Supplementary Material

Real-world Effectiveness of Long-acting Injectable and Oral Antipsychotic Agents in US Medicare Patients with Schizophrenia

Pengxiang Li[a], Zhi Geng[a], Carmela Benson[b], Charmi Patel[b], Jalpa A Doshi[a,c]

[a]Division of General Internal Medicine, University of Pennsylvania, Philadelphia, PA, USA; [b]Janssen Scientific Affairs, LLC, Titusville, NJ, USA; [c]Leonard Davis Institute of Health Economics, University of Pennsylvania, Philadelphia, PA, USA (jdoshi@pennmedicine.upenn.edu)

Table of Contents

Supplementary Methods

Schizophrenia CCW Indicator

Patients with schizophrenia were identified via the Chronic Conditions Warehouse (CCW) Indicator provided in the Chronic Conditions supplemental files provided by CMS along with the Medicare data. While Medicare Part D prescription claims data became first available for the year 2006 (and hence our study period starts from 2006 onwards), Medicare Part A and B medical claims data are available from 1999 onwards to CMS. Using data from 1999 onwards, CMS provides a schizophrenia indicator in the CCW Medicare files which uses the following criteria to classify patients as having schizophrenia:

- ICD-9 codes: DX 295.00, 295.01, 295.02, 295.03, 295.04, 295.05, 295.10, 295.11, 295.12, 295.13, 295.14, 295.15, 295.20, 295.21, 295.22, 295.23, 295.24, 295.25, 295.30, 295.31, 295.32, 295.33, 295.34, 295.35, 295.40, 295.41, 295.42, 295.43, 295.44, 295.45, 295.50, 295.51, 295.52, 295.53, 295.54, 295.55, 295.60, 295.61, 295.62, 295.63, 295.64, 295.65, 295.70, 295.71, 295.72, 295.73, 295.74, 295.75, 295.80, 295.81, 295.82, 295.83, 295.84, 295.85, 295.90, 295.91, 295.92, 295.93, 295.94, 295.95 (any DX on the claim)
- ICD-10 codes: DX F20.0, F20.1, F20.2, F20.3, F20.5, F20.81, F20.89, F20.9, F25.0, F25.1, F25.8, F25.9 (any DX on the claim)
- Number/type of claims to qualify: At least 1 inpatient claim OR 2 other non-drug claims (at least one day apart) of any service type with one of the above ICD-9-CM or ICD-10-CM diagnosis codes
- Reference period: 2 Years
- First recorded date of schizophrenia: An additional variable provided in the CCW data identifies the first date a schizophrenia diagnosis was ever recorded in the Medicare

claims starting January 1, 1999 for those qualifying as having schizophrenia based on the above criteria.

Additional information can be found at the CCW website:
https://www2.ccwdata.org/web/guest/condition-categories-other

Measure of Antipsychotic Discontinuation

Antipsychotic discontinuation was defined as a continuous gap of 60 days or more days without any antipsychotic use (Campagna 2014; Marcus 2015; Ray 2003; Greene 2018). To examine gaps in treatment, we spread the reported days' supply from each antipsychotic prescription from the fill date to the date the supply would have been exhausted (Sikka 2005).

All OAPs and the vast majority of LAIs were billed as prescription claims under Medicare Part D, which have a days' supply field available to allow counting of days covered. For the small number of LAI prescriptions found under Part B medical claims, which lack the days' supply field present on pharmacy claims, the days' supply was assigned based on the recommended dosage regimen in the prescribing information for that injection (see Appendix A3). In previous work, we similarly assigned the days' supply for LAI prescription claims billed under Part D, however, the results remained very similar and hence were not reported (Li 2023).

The discontinuation date was defined as the date of the beginning of the 60-day continuous gap. For example, for OAP users with no evidence of antipsychotic use for 60 continuous days after the date the 28-day supply of the last OAP prescription is exhausted, the discontinuation date would be the last fill date + 28 day. For LAI users who received an LAI with a 3-month dosing interval, the discontinuation date would be 12-weeks after the receipt of the last every 3-month LAI injection (i.e. last fill date + 84). Our claims-based discontinuation measure may

underestimate the discontinuation risk for OAP users given that some patients may stop taking oral antipsychotics before the days' supply exhausted (e.g., a patient may stop taking their OAP on day 7 despite having a 30-day supply fill). On the other hand, LAI users would not face this issue (e.g., a patient administrated a 3-month LAI would have all 84 days covered by their antipsychotic treatment without any possibility of skipping/stopping antipsychotics before the 84 day fill is exhausted).

Additional Methods Details on Within Individual Cox Regressions

The main analytic approach used within-individual Cox regression models to estimate each of the outcomes outlined in the article. The unit of analysis was the sub-period. We specified the starting time and ending time of each sub-period, and whether the event happened (it was censored if the event [outcome] did not happen) at the end of the sub-period. In addition, the model also included treatment variables (e.g., LAI agent α of specific dosing interval =1, OAP agent β =1, or no AP treatment) and other control variables associated with the sub-period. The within-individual model was a stratified Cox regression model in which each individual formed his or her own stratum. Note that all outcomes except death were recurrent and were treated as such in the regression models. Follow-up time was reset to zero after each outcome event to allow comparison of treatment sub-periods within each individual.

