and cardiometabolic markers were also associated with LAI use.** ***Conclusions.*** **Demographic and clinical factors are associated with increased LAI use irrespective of treatment adherence. Research on utilization variation informing equitable formulation use aligned with treatment guideline recommendations is warranted.**

Key words: schizophrenia/bipolar disorder/psychotic disorders/treatment adherence/health inequities

Introduction

Schizophrenia and bipolar spectrum disorders impact 0.25%-0.64%[1] and 4.4%[2] of the US population, respectively, and are associated with significant morbidity,[3,4] mortality,[4,5] and disability.[4,5] Antipsychotics are an evidence-based and guideline-recommended treatment approved by the Food and Drug Administration for the primary treatment of schizophrenia and bipolar disorders associated with improved psychosocial functioning,[6] morbidity,[7] and reduced mortality.[7] However, patient antipsychotic medication adherence is variable, with patient reports ranging from 24% to 90%[8,9] and 27% having expected plasma levels.[10] Low antipsychotic medication adherence has been associated with poor treatment outcomes,[9,11] significantly less symptom improvement,[11,12] a greater risk of hospital readmission,[13] and a higher risk of suicide and cognitive impairment[13] in schizophrenia and bipolar disorders. Strategies to improve antipsychotic medication adherence have been identified as a primary strategy to improve treatment failure.[9,14]

Long-acting injectable (LAI) formulations of antipsychotic medications are an effective strategy to improve

patient antipsychotic adherence[15,16] as they require medication injection once every few weeks or months rather than daily oral adherence and are superior to oral formulations for relapse prevention.[17] LAI treatment is associated with improved patient outcomes, functioning, quality of life, and lower rates of hospitalization in schizophrenia and bipolar disorders.[18–21] Current treatment guidelines by organizations including the American Psychiatric Association recommend LAI antipsychotic medications when treatment adherence is poor or uncertain,[22] and LAI use has been identified as a strategy to improve treatment adherence[14,23] yet LAI antipsychotic use in the United States is estimated at less than 20% of patients for whom LAIs would be appropriate based on treatment adherence.[11]

Previous work suggests LAI antipsychotics are more likely to be prescribed to patients who are young, male, and African American.[24–31] This literature was restricted to a binary categorization of race and did not examine other demographic variables including socioeconomic status, cardiometabolic risk factors that are associated with antipsychotic use,[22] or patient clinical characteristics such as psychiatric diagnosis, inpatient hospitalizations, outpatient care utilization, or oral medication adherence. Such factors have been recommended to consider when starting antipsychotic medications by treatment guidelines,[22] and may impact provider or patient decision-making in using an antipsychotic medication. Further, many LAI antipsychotics, including second-generation antipsychotics, are absent from this literature.[32] Finally, there are no studies examining patient characteristics associated with LAI antipsychotic use in real-world, large, diverse, community-based integrated health systems or if LAI use is in treatment guideline-recommend populations.

This study aimed to examine patient demographic and clinical predictors of LAI versus oral antipsychotic medication use. We hypothesized that previously reported demographic variables including age, gender, and African American race, along with clinical variables associated with clinical severity, would predict LAI use. Additionally, we performed subgroup analyses based on measures of treatment adherence to explore if LAI use conformed to treatment guideline recommendations for patients with an antipsychotic diagnosis in their medical history.

Methods

Study Design and Participants

This retrospective, observational study used electronic health record (EHR) data from Kaiser Permanente Northern California (KPNC); a large, diverse, community-based, integrated healthcare system in the United States serving more than four and a half million patients.[26] KPNC patients are highly representative of the ethnic and socioeconomic diversity of the surrounding and statewide populations.[33] Included subjects were 18-years-old or older prescribed and filled either an LAI or oral antipsychotic medication (defined as antipsychotic use, see list in Supplemental table 1) from January 1, 2017 to December 31, 2023 with at least 28 days of exposure to antipsychotic medications and at least one diagnosis of schizophrenia (ICD-10 F20-21), schizoaffective disorder (F25), psychotic disorder (F22-24, F28-29), or bipolar disorder (F30-31) in an outpatient, inpatient, emergency, rehabilitation facility, or skilled nursing setting, and with continuous health plan enrollment 2 years prior to antipsychotic drug treatment start. Each subject was included only once in the study, with subjects receiving an LAI during the time period exclusively counted in the LAI group for the study time period, regardless of preexisting oral history.

Exclusion criteria included subjects younger than 18-years-old or did not have any of the diagnoses listed above. This study followed the strengthening of the reporting of observational studies in epidemiology (STROBE) guidelines for observational studies and was approved by the KPNC Institutional Review Board. The research was conducted in accordance with the principles of the Declaration of Helsinki.

