Risk of Relapse Among Medicare Advantage Members Diagnosed With Schizophrenia and Receiving Once-Monthly Paliperidone Palmitate or First-Generation Long-Acting Injectable Antipsychotics

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Introduction

- Schizophrenia is a severe mental disorder characterized by hallucinations, delusions, disorganized behaviors, and disruptions in social interaction[1]
- In the United States, the prevalence of schizophrenia ranges from 0.25% to 0.64%[2,3] and can go up to 1.1%[4], with the estimated economic burden reaching $343.2 billion in 2019[5]
- Antipsychotic drugs can reduce symptoms of schizophrenia and are often used as maintenance therapy[6]
- There are 2 classes of antipsychotic drugs: first-generation (FG) antipsychotics and newer second-generation (SG) antipsychotics, such as the SG long-acting injectable (LAI) once-monthly paliperidone palmitate (PP1M)
- Previous studies suggest that SGLAIs have demonstrated greater effectiveness in reducing psychiatric hospitalization rate and relapse compared with FGLAIs. Additionally, SGLAIs and FGLAIs have different safety profiles, which may impact treatment selection for patients with schizophrenia[7]
- Half of the patients with schizophrenia have Medicare coverage[8]; however, there is a lack of studies investigating the effectiveness of FGLAIs and SGLAIs in the real world

Objective

- To compare real-world clinical outcomes of Medicare beneficiaries with schizophrenia who newly initiated once-monthly PP1M versus FGLAI antipsychotics

Methods

Study design

- The study utilized a retrospective, observational cohort study design

Data source

- Medicare Advantage claims from Optum's de-identified Clinformatics® Data Mart database (CDM)
  - CDM is derived from a database of administrative health claims for members of large commercial and Medicare Advantage health plans
  - The CDM database includes patient demographics, enrollment start and end dates, de-identified adjudicated pharmacy claims (e.g., outpatient prescriptions), and medical claims (e.g., inpatient and outpatient services)
  - The CDM database also includes socioeconomic measures for each beneficiary, including race/ethnicity, education level, and household income

Study period

- January 2009 to June 2023

Index date

- The first claim for PP1M or FGLAI

Follow-up period

- From index date until the end of continuous insurance enrollment

Inclusion criteria

- Aged ≥18 years on index date
- ≥1 pharmacy claim for PP1M or FGLAI during the study period
- ≥12 months continuous enrollment in the database before the index date (baseline period)
- ≥2 outpatient claims on 2 separate dates with a schizophrenia diagnosis code (ICD-9-CM: 295.xx, except for 295.7x; ICD-10-CM: F20.x, F21.x) or ≥1 inpatient claim with a schizophrenia diagnosis code during the 12-month baseline period
- ≥1 pharmacy claim for an oral antipsychotic medication during the 12-month baseline period
- Covered by Medicare Advantage on the index date

Exclusion criteria

- ≥1 claim for an LAI any time before the index date
- Claims for both an FGLAI and an SGLAI on the index date or ≥1 claim for any SGLAI other than PP1M on the index date (use of oral antipsychotics within a certain time window will not be an exclusion criterion as patients who use LAIs start with an oral antipsychotic to establish safety/tolerability)
- ≥1 claim with a diagnosis code for bipolar disorder (ICD-10-CM: F31.x, ICD-9-CM: 296.0x, 296.4x, 296.5x, 296.6x, 296.7, 296.8x) between the most recent schizophrenia diagnosis before the index date and the index date

Outcomes

- Relapse is a composite measure that was defined as schizophrenia-related hospitalization or emergency department visits
  - Number and rate of relapses
  - Time to first relapse

Statistical analysis

- Descriptive statistics were used to report patient baseline characteristics
  - Means and standard deviations (SD) for continuous variables
  - Numbers and percentages for categorical variables
- Key outcomes were evaluated for the PP1M- versus FGLAI-treated cohorts during the follow-up period. Propensity score based standardized mortality ratio weighting was applied to reduce confounding
  - After propensity score was generated for the initiation of PP1M versus FGLAI, a logistic regression was conducted using all baseline variables except for socioeconomic status variables
- Poisson regression models were used for analyzing the number of relapses during the follow-up period (reported as incidence rate ratio [IRR] with 95% CI)
- Kaplan-Meier and Cox proportional hazards models were used to analyze the time to the first relapse during follow-up
- All data analyses were conducted using SAS Enterprise Guide 8 (SAS Institute, Cary, NC)

Sensitivity analysis

- The outcomes were reassessed for subgroups of patients with dual-Medicare/Medicaid coverage, patients stratified by socioeconomic status variables (race, education, and household income), and censored patients who had different LAIs recorded during follow-up than on the index date