Within-individual analyses have been used in studies on psychotropic drug use published in top tier journals such as *JAMA Psychiatry* (Tiihonen 2016), *N Engl J Med* (Lichtenstein 2012) and *JAMA* (Chang 2016). In within-individual Cox regression analysis, only individuals with variation in the exposure and outcome contribute to the regression, whereas in traditional Cox regression analysis, all individuals contribute to the regression (Tiihonen 2016).

We illustrate the approach by adapting an example from Lichtenstein (2012) for our comparison of LAI agent α of specific dosing interval (LAI) vs. OAP agent β (OAP) and specifically focusing on the outcome of psychiatric hospitalization. Consider Figure S1, which displays the follow-up for two fictitious individuals with schizophrenia, A and B. At the start of the observation period (month 0), neither A nor B was on an LAI and instead both were using an OAP (OAP=1). Individual A began taking the LAI medication after 12 months (LAI=1) and continued until the patient was censored at 20 months after the start of the patient's observation period. Individual B started taking the LAI medication after 10 months and continued until the patient was censored at 32 months after the start of the patient's observation period. Individual A had a psychiatric hospitalization 2 months after the start date, and 8 months after the start date. Individual B had a psychiatric hospitalization 9 months after the start date, and 17 months after the start date. We use unfilled circles for censoring and filled circles for psychiatric hospitalization.

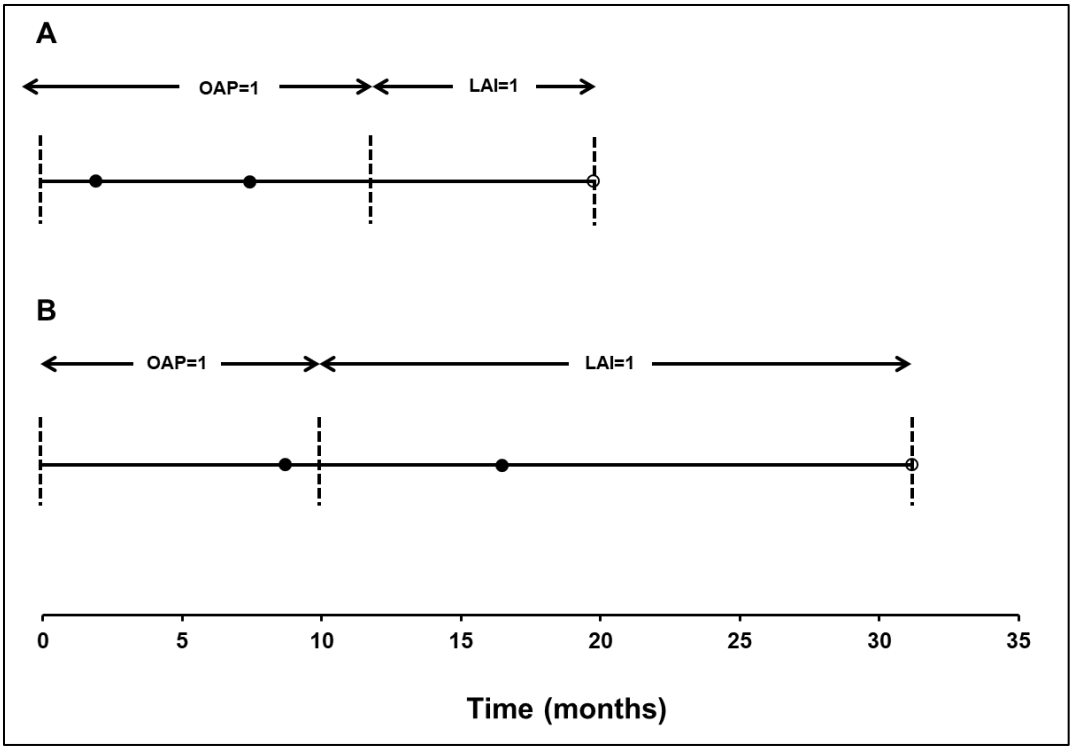

Figure S1

For execution of this approach, we needed to first “preprocess” the data so that the follow-up was divided into sub-periods for each individual based on events and treatments. Specifically, every psychiatric hospitalization and every change in AP category exposure (e.g., from OAP to LAI or vice versa) initiated a new sub-period for the individual. A sub-period that followed a psychiatric hospitalization was considered as starting at “baseline” (time 0 in the analyses), whereas a sub-period that followed a change in AP category was considered left-truncated at the time of the change. A sub-period that ended with an AP category change and without event was considered censored. Figure S2 displays the sub-periods produced by the fictitious Individuals A (left panel) and B (right panel). For instance, the topmost line to the left in Figure S2 corresponds to the first sub-period for A, that started when A’s observation period started, and ended with the psychiatric hospitalization at 2 months after observation start date. The bottommost line to the left in Figure S2 corresponds to the last sub-period for A, that started immediately after the switch in AP category at 12 months after enrollment, and ended with the censoring at 20 months after enrollment.