Exposure Measures

All exposures were derived at the time of antipsychotic medication start in the study period. For our main study exposure for prescribed and filled LAI or oral antipsychotic medication, we required at least 28 days of exposure from the first medication dispensed to the end of supply for the next medication in order to define "start" of antipsychotic medication. Patient demographic and clinical characteristics were considered study exposures. Patient demographic characteristics were obtained from the EHR and included age, reported gender (categorized as self-identified as female vs any other gender), race, ethnicity, and neighborhood deprivation index (NDI; a geocoded measure of socio-economic status with categories based on the quartiles of the overall cohort; higher numbers indicate more deprivation). Patient clinical characteristics from the EHR included current or history of smoking (defined as ever smoking); body mass index (BMI); and last year history of or current hyperlipidemia or hypertension diagnoses. Diabetes status was determined using the KPNC Diabetes registry. Inpatient hospitalization or emergency department utilization was defined as at least one encounter in the year prior to antipsychotic medication start, while outpatient psychiatry encounters in the year prior to antipsychotic medication start were treated as ordinal values. We used electronic health records (EHR) documented diagnoses for schizophrenia (ICD-10 F20-21), schizoaffective disorder (F25), psychotic disorder (F22-24, F28-29), or bipolar disorder (F30-31) in an outpatient, inpatient, emergency, rehabilitation facility, or skilled nursing

setting during the 2 years, or any active diagnoses listed in the patient charts prior to drug start date to define our criteria for antipsychotic medication-associated diagnosis We created indicators for each diagnoses type as some patients had multiple diagnoses. Patients with no psychotic diagnoses were excluded from the study. Patients with active substance abuse in the year prior were defined with at least two encounters with documented diagnoses (ICD-10 F10.x to F19.x, excluding any indicating counseling, remission, or history). We defined oral antipsychotic medication adherence as a dichotomous variable, that is, medication possession ratio (MPR) ≥ 80% for outpatient dispensed medications.[34] Since this patient population could have concurrent usage of multiple oral or LAI medications we calculated MPR per dispensed medication and used the maximum MPR per patient to define adherence.

Outcome

The main study outcome was a dichotomous variable defined as the first use of LAI antipsychotic medication use during the study period. Patients in the oral group had no LAI antipsychotic medication use during the study period. We understand that these patients may be prevalent users of antipsychotic medications, and hence patients with an outcome defined as LAI use at study start of January 2017, may be concurrent or prior oral users, and similarly the patients with an outcome defined as oral use may have had LAI usage prior to study start date. We also created dichotomous variables to indicate prior use of oral or LAI medications to define the prevalent use of antipsychotic medications.

In order to validate our main exposure and outcomes, we chart reviewed 50 cases randomly selected by year, exposure, and diagnosis. 100% of patients were correctly identified.

Statistical Analysis

A significance level (Type I error rate) of .05 was set for all tests. Clinical and demographic baseline characteristics were summarized using means and proportions. Multivariable logistic regression was used to estimate the association between each exposure of interest and the dichotomous outcome (use of LAIs), controlling for all other exposures. To examine predictors of LAI antipsychotic medication use as related to treatment guidelines, we examined subgroups that represent treatment adherence.[35,36] These included past-year history of inpatient hospitalization (which has been strongly associated with treatment adherence[35–38]), oral antipsychotic medication adherence (defined as MPR ≥80% for outpatient dispensed medications),[34] and outpatient psychiatry utilization (which has been strongly associated with treatment adherence[35–38]) in the year prior to LAI start. All analyses were performed using SAS 9.4 (Cary, North Carolina).

Results

Patient Population and Characteristics

From January 1, 2017 to December 31, 2023, $N = 34\,216$ adults met study inclusion criteria (Supplemental figure 1), with $n = 2685$ (7.8%) patients using an LAI and $n = 31\,531$ (92.2%) patients using an oral antipsychotic (table 1). Overall, 56.4% of patients were White, 10.3% African American, 10.3% Asian, 11.9% Hispanic, and 11.1% Other/Unknown. Fifty-eight percent (58.5%) identified as female, 38.6% were aged 18-39 whereas 39.2% were aged 40-64 and 22.2% were ≥65; most patients lived in a neighborhood with an NDI > 1 (76.6%). The majority had a BMI higher than normal range (58.2%). The majority had no history of or current smoking (53.4%), hyperlipidemia (67.9%), hypertension (69.2%), or diabetes (84.5%). Only 7.7% had any substance abuse disorders in the year prior. Antipsychotic-associated diagnoses were schizophrenia (13.4%), bipolar (66.0%), schizoaffective (13.1%), and other psychotic disorders (32.6%). Most patients had at least one prior outpatient psychiatric encounter (79.1%) and at least one emergency department encounter (55.4%) in the last year; 27.6% had an inpatient hospitalization in the last year.

Patient Demographic and Clinical Associations with LAI Versus Oral Antipsychotic Use

The adjusted odds ratio (aOR) showed a significant association of most patient demographic and clinical characteristics with the use of LAI versus oral antipsychotic medications. All races and ethnicities had a higher odds of LAI use versus White ($P < .0001$ for all except Other/Unknown, $P = .0017$; figure 1); as did patients identifying as non-female versus female ($P < .0001$). Patients aged 18-39 had the highest odds of LAI use ($P < .0001$ compared to age groups 40-64 or ≥ 65). Highest NDI (quartile 4) was significantly associated with higher odds of LAI use ($P = .0007$)

Having a BMI above the normal range was significantly associated with higher odds of LAI use ($P < .001$ for all). A history of smoking ($P < .0001$), diabetes ($P < .05$), hyperlipidemia ($P = .01$) were associated with higher odds while a history of hypertension was associated with lower odds of LAI use ($P = .02$).Patient with substance use disorder diagnoses in the year prior had higher odds of LAI use ($P < .0001$). All psychiatric diagnoses had higher odds of LAI use except for bipolar disorder ($P < .0001$ for all).