TABLE 1: Baseline characteristics

	Unweighted			Weighted		
	PP1M (N = 870)	FGLAI (N = 1801)	Standardized Difference[a]	PP1M (N = 870)	FGLAI (N = 866)	Standardized Difference[a]
Sex, n (%)						
Female	377 (43.3)	879 (48.8)		377 (43.3)	377 (43.5)	
Male	493 (56.7)	922 (51.2)	11.0%	493 (56.7)	489 (56.5)	0.4%
Race, n (%)						
White	461 (53.0)	958 (53.2)	0.4%	461 (53.0)	445 (51.3)	3.2%
Black	243 (27.9)	548 (30.4)	5.5%	243 (27.9)	271 (31.3)	7.4%
Asian/Hispanic	106 (12.2)	183 (10.2)	6.4%	106 (12.2)	96 (11.0)	3.4%
Information missing	60 (6.9)	112 (6.2)	2.7%	60 (6.9)	55 (6.3)	2.2%
Dual Medicare/Medicaid coverage, n (%)	559 (64.3)	1058 (58.7)	11.3%	559 (64.3)	565 (65.2)	2.1%
Age, years						
Mean (SD)	52.4 (13.1)	58.8 (14.1)	47.0%	52.4 (13.1)	53.7 (9.7)	11.2%
Median (range)	53 (22.0-89.0)	59 (23.0-90.0)		53 (22.0-89.0)	53 (23.0-90.0)	
Age group, years, n (%)						
18-35	106 (12.2)	105 (5.8)	22.3%	106 (12.2)	100 (11.5)	2.0%
36-54	372 (42.8)	572 (31.8)	22.9%	372 (42.8)	379 (43.8)	2.0%
≥55	392 (45.1)	1124 (62.4)	35.3%	392 (45.1)	387 (44.7)	0.7%
Education, n (%)						
Up to high school diploma	354 (40.7)	762 (42.3)	3.3%	354 (40.7)	374 (43.2)	5.1%
Less than bachelor's degree	385 (44.3)	803 (44.6)	0.7%	378 (44.3)	378 (43.7)	1.2%
Bachelor's degree plus	82 (9.4)	145 (8.1)	4.9%	82 (9.4)	68 (7.9)	5.6%
Unknown	49 (5.6)	91 (5.1)	2.6%	49 (5.6)	46 (5.3)	1.4%
Income level, n (%)						
Unknown	192 (22.1)	459 (25.5)	8.0%	192 (22.1)	213 (24.6)	6.0%
<$40,000	424 (48.7)	778 (43.2)	11.1%	424 (48.7)	396 (45.7)	6.0%
$40,000-60,000	119 (13.7)	277 (15.4)	4.8%	119 (13.7)	134 (15.5)	5.1%
>$60,000	135 (15.5)	287 (15.9)	1.1%	135 (15.5)	123 (14.2)	3.7%
Quan-Charlson Comorbidity index						
Mean (SD)	1.4 (1.82)	2.1 (2.29)	33.8%	1.4 (1.8)	1.4 (1.3)	0.0%
Median (range)	1 (0.0-11.0)	1 (0.0-15.0)		1 (0.0-11.0)	1 (0.0-15.0)	
Atypical oral antipsychotic, n (%)	833 (95.7)	1523 (84.6)	38.2%	833 (95.7)	829 (95.7)	0.1%
Typical oral antipsychotic, n (%)	229 (26.3)	827 (45.9)	41.7%	229 (26.3)	238 (27.5)	2.6%
Relapse events within 90 days prior to index date, n (%)	352 (40.5)	479 (26.6)	29.7%	352 (40.5)	346 (40.0)	1.0%
Medication-induced movement disorders and other adverse effects of medications, n (%)	54 (6.2)	150 (8.3)	8.2%	54 (6.2)	57 (6.6)	1.5%

FGLAI, first-generation long-acting injectable; PP1M, paliperidone palmitate once monthly; SD, standard deviation.
[a]The standardized difference is not influenced by sample size and allows for the comparison of the relative balance of variables measured in different units. A standard difference of <10% indicates a negligible difference in the mean or prevalence of a covariate between treatment groups.
Covariates used in propensity score calculation included sex, race, age group, education, income level, dual Medicare/Medicaid coverage, Quan-Charlson Comorbidity index score, use of atypical/typical oral antipsychotic, relapse within 90 days prior to index date, prediabetes, hypothyroidism, obesity, hypertension, congestive heart failure, chronic pulmonary disease, coagulation deficiency, medication-induced movement disorder/other adverse effects of medication, sleep-wake disorders, anxiety disorders, trauma- and stress-related disorders, neurodevelopmental disorders, neurocognitive disorders, depressive disorders, elimination disorders, personality disorders, substance-related and addictive disorder, other mental disorders, suicidal ideation, and disruptive, impulsive, and control disorder.