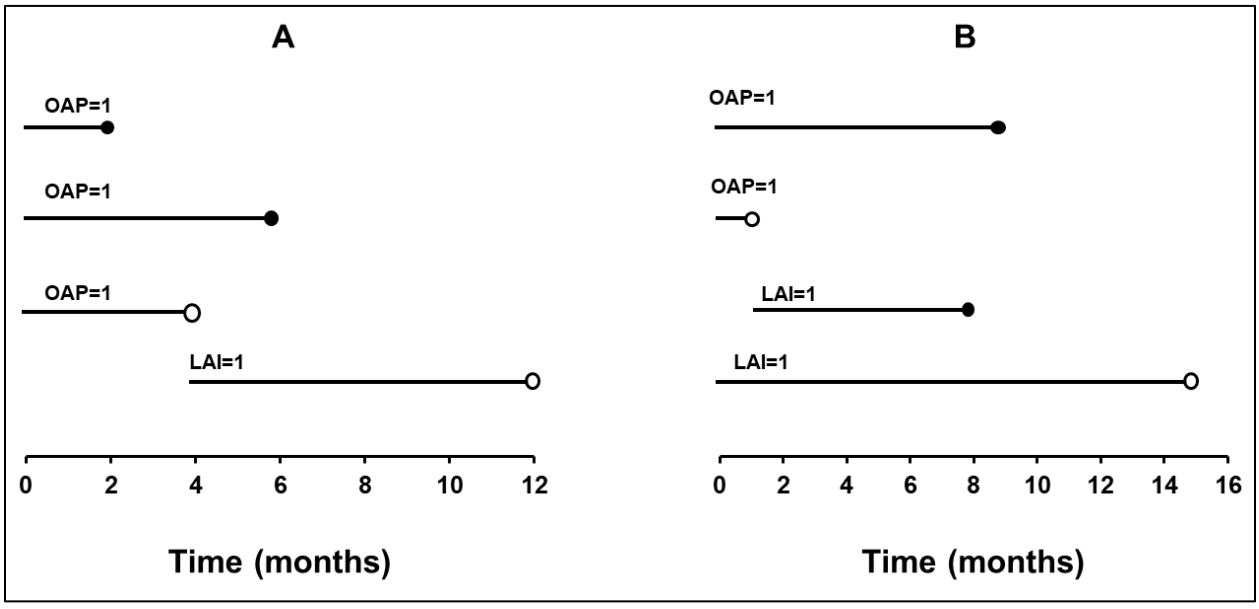

Figure S2

Figure S3 displays the same sub-periods, but divided into OAP (left panel, OAP=1) and LAI (right panel, LAI=1) subperiods.

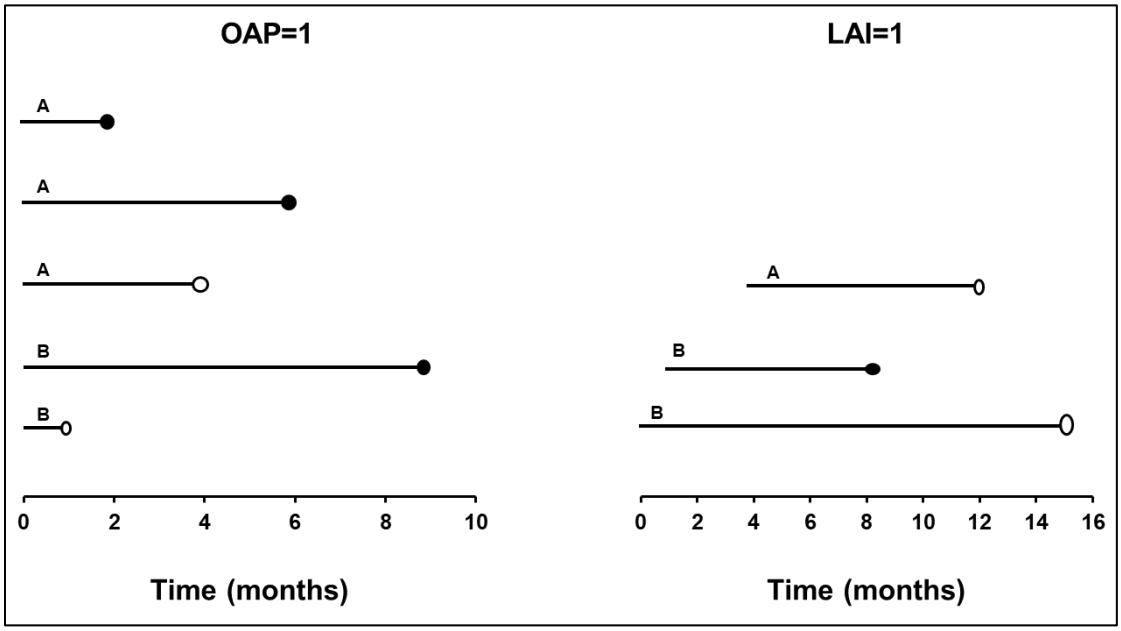

Figure S3

By comparing the psychiatric hospitalization rate for the same individual under OAP (left panel, OAP=1) and LAI (right panel, LAI=1) sub-periods in Figure S3, this study design and approach reduced confounding by letting each individual serve as his or her own control.

For illustration purposes, we have used simplistic scenarios for Figure S1 to S3, wherein the individuals have either LAI=1 only (i.e., OAP=0) or OAP=1 only (i.e., LAI=0) in any given sub-period. In reality, individuals can have certain sub-periods on both OAP and LAI (i.e., OAP=1 and LAI=1) or without any antipsychotics (i.e., OAP=0 and LAI=0). Our study design and analytical approach also accounted for these situations.