Patients with a history of two or more outpatient psychiatry encounters in the year prior to antipsychotic medication start had a significantly higher odds of LAI use ($P < .0001$ for all), as did patients with one or more inpatient hospitalization ($P < .0001$). All years after the study index year of 2017 showed significantly higher odds of LAI use ($P < .0001$ for all).

Table 1. Baseline Characteristics of Patients Overall and by Antipsychotic Medication Route

Patient Characteristics		All Patients	Long-acting Injectable	Oral
		N = 34 216	*N* = 2685 (7.8%)	*N* = 31 531 (92.2%)
Race or ethnicity	African American	3520 (10.3%)	523 (19.5%)	2997 (9.5%)
	Asian	3533 (10.3%)	361 (13.4%)	3172 (10.1%)
	Hispanic	4079 (11.9%)	444 (16.5%)	3635 (11.5%)
	Other/unknown	3800 (11.1%)	319 (11.9%)	3481 (11.0%)
	White	19 284 (56.4%)	1038 (38.7%)	18 246 (57.9%)
Age at start of medication, years	18-39	13 217 (38.6%)	1610 (60.0%)	11 607 (36.8%)
	40-64	13 410 (39.2%)	879 (32.7%)	12 531 (39.7%)
	≥65	7589 (22.2%)	196 (7.3%)	7393 (23.4%)
	Mean (SD)	47.9 (19.8)	38.2 (15.9)	48.8 (19.9)
Gender	Female	20 020 (58.5%)	1122 (41.8%)	18 898 (59.9%)
	Male/other	14 196 (41.5%)	1563 (58.2%)	12 633 (40.1%)
Neighborhood deprivation index	Missing	9 (0.0%)		9 (0.0%)
	Quartile 1	8012 (23.4%)	496 (18.5%)	7516 (23.8%)
	Quartile 2	8228 (24.0%)	546 (20.3%)	7682 (24.4%)
	Quartile 3	8714 (25.6%)	693 (25.8%)	8021 (25.4%)
	Quartile 4	9253 (27.0%)	950 (35.4%)	8303 (26.3%)
Body mass index, kg/m^2	Under/normal	9431 (27.6%)	629 (23.4%)	8802 (27.9%)
	Overweight	8682 (25.4%)	641 (23.9%)	8041 (25.5%)
	Obese	11 237 (32.8%)	1031 (38.4%)	10 206 (32.4%)
	Missing	4866 (14.2%)	384 (14.3%)	4482 (14.2%)
	Mean (SD)	29.0 (7.4)	29.9 (7.6)	29.0 (7.4)
Smoking	No	18 280 (53.4%)	1208 (45.0%)	17 072 (54.1%)
	Yes	15 936 (46.6%)	1477 (55.0%)	14 459 (45.9%)
Hyperlipidemia	No	23 232 (67.9%)	1911 (71.2%)	21 321 (67.6%)
	Yes	10 984 (32.1%)	774 (28.8%)	10 210 (32.4%)
Hypertension	No	23 685 (69.2%)	2008 (74.8%)	21 677 (68.7%)
	Yes	10 531 (30.8%)	677 (25.2%)	9854 (31.3%)
Diabetes	No	28 908 (84.5%)	2283 (85.0%)	26 625 (84.4%)
	Yes	5308 (15.5%)	402 (15.0%)	4906 (15.6%)
Substance use disorder diagnosis	No	31 595 (92.3%)	2230 (83.1%)	29 365 (93.1%)
	Yes	2621 (7.7%)	455 (16.9%)	2166 (6.9%)
Schizophrenia disorder diagnosis	No	29 625 (86.6%)	1282 (47.7%)	28 343 (89.9%)
	Yes	4591 (13.4%)	1403 (52.3%)	3188 (10.1%)
Schizoaffective disorder diagnosis	No	29 740 (86.9%)	1400 (52.1%)	28 340 (89.9%)
	Yes	4476 (13.1%)	1285 (47.9%)	3191 (10.1%)
Bipolar disorder diagnosis	No	11 645 (34.0%)	1451 (54.0%)	10 194 (32.3%)
	Yes	22 571 (66.0%)	1234 (46.0%)	21 337 (67.7%)
Psychotic disorder diagnosis	No	23 055 (67.4%)	1069 (39.8%)	21 986 (69.7%)
	Yes	11 161 (32.6%)	1616 (60.2%)	9545 (30.3%)
Outpatient psychiatry utilization prior year	0	7137 (20.9%)	162 (6.0%)	6975 (22.1%)
	1	5430 (15.9%)	141 (5.3%)	5289 (16.8%)
	2-3	6728 (19.7%)	311 (11.6%)	6417 (20.4%)
	4+	14 921 (43.6%)	2071 (77.1%)	12 850 (40.8%)
Emergency department utilization prior year	No	15 244 (44.6%)	624 (23.2%)	14 620 (46.4%)
	Yes	18 972 (55.4%)	2061 (76.8%)	16 911 (53.6%)
Inpatient hospital utilization prior year	No	24 777 (72.4%)	1043 (38.8%)	23 734 (75.3%)
	Yes	9439 (27.6%)	1642 (61.2%)	7797 (24.7%)
Any use of antipsychotic drugs prior year	No	18 876 (55.2%)	272 (10.1%)	18 604 (59.0%)
	Yes	15 340 (44.8%)	2413 (89.9%)	12 927 (41.0%)
If any use, MPR ≥80%	Yes	14 048 (91.6%)	2288 (94.8%)	11 760 (91.0%)
Any use of oral antipsychotic drugs prior year	No	18 891 (55.2%)	373 (13.9%)	18 518 (58.7%)
	Yes	15 325 (44.8%)	2312 (86.1%)	13 013 (41.3%)
Any use of LAI antipsychotic drugs prior year	No	33 531 (98.0%)	2053 (76.5%)	31 478 (99.8%)
	Yes	685 (2.0%)	632 (23.5%)	53 (0.2%)
Year at start of medication	2017	17 320 (50.6%)	908 (33.8%)	16 412 (52.1%)
	2018	3400 (9.9%)	313 (11.7%)	3087 (9.8%)
	2019	2958 (8.6%)	292 (10.9%)	2666 (8.5%)
	2020	2712 (7.9%)	252 (9.4%)	2460 (7.8%)
	2021	2743 (8.0%)	347 (12.9%)	2396 (7.6%)