Results

Baseline characteristics

- Unweighted cohorts (**Table 1**)
  - 870 patients newly initiated on PP1M and 1801 patients newly initiated on FGLAI were included
  - PP1M patients were younger than FGLAI patients, with mean age of 52.4 years versus 58.8 years, respectively
  - 43.3% of PP1M patients and 48.8% of FGLAI patients were female
  - 27.9% of PP1M patients and 30.4% of FGLAI patients were Black
  - PP1M patients had lower baseline comorbidity compared with FGLAI patients (mean Quan-Charlson Comorbidity index: 1.4 vs 2.1)
  - Relapse events within 90-days pre-index were more prevalent for PP1M patients (40.5%) versus FGLAI patients (26.6%)
- Weighted cohorts
  - After applying PS-based standardized mortality ratio weighting, 870 patients were included in the PP1M cohort, and 866 patients were included in the FGLAI cohort
  - After weighting, patient baseline characteristics were comparable between the 2 cohorts

Follow-up duration

- The median (interquartile range) follow-up duration for the PP1M and FGLAI cohorts was 654 (295-1362) versus 516 (210-1160) days

Relapse rates

- The weighted relapse rate was lower for the PP1M versus the FGLAI cohort (35.3 vs 62.8 per 100 patient years; IRR: 0.56 [95% CI: 0.40-0.71]; **Table 2**)

Time to first relapse

- The weighted median time to first relapse was 1772 days for the PP1M cohort versus 816 days for the FGLAI cohort ($P < 0.0001$; **Table 3, Figure 1**)
- Patients treated with PP1M had a 40% lower risk of first relapse compared with those treated with FGLAI (weighted hazard ratio: 0.60 [95% CI: 0.51-0.69)

Sensitivity analysis

- Results for the sensitivity analysis subgroups were consistent with those for the overall study population

TABLE 2: Relapse rates during follow-up (PP1M vs FGLAI)

	PP1M	FGLAI
Follow-up time (days)		
Median	653.5	516
Mean	960.3	813.5
5th percentile	57	37
25th percentile	295	210
75th percentile	1,362	1,160
Unweighted[a]		
Rate per 100 py	35.3	50.8
IRR (95% CI)	0.70 (0.54-0.89)	
Weighted[b]		
Rate per 100 py	35.3	62.8
IRR (95% CI)	0.56 (0.40-0.71)	

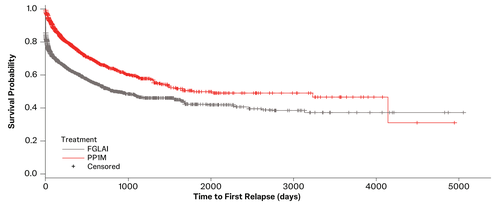
FGLAI, first-generation long-acting injectable; IRR, incidence rate ratio; PP1M, paliperidone palmitate once monthly; py, person year.
[a]Unweighted IRR (95% CI) was estimated by sandwich covariance and scaled Pearson option to correct over-dispersion of Poisson regression.
[b]Weighted IRR (95% CI) was estimated by bootstrap methods and scaled Pearson option to correct over-dispersion of Poisson regression.

TABLE 3: Time to first relapse during follow-up (PP1M vs FGLAI)

	PP1M	FGLAI
Log-rank test, Unweighted		
Chi-square	23.6440	
P value	<0.0001	
Log-rank test, Weighted		
Chi-square	52.3210	
P value	<0.0001	
Median (days)		
Unweighted	1,772	1,668
Weighted	1,772	816
HR (95% CI)[a]		
Unweighted	0.71 (0.62-0.82)	
Weighted	0.60 (0.51-0.69)	

FGLAI, first-generation long-acting injectable; HR, hazard ratio; PP1M, paliperidone palmitate once monthly.
Cox proportion assumption was assessed by the interaction term between the follow-up time and the treatment (PP1M vs FGLAI). FGLAI was used as the reference group.
[a]HR (95% CI) based on sandwich covariance.

FIGURE 1: Time to first relapse during follow-up: Kaplan-Meier curves (weighted PP1M vs FGLAI)



FGLAI, first-generation long-acting injectable; PP1M, paliperidone palmitate once monthly.

Limitations

- Administrative claims data, designed for billing purposes, may contain coding inaccuracies in diagnosis data, leading to potential misclassification
- Results may not be generalizable to patients with insurance coverage other than Medicare Advantage or those without health insurance coverage
- Methods for controlling confounding may not fully address potential bias due to unmeasured confounders in administrative claims

Conclusions

- This study demonstrates that, among patients covered by Medicare Advantage with schizophrenia who were LAI-naive, treatment with PP1M was associated with a significantly lower rate of relapse and delayed time to first relapse event compared with FGLAIs
- The findings highlight the potential clinical benefits of PP1M in managing schizophrenia and suggest its consideration in treatment decision making

Disclosures
All authors are employees of Janssen Scientific Affairs, LLC and hold stock in Johnson & Johnson.

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