References

Campagna EJ, Muser E, Parks J, et al. Methodological considerations in estimating adherence and persistence for a long-acting injectable medication. J Manag Care Spec Pharm. 2014;20:756–766.

Greene M, Yan T, Chang E, Hartry A, Touya M, Broder MS. Medication adherence and discontinuation of long-acting injectable versus oral antipsychotics in patients with schizophrenia or bipolar disorder. J Med Econ. 2018;21(2):127-134. doi:10.1080/13696998.2017.1379412

Li P, Benson C, Geng Z, Seo S, Patel S, Doshi J. Antipsychotic utilization, healthcare resource use and costs, and quality of care among fee-for-service Medicare beneficiaries with schizophrenia in the United States. J Med Econ. 2023 Jan-Dec;26(1):525-536. doi: 10.1080/13696998.2023.2189859.

Marcus SC, Zummo J, Pettit AR, Stoddard J, Doshi JA. Antipsychotic Adherence and Rehospitalization in Schizophrenia Patients Receiving Oral Versus Long-Acting Injectable Antipsychotics Following Hospital Discharge. J Manag Care Spec Pharm. 2015;21(9):754-768. doi:10.18553/jmcp.2015.21.9.754

Ray WA, Daugherty JR, Meador KG. Effect of a mental health “carve-out” program on the continuity of antipsychotic therapy. N Engl J Med. 2003;348(19):1885-1894. doi:10.1056/NEJMsa020584

Sikka R, Xia F, Aubert RE. Estimating medication persistency using administrative claims data. Am J Manag Care. 2005;11(7):449-457.

Supplementary Tables

Supplemental Table S1. Treatment Exposure Categories

Treatment Exposure Categories for the First Set of Analyses
LAI (every 0.5 month)
LAI (every 1 month)
LAI (every 1.5 month)
LAI (every 2 months)
LAI (every 3 months)
Oral (daily)
No AP (i.e. subperiods of ≥60 days during follow-up without antipsychotic use)
Treatment Exposure Categories for the Second Set of Analyses
LAI aripiprazole (every 1 month)
LAI aripiprazole (every 1.5–2 months)[a]
LAI fluphenazine (every month)
LAI fluphenazine (every 1.5 months)
LAI haloperidol (every 1 month)
LAI olanzapine (primarily consisting of every month)[b]
LAI paliperidone (every 1 month)
LAI paliperidone (every 3 months)
LAI risperidone (primarily consisting of every 0.5 month)[c]
Oral aripiprazole
Oral clozapine
Oral fluphenazine
Oral haloperidol
Oral lurasidone
Oral olanzapine
Oral paliperidone
Oral quetiapine
Oral risperidone
Oral ziprasidone
Other oral FGA[d]
Other oral SGA[e]
No AP (i.e. subperiods of ≥60 days during follow-up without antipsychotic use)

AP, antipsychotic; FGA, first-generation antipsychotic; LAI, long-acting injectable; SGA, second-generation antipsychotic.

[a]Although use of LAI aripiprazole formulations for every 1.5 months and every 2 months were observed, their individual number of users were very small so the two were combined into a single category of LAI aripiprazole every 1.5-2 months (see Supplemental Table 5).

[b]Although use of biweekly and monthly LAI olanzapine formulations were observed in our study, the vast majority (>83%) of LAI olanzapine use was for the monthly formulation (see Supplemental Table 5).

[c]Although use of biweekly and monthly LAI risperidone formulations were observed in our study, the vast majority (>99%) of LAI risperidone use was for the biweekly formulation (i.e., every 0.5 months)(see Supplemental Table 5).

[d]Perphenazine, chlorpromazine, thiothixene, thioridazine, loxapine, molindone or mesoridazine had small sample sizes and were grouped together as "other oral FGA."

[e]Asenapine, iloperidone, cariprazine, or brexiprazole had small sample sizes and were grouped together as "other oral SGA."

Supplemental Table S2. Assignment of LAI Dosing Interval Category

LAI Generic Name	LAI Brand Name	Dosing Interval Category Assignment[a]	LAI by Dosing Interval	LAI by Dosing Interval and Antipsychotic agent[b]
Aripiprazole	ABILIFY MAINTENA	Every 4 weeks	LAI every 1 month	LAI aripiprazole (every 1 month)
Aripiprazole lauroxil[c]	ARISTADA	441 mg: every 4 weeks 662 mg: every 4 weeks	LAI every 1 month	
		882 mg: every 4 weeks if value in days' supply field on claim ≤30, else every 6 weeks if >30	LAI every 1.5 month	LAI aripiprazole (every 1.5-2 month)[d]
		1064 mg: every 8 weeks	LAI every 2 month	
Fluphenazine decanoate	Generic	Every 4 weeks if value in days' supply field on claim ≤30 days	LAI every 1 month	LAI fluphenazine (every 1 month)
		Every 6 weeks if value in days' supply field on claim >30 days	LAI every 1.5 month	LAI fluphenazine (every 1.5 month)
Haloperidol decanoate	Generic	Every 4 weeks	LAI every 1 month	LAI haloperidol (every 1 month)
Haloperidol decanoate	HALDOL DECANOATE	50 mg: Every 4 weeks 100 mg: Every 4 weeks		
Olanzapine pamoate	ZYPREXA RELPREVV	210 mg: every 2 weeks 300 mg: every 2 weeks if value in days' supply field on claim ≤15 days	LAI every 0.5 month	LAI olanzapine (primarily consisting of every 1 month)[e]
		300 mg: every 4 weeks if value in days' supply field on claim >15 days 405 mg: every 4 weeks	LAI every 1 month	
Paliperidone palmitate	INVEGA SUSTENNA	Every 4 weeks	LAI every 1 month	LAI paliperidone (every 1 month)
Paliperidone palmitate	INVEGA TRINZA	Every 12 weeks	LAI every 3 month	LAI paliperidone (every 3 month)
Risperidone microspheres	RISPERDAL CONSTA	Every 2 weeks	LAI every 0.5 month	LAI risperidone (primarily consisting of every 1 month)[f]
Risperidone	PERSERIS	Every 4 weeks	LAI every 1 month	