Table 1. Continued

Patient Characteristics		All Patients	Long-acting Injectable	Oral
	2022	2597 (7.6%)	312 (11.6%)	2285 (7.2%)
	2023	2486 (7.3%)	261 (9.7%)	2225 (7.1%)

Note: LAI, long-acting injectable; SD, standard deviation; kg, kilogram; m, meters. Body mass index categories are defined as <25 underweight/normal, ≥25 to <30 overweight, ≥30 obese/severely obese. Neighborhood deprivation index is a geocoded measure of socioeconomic status with categories based on the quartiles of the overall cohort, with higher scores indicating more deprivation. Substance use, smoking, hyperlipidemia, hypertension, and diabetes are defined as documented in the electronic health record in the year prior to or concurrent with medication start. Diagnoses are defined as documented in electronic health records 2 years prior to drug start or noted in patient health history.

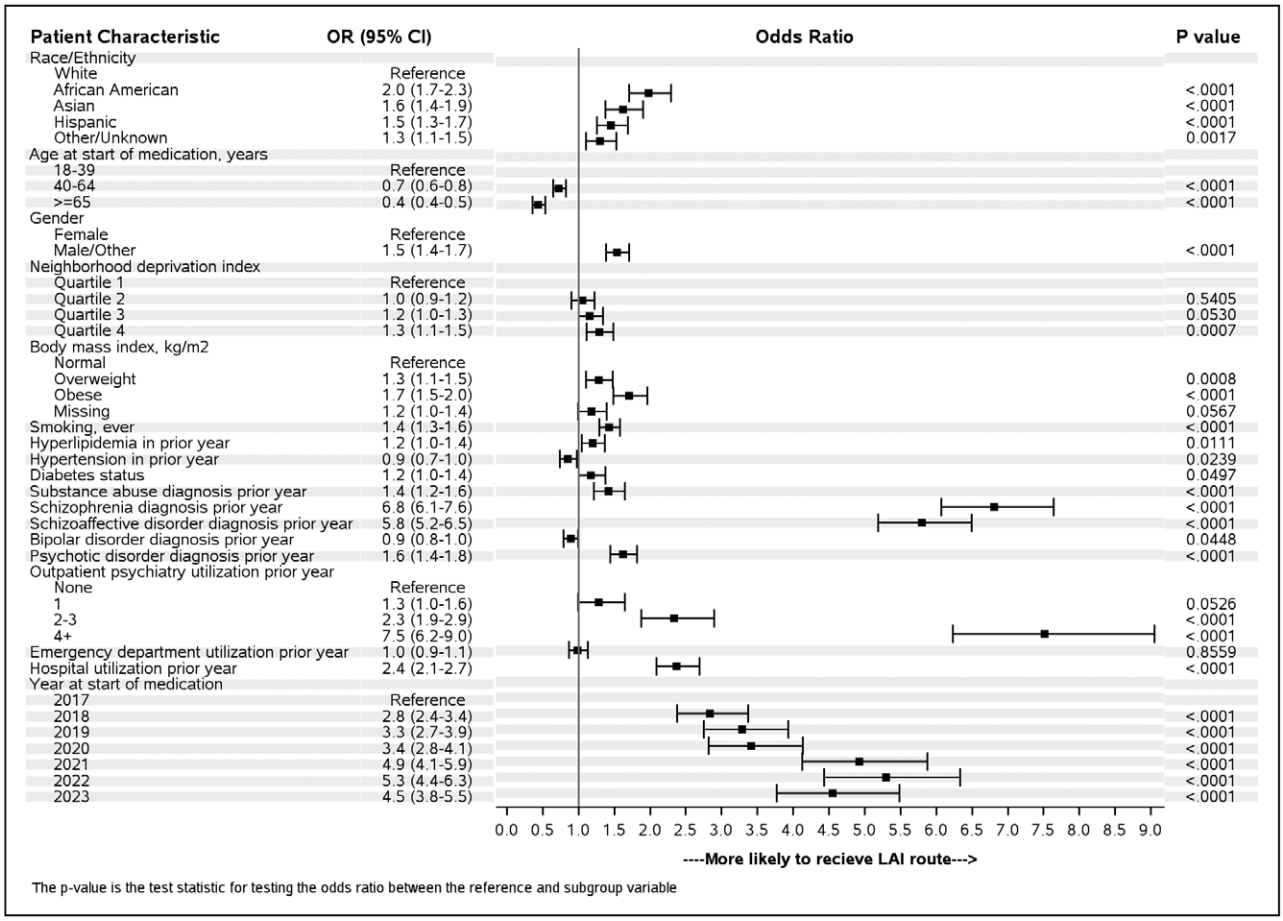

Fig. 1. Association of LAI versus oral administered antipsychotic medication route by patient characteristic. Patients had a higher odds of using the LAI antipsychotic medication route by race and ethnicity, age, body mass index, neighborhood deprivation index, smoking status, hyperlipidemia status, diabetes status, by primary diagnosis, history of inpatient or outpatient department utilization, and by year of medication start. OR, odds ratio; CI, confidence interval; kg, kilogram; m, meters. Body mass index categories are defined as <18.5 underweight, ≤18.5 to <25 normal, ≤25 to <30 overweight, ≤30 to <40 obese, ≥40 severely obese. Neighborhood deprivation index is a geocoded measure of socioeconomic status with categories based on the quartiles of the overall cohort, with higher scores indicating more deprivation. Substance use, smoking, hyperlipidemia, hypertension, and diabetes defined as documented in the electronic health record in the year prior to or concurrent with medication start. Diagnoses defined as documented in electronic health records 2 years prior to drug start or noted in patient health history.

LAI Versus Oral Antipsychotic Use in Patients With a History of Inpatient Hospitalization

When examining patients with a history of inpatient hospitalization in the year prior to antipsychotic medication start, the same pattern of significant associations of clinical and demographic characteristics with the odds of LAI versus oral antipsychotic use were observed, except for NDI categories and cardiometabolic markers

Table 2. Association of LAI Versus Oral Antipsychotic Medication Route for Patients With History of Inpatient Hospitalization During the Prior Year

Patient Characteristic		Odds Ratio (95% CI)	*P* Value
Race/ethnicity	White	Reference	
	African American	1.8 (1.4-2.2)	<.0001
	Asian	1.6 (1.3-2.0)	<.0001
	Hispanic	1.5 (1.2-1.9)	<.0001
	Other/unknown	1.3 (1.0-1.6)	.047
Gender	Female	Reference	
	Male/other	1.5 (1.3-1.8)	<.0001
Age at start of medication, years	18-39	Reference	
	40-64	0.8 (0.7-1.0)	.0252
	≥65	0.5 (0.4-0.7)	<.0001
Body mass index, kg/m^2	Normal	Reference	
	Overweight	1.2 (1.0-1.5)	.0245
	Obese	1.6 (1.3-1.9)	<.0001
	Missing	1.0 (0.8-1.3)	.8328
Neighborhood deprivation index	Quartile 1	Reference	
	Quartile 2	1.0 (0.8-1.2)	.94
	Quartile 3	1.0 (0.8-1.2)	.954
	Quartile 4	1.0 (0.9-1.3)	.6775
Smoking, ever		1.3 (1.1-1.5)	.0012
Hyperlipidemia in the prior year		1.2 (1.0-1.4)	.1379
Hypertension in the prior year		0.9 (0.7-1.1)	.3323
Diabetes status		1.0 (0.8-1.3)	.9662
Substance use disorder diagnosis		1.4 (1.1-1.7)	.001
Bipolar disorder diagnosis		1.5 (1.2-1.7)	<.0001
Psychotic disorder diagnosis		2.6 (2.2-3.1)	<.0001
Schizophrenia disorder diagnosis		4.9 (4.2-5.8)	<.0001
Schizoaffective disorder diagnosis		6.3 (5.3-7.4)	<.0001
Outpatient psychiatry utilization prior year	None	Reference	
	1	1.8 (1.2-2.6)	.0036
	2-3	4.8 (3.5-6.6)	<.0001
	4+	15 (12-21)	<.0001
Emergency department utilization prior year		1.8 (1.1-2.7)	.01
Year at start of medication	2017	Reference	
	2018	4.2 (3.3-5.4)	<.0001
	2019	5.0 (3.9-6.4)	<.0001
	2020	6.8 (5.2-8.8)	<.0001
	2021	7.9 (6.1-10)	<.0001
	2022	8.4 (6.5-11)	<.0001
	2023	7.0 (5.3-9.2)	<.0001