[a]The vast majority of LAI claims for all agents were processed as prescription claims under Medicare Part D. The National Drug Code (NDC) codes on the prescription claims permitted identification of brand name and strength of LAI agent and the days' supply field on the prescription claim was used to assign dosing interval category when the same strength of the brand-name agent could be used for varying dosing intervals (for example, for Aristada 882 mg or Zyprexa Relprevv 300 mg).
[b]For the very few LAI claims processed as medical claims under Medicare Part B separate 5-digit HCPCS codes were not available for LAI formulations with different dosing intervals of the same LAI agent and there is no days' supply field in medical claims. Since most of the Part B claims for LAI paliperidone occurred prior to the FDA approval date of Invega Trinza (i.e. LAI paliperidone every 3 months) they were all assigned as Invega Sustenna (i.e., LAI paliperidone every 1 month). The few Medicare

Part B claims for the remaining agents were assigned the highest dosing interval available for that LAI agent dosing interval categories as shown: Aristada (every 8 weeks), Fluphenazine decanoate (every 6 weeks), Zyprexa Relprevv (every 4 weeks).
[c]Aripiprazole lauroxil is also available as Aristada Initio 675 mg injection, which is indicated for the initiation of Aristada (441 mg, 662 mg, 882 mg, or 1064 mg). Since it is to be given as a single injection in conjunction with the Aristada injection, the dosing interval category assignment for Aristada Initio was based on the dosing interval of the Aristada injection that the patient was initiated on.
[d]Although use of LAI aripiprazole formulations for every 1.5 months and every 2 months were observed, their individual number of users were very small so the two were combined into a single category of LAI aripiprazole every 1.5-2 months (see Supplemental Table 5).
[e]Although use of biweekly and monthly LAI olanzapine formulations were observed in our study, the vast majority (>94%) of LAI olanzapine use was for the monthly formulation (see Supplemental Table 5).
[f]Although use of biweekly and monthly LAI risperidone formulations were observed in our study, the vast majority (>99%) of LAI risperidone use was for the biweekly formulation (i.e., every 0.5 months) (see Supplemental Table 5).

Supplemental Table S3. Sample Attrition

Selection Criteria	N	%
Patients with schizophrenia receiving an antipsychotic (LAI or OAP) prescription between January 1, 2006 to December 31, 2019 (index date=first observed antipsychotic fill date)	872,912	
Patients aged 18 years or older on index date	872,660	99.90%
Patients with 6-months continuous Medicare fee-for-service coverage in the pre-index period	262,798	30.10%
Patients with 6-months continuous Medicare Part D coverage in the pre-index period	174,360	66.30%
Patients with 6-months continuous Medicare fee-for-service coverage in the post-index period	155,166	89.00%
Patients with 6-months continuous Medicare Part D coverage in the post-index period	152,835	98.50%
Total number of person-years over follow up (i.e. until death, transition to MAPD plan or Dec 31, 2019 whichever occurred earlier) for the sample of 152,835 patients	781,848	

Supplemental Table S4. Sample Characteristics[a]

Characteristics	N	%
Number of patients	152,835	100%
Age, mean (SD)	53.5 (16.7)	
≤24 years	3,557	2.3%
25 to 34 years	18,814	12.3%
35 to 44 years	25,268	16.5%
45 to 54 years	35,706	23.4%
55 to 64 years	27,096	17.7%
≥65 years	42,394	27.7%
Sex		
Female	70,271	46.0%
Male	82,564	54.0%
Race[b]		
White	94,050	61.5%
Black	45,936	30.1%
Hispanic	6,486	4.2%
Other	6,363	4.2%
Part D Low-income Subsidy Status		
Full LIS	130,604	85.5%
Partial LIS	1,884	1.2%
Non-LIS	20,347	13.3%
Original Reason for Medicare Eligibility		
Age	26,153	17.1%
Disability	126,210	82.6%
ESRD	1210	0.8%
Census Region		
Midwest	35,609	23.3%
Northeast	27,656	18.1%
South	61,672	40.4%
West	27,455	18.0%
Metropolitan Status		
Urban	127,216	83.2%
Rural	25,619	16.8%
Number of Elixhauser comorbidities		
0	7,348	4.8%
1 to 2	45,478	29.8%
3 to 4	39,509	25.9%
5+	60,500	39.6%

ESRD, end-stage renal disease; LIS, low-income subsidy; SD, standard deviation.