Note. CI, confidence interval; kg, kilogram; m, meters. Body mass index categories are defined as <25 underweight/normal, ≤25 to <30 overweight, ≥30 obese/severely obese. Neighborhood deprivation index is a geocoded measure of socioeconomic status with categories based on the quartiles of the overall cohort, with higher scores indicating more deprivation. Substance use, smoking, hyperlipidemia, hypertension, and diabetes are defined as documented in the electronic health record in the year prior to or concurrent with medication start. Antipsychotic diagnoses are defined as documented in electronic health records 2 years prior to drug start or noted in patient health history.

($P > .05$; table 2) and bipolar disorder (aOR = 1.5; $P < .0001$). Patients with one or more emergency department visits had higher odds ($P = .01$).

LAI Versus Oral Antipsychotic Use in Patients Based on Last Year Oral Antipsychotic Medication Adherence

In a stratified analysis, patients with oral antipsychotic medication adherence followed the same patterns of higher odds of LAI use as our main analysis results, including patients with BMI missing levels ($P < .0001$). However, cardiometabolic markers and bipolar diagnoses were not associated, while patients with emergency department visits had higher odds ($P < .0001$; table 3).

LAI Versus Oral Antipsychotic Use in Patients With Outpatient Psychiatric Healthcare Utilization

Similarly, in a stratified analysis, patients with kept outpatient psychiatry appointments in the prior year followed the same pattern of higher odds by patient characteristics as our main analyses, with significant associations of most clinical and demographic characteristics with the assignment to LAI antipsychotic medication except for

Table 3. Association of LAI Versus Oral Antipsychotic Medication Route by Patient Medication Adherence During the Prior Year

Patient Characteristic		With Medication Adherence	
		N = 14 047	
		Odds Ratio (95% CI)	*P* Value
Race/ethnicity	White	Reference	
	African American	2.3 (1.9-2.7)	<.0001
	Asian	1.6 (1.3-1.9)	<.0001
	LatinX	1.6 (1.3-1.9)	<.0001
	Other/unknown	1.3 (1.1-1.5)	.0087
Gender	Not female	Reference	
	Female	1.5 (1.3-1.7)	<.0001
Age at start of medication, years	18-39	Reference	
	40-64	0.5 (0.5-0.6)	<.0001
	65+	0.3 (0.3-0.4)	<.0001
Neighborhood deprivation index	1	Reference	
	2	1.2(1.0,1.4)	.024
	3	1.4(1.2,1.6)	<.001
	4	1.5(1.3,1.7)	<.0001
Body mass index, kg/m^2	Not obese	Reference	
	Obese	1.1 (1.0-1.3)	.0424
	Missing	1.6 (1.4-2.0)	<.0001
Smoking, ever		1.2 (1.1-1.4)	.0015
Hyperlipidemia in the prior year		1.0 (0.8-1.1)	.7013
Hypertension in the prior year		0.9 (0.8-1.1)	.304
Diabetes status		1.1 (1.0-1.4)	.1232
Substance use disorder diagnosis		1.4 (1.1-1.6)	.0008
Schizophrenia disorder diagnosis		3.4 (3.0-3.9)	<.0001
Schizoaffective disorder diagnosis		2.6 (2.3-2.9)	<.0001
Bipolar disorder diagnosis		1.0 (0.8-1.1)	.5465
Psychotic disorder diagnosis		2.1 (1.8-2.4)	<.0001
Outpatient psychiatry utilization prior year	None	Reference	
	1	1.1 (0.8-1.6)	.432
	2-3	1.9 (1.4-2.5)	<.0001
	4+	4.0 (3.1-5.1)	<.0001
Emergency department utilization prior year		1.6 (1.4-1.9)	<.0001
Inpatient hospitalization prior year		2.8 (2.4-3.3)	<.0001

Note. Medication adherence defined as ≥two refills in the previous year. LAI, long-acting injectable; CI, confidence interval; kg, kilogram; m, meters. Body mass index categories based on available data and defined as <30 not obese, and ≥30 obese. Neighborhood deprivation index is a geocoded measure of socioeconomic status with categories based on the quartiles of the overall cohort, with higher scores indicating more deprivation. Substance use, smoking, hyperlipidemia, hypertension, and diabetes are defined as documented in the electronic health record in the year prior to or concurrent with medication start. Antipsychotic diagnoses are defined as documented in electronic health records 2 years prior to drug start or noted in patient health history.

diabetes and schizophrenia diagnosis ($P > .05$; table 4). Patients with no outpatient psychiatry utilization in the year prior to antipsychotic start showed significantly higher odds of LAI only for African American race ($P < .05$) age 18-39; $P < .005$), smoking ($P < .001$), diabetes ($P = .03$), substance use ($P < .05$), bipolar or psychotic diagnoses ($P < .0001$), and all years except 2019 ($P < .03$).