[a]All sample characteristics were measured on the index date (first observed antipsychotic prescription date) except the number of Elixhauser comorbidities, which was measured based on claims during the 6 months before the index date.

[b]Medicare's data on race/ethnicity come from Social Security Administration (SSA) records.

Supplemental Table S5. Antipsychotic by Dosing Interval and Type of Agent Used at any Time Over Follow-up

	Number of Users	% of Users	Person-years
Total	152,835	100%	909,733
Any LAI	28,075	18.4%	61,628
By Dosing Interval			
LAI (every 0.5 month)	8,951	5.9%	14,690
LAI (every 1 month)	22,534	14.7%	42,409
LAI (every 1.5 month)	2,274	1.5%	3,027
LAI (every 2 months)	162	0.1%	96
LAI (every 3 months)	1,080	0.7%	1,624
OAP	149,839	98.0%	402,557
No AP (i.e. subperiods of ≥60 days during follow-up without antipsychotic use)	123,090	80.5%	341,429
By Type of Agent and Dosing Interval			
LAI aripiprazole	2,835	1.9%	2,999
Every 1 month	2,760	1.8%	2,889
Every 1.5 months	34	0.0%	21
Every 2 months	162	0.1%	96
LAI fluphenazine	5,343	3.5%	8,320
Every 1 month	4,365	2.9%	5,397
Every 1.5 months	2,733	1.8%	3,006
LAI haloperidol	10,769	7.0%	19,797
LAI olanzapine	551	0.4%	254
Every 0.5 month	90	0.1%	50
Every 1 month	520	0.3%	207
LAI paliperidone	8,897	5.8%	15,871
Every 1 month	8,868	5.8%	14,278
Every 3 months	1,080	0.7%	1,624
LAI risperidone	8,899	5.8%	14,643
Every 0.5 month	8,891	5.8%	14,641
Every 1 month	16	0.0%	3
Oral aripiprazole	40,312	26.4%	54,862
Oral clozapine	5,733	3.8%	20,928
Oral fluphenazine	7,916	5.2%	10,170
Oral haloperidol	28,255	18.5%	32,204
Oral lurasidone	8,952	5.9%	8,765
Oral olanzapine	43,290	28.3%	72,108
Oral paliperidone	10,318	6.8%	11,309
Oral quetiapine	61,768	40.4%	96,334
Oral risperidone	65,145	42.6%	103,007
Oral ziprasidone	18,016	11.8%	22,349
Other oral FGA[a]	15,822	10.4%	21,005
Other oral SGA[b]	5,942	3.9%	5,241
No AP (i.e. subperiods during follow-up without antipsychotic use)	123,090	80.5%	341,429

AP, antipsychotic; FGA, first-generation antipsychotic; LAI, long-acting injectable; OAP, oral antipsychotic; SGA, second-generation antipsychotic.

[a]Perphenazine, chlorpromazine, thiothixene, thioridazine, loxapine, molindone or mesoridazine had small sample sizes and were grouped together as "other oral FGA."

[b]Asenapine, iloperidone, cariprazine, or brexiprazole had small sample sizes and were grouped together as "other oral SGA."

Supplemental Table S6. Adjusted Hazard Ratios and 95% CIs for Treatment Failure During Each Treatment using Three Alternative Reference Groups

	LAI Risperidone as Reference Group			LAI Haloperidol Q1M as Reference Group			LAI Aripiprazole Q1M as Reference Group		
Index Agent	**HR**	**95% CI**	**p-value**	**HR**	**95% CI**	**p-value**	**HR**	**95% CI**	**p-value**
LAI aripiprazole (Q1M)	1.08	1.02–1.15	0.009	0.88	0.83–0.93	<.0001	Reference		
LAI aripiprazole (Q1.5M-2M)	1.00	0.80–1.24	0.989	0.81	0.65–1.01	0.062	0.92	0.74–1.15	0.475
LAI fluphenazine (Q1M)	1.48	1.41–1.54	<.0001	1.20	1.15–1.25	<.0001	1.36	1.28–1.45	<.0001
LAI fluphenazine (Q1.5M)	0.93	0.88–0.99	0.016	0.76	0.72–0.80	<.0001	0.86	0.80–0.93	<.0001
LAI haloperidol (Q1M)	1.23	1.19–1.27	<.0001	Reference			1.14	1.07–1.20	<.0001
LAI olanzapine[a]	1.92	1.73–2.13	<.0001	1.56	1.41–1.73	<.0001	1.77	1.58–1.98	<.0001
LAI paliperidone (Q1M)	0.95	0.92–0.99	0.018	0.78	0.75–0.80	<.0001	0.88	0.83–0.94	<.0001
LAI paliperidone (Q3M)	0.67	0.60–0.76	<.0001	0.55	0.49–0.62	<.0001	0.62	0.55–0.71	<.0001
LAI risperidone[b]	Reference			0.81	0.79–0.84	<.0001	0.92	0.87–0.98	0.009
Oral aripiprazole	1.30	1.26–1.34	<.0001	1.06	1.03–1.08	<.0001	1.20	1.14–1.27	<.0001
Oral clozapine	0.97	0.93–1.01	0.119	0.79	0.76–0.82	<.0001	0.90	0.84–0.95	0.000
Oral fluphenazine	1.25	1.20–1.30	<.0001	1.01	0.98–1.05	0.418	1.15	1.09–1.22	<.0001
Oral haloperidol	1.29	1.26–1.34	<.0001	1.05	1.03–1.08	<.0001	1.20	1.13–1.26	<.0001
Oral lurasidone	1.36	1.31–1.42	<.0001	1.11	1.07–1.15	<.0001	1.26	1.18–1.34	<.0001
Oral olanzapine	1.22	1.18–1.26	<.0001	0.99	0.97–1.02	0.549	1.13	1.07–1.19	<.0001
Oral paliperidone	1.23	1.19–1.28	<.0001	1.00	0.97–1.04	0.900	1.14	1.07–1.21	<.0001
Oral quetiapine	1.27	1.23–1.31	<.0001	1.03	1.01–1.06	0.008	1.17	1.11–1.24	<.0001
Oral risperidone	1.27	1.23–1.30	<.0001	1.03	1.01–1.06	0.018	1.17	1.11–1.23	<.0001
Oral ziprasidone	1.37	1.33–1.42	<.0001	1.12	1.08–1.15	<.0001	1.27	1.20–1.34	<.0001
Other oral FGA	1.31	1.27–1.35	<.0001	1.06	1.03–1.10	<.0001	1.21	1.14–1.28	<.0001
Other oral SGA	1.36	1.29–1.42	<.0001	1.10	1.05–1.15	<.0001	1.25	1.17–1.34	<.0001
None	NA	NA	NA	NA	NA	NA	NA	NA	NA

CI, confidence interval; FGA, first-generation antipsychotic; HR, hazard ratio; LAI, long-acting injectable; NA, not available; QXM, every X months; SGA, second-generation antipsychotic.

[a]Although use of biweekly and monthly LAI olanzapine formulations were observed in our study, the vast majority (>83%) of LAI olanzapine use was for the monthly formulation (i.e., Q1M).

[b]Although use of biweekly and monthly LAI risperidone formulations were observed in our study, the vast majority (>99%) of LAI risperidone use was for the biweekly formulation (i.e., every 2 weeks).

Supplemental Table S7. Adjusted Hazard Ratios and 95% CIs for Antipsychotic Discontinuation During Each Treatment using Three Alternative Reference Groups

	LAI Risperidone as Reference Group			LAI Haloperidol Q1M as Reference Group			LAI Aripiprazole Q1M as Reference Group		
Index Agent	**HR**	**95% CI**	**p-value**	**HR**	**95% CI**	**p-value**	**HR**	**95% CI**	**p-value**
LAI aripiprazole (Q1M)	1.07	0.94–1.22	0.288	0.59	0.52–0.66	<.0001	Reference		
LAI aripiprazole (Q1.5M-2M)	0.78	0.45–1.33	0.355	0.42	0.25–0.73	0.002	0.72	0.42–1.24	0.240
LAI fluphenazine (Q1M)	2.89	2.65–3.16	<.0001	1.58	1.47–1.71	<.0001	2.69	2.36–3.07	<.0001
LAI fluphenazine (Q1.5M)	1.15	1.03–1.27	0.010	0.63	0.57–0.69	<.0001	1.07	0.93–1.23	0.361
LAI haloperidol (Q1M)	1.83	1.70–1.97	<.0001	Reference			1.70	1.50–1.93	<.0001
LAI olanzapine[a]	2.08	1.48–2.93	<.0001	1.14	0.81–1.60	0.446	1.94	1.36–2.77	0.000
LAI paliperidone (Q1M)	0.94	0.86–1.02	0.126	0.51	0.48–0.55	<.0001	0.87	0.77–0.99	0.038
LAI paliperidone (Q3M)	0.31	0.24–0.39	<.0001	0.17	0.13–0.21	<.0001	0.29	0.22–0.37	<.0001
LAI risperidone[b]	Reference			0.55	0.51–0.59	<.0001	0.93	0.82–1.06	0.288
Oral aripiprazole	1.72	1.61–1.84	<.0001	0.94	0.90–0.99	0.020	1.60	1.43–1.80	<.0001
Oral clozapine	1.23	1.11–1.36	0.000	0.67	0.61–0.74	<.0001	1.14	0.99–1.32	0.065
Oral fluphenazine	1.66	1.52–1.80	<.0001	0.91	0.85–0.97	0.005	1.54	1.36–1.75	<.0001
Oral haloperidol	1.76	1.64–1.89	<.0001	0.96	0.92–1.01	0.127	1.64	1.46–1.85	<.0001
Oral lurasidone	1.76	1.62–1.92	<.0001	0.96	0.90–1.04	0.313	1.64	1.44–1.87	<.0001
Oral olanzapine	1.60	1.49–1.71	<.0001	0.87	0.83–0.92	<.0001	1.49	1.32–1.67	<.0001
Oral paliperidone	1.55	1.43–1.68	<.0001	0.85	0.79–0.91	<.0001	1.44	1.27–1.64	<.0001
Oral quetiapine	1.52	1.43–1.63	<.0001	0.83	0.79–0.87	<.0001	1.42	1.26–1.60	<.0001
Oral risperidone	1.60	1.50–1.70	<.0001	0.87	0.83–0.92	<.0001	1.49	1.32–1.67	<.0001
Oral ziprasidone	1.66	1.54–1.79	<.0001	0.91	0.86–0.96	0.001	1.55	1.37–1.75	<.0001
Other oral FGA	1.72	1.60–1.85	<.0001	0.94	0.89–1.00	0.041	1.60	1.41–1.81	<.0001
Other oral SGA	1.92	1.74–2.11	<.0001	1.05	0.96–1.14	0.258	1.79	1.56–2.05	<.0001
None	NA	NA	NA	NA	NA	NA	NA	NA	NA

CI, confidence interval; FGA, first-generation antipsychotic; HR, hazard ratio; LAI, long-acting injectable; NA, not available; QXM, every X months; SGA, second-generation antipsychotic.