Discussion

Here, we utilized EHR data from 34 216 patients in a diverse, community-based, integrated healthcare delivery system to examine the associations between patient characteristics and LAI antipsychotic medication use overall and in subgroups representing populations recommended to take LAI antipsychotics by treatment guidelines.[22] We found demographic and clinical characteristics predicted LAI antipsychotic use, including African American or Asian race, LatinX ethnicity, non-female gender, younger age, and higher NDI. Clinical characteristics including smoking, BMI, hyperlipidemia, hypertension, diabetes, substance use disorder diagnoses, a schizophrenia disorder diagnosis, or a history of outpatient psychiatry utilization, or inpatient hospitalization in the last year were also associated with higher LAI use. Finally, patients had higher LAI use with each subsequent year of the time period studied. LAI use remained higher for non-white, non-female, 18–39-year-old, and high NDI patients in subgroups representing populations for which LAI use is

Table 4. Association of LAI Versus Oral Antipsychotic Medication Route Stratified by Outpatient Psychiatry Encounters in the Prior Year

Patient Characteristic		No Encounters		With at Least 1 or More Encounters	
		Odds Ratio (95% CI)	*P* Value	Odds Ratio (95% CI)	*P* Value
Race/ethnicity	White	Reference		Reference	
	African American	1.8 (1.1-3.0)	.017	1.9 (1.7-2.2)	<.0001
	Asian	1.6 (1.0-2.8)	.067	1.6 (1.3-1.8)	<.0001
	LatinX	1.3 (0.8-2.2)	.349	1.4 (1.2-1.7)	<.0001
	Other/unknown	0.9 (0.5-1.8)	.841	1.3 (1.1-1.6)	.0011
Gender	Not female	Reference		Reference	
	Female	1.0 (0.7-1.4)	.876	1.5 (1.3-1.6)	<.0001
Age at start of medication, years	18-39	Reference			
	40-64	0.5 (0.3-0.8)	.005	0.7 (0.6-0.8)	<.0001
	65+	0.3 (0.1-0.6)	.0002	0.4 (0.3-0.5)	<.0001
Neighborhood deprivation index	Quartile 1	Reference		Reference	
	Quartile 2	0.6 (0.3-1.0)	.054	1.1 (0.9-1.3)	.259
	Quartile 3	0.8 (0.5-1.2)	.271	1.1 (1.0-1.3)	.102
	Quartile 4	0.8 (0.5-1.3)	.319	1.3 (1.1-1.5)	.002
Body mass index, kg/m^2	Not obese	Reference		Reference	
	Obese	1.8 (1.2-2.8)	.005	1.5 (1.4-1.7)	<.0001
	Missing	1.1 (0.7-1.8)	.614	0.9 (0.8-1.1)	.290
Smoking, ever		2.0 (1.4-2.9)	.0003	1.3 (1.2-1.5)	<.0001
Hyperlipidemia in the prior year		0.9 (0.5-1.4)	.562	1.3 (1.1-1.5)	.001
Hypertension in the prior year		0.7 (0.4-1.1)	.127	0.9 (0.8-1.0)	.056
Diabetes status		1.8 (1.1-3.1)	.025	1.1 (0.9-1.3)	.231
Substance use disorder diagnosis		1.7 (1.0-3.0)	.048	1.5 (1.2-1.7)	<.0001
Schizophrenia disorder diagnosis		1.4 (0.9-2.0)	.122	1.0 (0.9-1.1)	.668
Schizoaffective disorder diagnosis		1.3 (0.9-2.0)	.186	1.6 (1.4-1.8)	<.0001
Bipolar disorder diagnosis		7.9 (5.4-12)	<.0001	6.8 (6.0-7.6)	<.0001
Psychotic disorder diagnosis		6.0 (4.1-8.9)	<.0001	6.4 (5.7-7.2)	<.0001
Emergency encounter prior year		0.7 (0.4-1.1)	.128	1.0 (0.9-1.2)	.772
Inpatient hospitalization encounter prior year	Yes	0.9 (0.6-1.3)	.560	2.7 (2.4-3.1)	<.0001
Year of drug start	2017	Reference		Reference	
	2018	2.1 (1.1-4.2)	.023	2.6 (2.1-3.0)	<.0001
	2019	1.7 (0.8-3.7)	.152	3.1 (2.6-3.7)	<.0001
	2020	2.7 (1.3-5.5)	.007	3.0 (2.4-3.6)	<.0001
	2021	3.2 (1.6-6.4)	.001	4.6 (3.9-5.5)	<.0001
	2022	7.0 (4.1-12)	<.0001	4.4 (3.7-5.3)	<.0001
	2023	6.2 (3.4-11)	<.0001	3.9 (3.2-4.8)	<.0001

Note. LAI, long-acting injectable; CI, confidence interval; kg, kilogram; m, meters. Body mass index categories based on available data and defined as <30 not obese and ≥30 obese. Neighborhood deprivation index is a geocoded measure of socioeconomic status with categories based on the quartiles of the overall cohort, with higher scores indicating more deprivation. Substance use, smoking, hyperlipidemia, hypertension, and diabetes are defined as documented in the electronic health record in the year prior to or concurrent with medication start. Diagnoses are defined as documented in electronic health records 2 years prior to drug start or noted in patient health history.

recommended by treatment guidelines (ie, poor or uncertain treatment adherence).

Previous reports from small community samples, inpatient units, or Medicaid claims data[24,26,31] reported that patients who were African American, male, or younger were more likely to be prescribed an LAI than oral antipsychotic, and that African American or LatinX Medicaid patients had higher odds of being prescribed an oral or LAI antipsychotic medication and Asian patients had a higher odds of being prescribed an oral antipsychotic medication in 2011–2012.[39] Our finding align with these findings while expanding them in a population including multiple insurance types across an entire health system, examining the use of LAIs versus oral antipsychotic medications across a broad categorization of race and ethnicities, NDI, and relation to treatment guideline recommendations. While we found African American patients had higher odds of LAI use overall and in subgroups, we also found that, even in medically adherent patients, all non-White races and ethnicities had higher odds of LAI prescription, as do individuals with a higher NDI compared to those with lower NDI. Previous work suggests patient perspectives of LAI antipsychotic medications are similar by race,[40] or are more favorable in

White populations,[41] suggesting that patient preference is not the sole driver of the study findings. Together, these data suggest the higher odds of LAI use by race, ethnicity, gender, age, and NDI were not solely due to poorer treatment adherence and hence, being prescribed a guideline-recommended LAI rather than an oral formulation.

This work presents novel results regarding patient clinical factors and antipsychotic medication administration route that can help inform best practices for LAI use. The odds of LAI use were higher in patients with a history of inpatient hospitalization and outpatient psychiatry utilization in the prior year (figure 1), suggesting that LAIs were prescribed to individuals utilizing more mental healthcare services or high acuity services. LAI use can decrease disease relapse and severity and has been shown to decrease inpatient healthcare utilization[18,19,21]; so prescribing to high healthcare utilizers may help improve patient outcomes while reducing healthcare costs. We found that LAIs were most used by patients with schizophrenia compared to other disorders, an observation that remained significant in subgroup analyses by medication adherence. Evidence suggests and guidelines recommend LAIs in bipolar, schizoaffective, and other psychotic disorders[22]; these data suggest expanding LAI use in patients with these diagnoses may help improve outcomes.

Interestingly, LAI prescriptions were higher in patients with BMIs above the normal range, diabetes, or hyperlipidemia, yet lower in patients with a history of hypertension (figure 1). Similar results were seen in subgroup analyses representing treatment guideline-recommended populations with poor or uncertain treatment adherence (tables 2-4) as well as those with better treatment adherence (table 3). It may be that associations between LAI use and these clinical characteristics reflect overall antipsychotic length of treatment as second-generation antipsychotics are associated with metabolic side effects regardless of administration route.[22] Further, these data suggest that metabolic side effects of second-generation antipsychotics may not contribute to patient or provider decision-making regarding LAI use. As smoking can lower antipsychotic blood levels by as much as 50%[42,43] and was also significantly associated with LAI use, provider attention regarding LAI dose adjustments would help assure therapeutic efficacy of LAIs in patients who smoke.

Limitations of this study include utilization of retrospective EHR data. As such, we are unable to determine causality for the observations and are only able to examine variables to the extent they are complete in the EHR.[44] However, these results provide vital information related to the real-world clinical practice and use of LAI antipsychotics. The study setting was an insured population in an integrated healthcare system; as such, some findings may not generalize to populations without similar insurance or access to care.

Together, these data fill an important literature gap regarding racial, ethnic, and socioeconomically related differences in patient LAI versus oral antipsychotic medication use. These results suggest that LAIs may be used more frequently in non-white, younger, male, and poorer populations regardless of clinical status and treatment guidelines in the United States compared to oral antipsychotic medications. While the reason for this increased use is likely multimodal, it may be that perceived severity related to provider or patient biases may influence these prescribing patterns. These characteristics associated with LAI antipsychotic medication use clarify opportunities in provider and patient education regarding treatment guideline-recommended LAI antipsychotic medication use and should be considered as sources of indication bias in real-world observational studies. LAIs remain an evidence-based treatment option for patients with severe mental illness that can improve medication adherence and patient outcomes.[21] These data can inform future studies examining implementation strategies to increase LAI antipsychotic medication prescribing by providers, LAI antipsychotic medication acceptance by patients, and equity in care across patient demographic and clinical categories.

Supplementary Material

Supplementary data are available at *Schizophrenia Bulletin Open* online.

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Data sharing

Kaiser Permanente does not release datasets related to patient data. Data are derived from EHR records. Any supporting results or data, including explanations about the structure of the data or how it was obtained beyond the scope of the materials and methods section can be obtained from the corresponding author.

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