[a]Although use of biweekly and monthly LAI olanzapine formulations were observed in our study, the vast majority (>83%) of LAI olanzapine use was for the monthly formulation (i.e., Q1M).

[b]Although use of biweekly and monthly LAI risperidone formulations were observed in our study, the vast majority (>99%) of LAI risperidone use was for the biweekly formulation (i.e., every 2 weeks).

Supplemental Table S8. Adjusted Hazard Ratios and 95% CIs for Psychiatric Hospitalization During Each Treatment using Three Alternative Reference Groups

	LAI Risperidone as Reference Group			LAI Haloperidol Q1M as Reference Group			LAI Aripiprazole Q1M as Reference Group		
Index Agent	**HR**	**95% CI**	**p-value**	**HR**	**95% CI**	**p-value**	**HR**	**95% CI**	**p-value**
LAI aripiprazole (Q1M)	1.08	1.01–1.16	0.027	1.08	1.01–1.16	0.022	Reference		
LAI aripiprazole (Q1.5M-2M)	1.22	0.95–1.55	0.116	1.22	0.95–1.55	0.114	1.12	0.88–1.44	0.352
LAI fluphenazine (Q1M)	0.96	0.91–1.02	0.198	0.96	0.91–1.02	0.191	0.89	0.82–0.96	0.004
LAI fluphenazine (Q1.5M)	1.08	1.00–1.16	0.062	1.08	1.00–1.16	0.056	1.00	0.91–1.09	0.939
LAI haloperidol (Q1M)	1.00	0.96–1.04	0.978	Reference			0.92	0.86–0.99	0.022
LAI olanzapine[a]	2.12	1.90–2.37	<.0001	2.13	1.91–2.37	<.0001	1.97	1.74–2.22	<.0001
LAI paliperidone (Q1M)	0.93	0.89–0.97	0.001	0.93	0.89–0.97	0.000	0.86	0.80–0.92	<.0001
LAI paliperidone (Q3M)	0.91	0.78–1.05	0.183	0.91	0.78–1.05	0.184	0.84	0.72–0.98	0.025
LAI risperidone[b]	Reference			1.00	0.96–1.04	0.978	0.93	0.86–0.99	0.027
Oral aripiprazole	1.16	1.12–1.21	<.0001	1.17	1.13–1.20	<.0001	1.08	1.01–1.15	0.021
Oral clozapine	0.92	0.88–0.96	0.000	0.92	0.88–0.96	<.0001	0.85	0.79–0.91	<.0001
Oral fluphenazine	1.13	1.08–1.18	<.0001	1.13	1.08–1.18	<.0001	1.05	0.98–1.12	0.200
Oral haloperidol	1.17	1.13–1.21	<.0001	1.17	1.13–1.21	<.0001	1.08	1.01–1.15	0.018
Oral lurasidone	1.27	1.21–1.34	<.0001	1.27	1.21–1.33	<.0001	1.18	1.09–1.26	<.0001
Oral olanzapine	1.11	1.07–1.15	<.0001	1.11	1.08–1.15	<.0001	1.03	0.96–1.09	0.397
Oral paliperidone	1.12	1.07–1.18	<.0001	1.13	1.08–1.18	<.0001	1.04	0.97–1.12	0.263
Oral quetiapine	1.27	1.23–1.31	<.0001	1.27	1.23–1.31	<.0001	1.18	1.10–1.25	<.0001
Oral risperidone	1.19	1.16–1.23	<.0001	1.19	1.16–1.23	<.0001	1.10	1.04–1.18	0.002
Oral ziprasidone	1.33	1.28–1.39	<.0001	1.34	1.29–1.39	<.0001	1.24	1.16–1.32	<.0001
Other oral FGA	1.21	1.16–1.26	<.0001	1.21	1.17–1.25	<.0001	1.12	1.05–1.19	0.001
Other oral SGA	1.21	1.14–1.28	<.0001	1.21	1.14–1.28	<.0001	1.12	1.04–1.21	0.004
None	1.32	1.28–1.37	<.0001	1.32	1.28–1.36	<.0001	1.22	1.15–1.30	<.0001

CI, confidence interval; FGA, first-generation antipsychotic; HR, hazard ratio; LAI, long-acting injectable; NA, not available; QXM, every X months; SGA, second-generation antipsychotic.

[a]Although use of biweekly and monthly LAI olanzapine formulations were observed in our study, the vast majority (>83%) of LAI olanzapine use was for the monthly formulation (i.e., Q1M).

[b]Although use of biweekly and monthly LAI risperidone formulations were observed in our study, the vast majority (>99%) of LAI risperidone use was for the biweekly formulation (i.e., every 2 weeks).