Comparative Effectiveness of Oral and Long-Acting Injectable Antipsychotics in Schizophrenia: A Real-World Study in the US Medicare Population

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Background

- Schizophrenia is a chronic mental illness characterized by delusions, hallucinations, and other disabling psychiatric symptoms
- Sustained treatment with antipsychotic medications is crucial in the management of schizophrenia to reduce the risk of acute psychotic episodes and prevent relapse or psychiatric hospitalization[1]
- Oral antipsychotics (OAPs) have been the mainstay of schizophrenia treatment, although their effectiveness has been hindered by poor adherence[2]
- Long-acting injectable antipsychotics (LAIs) that require less frequent administration (e.g., every month, every 3 months) were developed to improve medication adherence relative to daily OAPs[3]
- Little real-world evidence exists on the comparative effectiveness of antipsychotic agents among individuals enrolled in Medicare, which covers half of US patients with schizophrenia[3]

Objective

- To compare the effectiveness of LAIs and daily OAPs across different agents and dosing intervals in a national sample of Medicare beneficiaries with schizophrenia

Methods

Data source

- Data were taken from the 2006-2019 national Chronic Conditions Warehouse (CCW) 100% Medicare Part A, B, and D claims and beneficiary summary files available from the Centers for Medicare and Medicaid Services

Study sample

- The sample included all fee-for-service Medicare beneficiaries with standalone Part D prescription drug coverage with schizophrenia and ≥1 antipsychotic fill between January 1, 2006, and December 31, 2019
  - Index date was the date of first antipsychotic prescription
- Patients were required to meet the following criteria:
  - Age ≥18 years on index date
  - Continuous fee-for-service Medicare Parts A, B, and D coverage 6 months before and after the index date

Follow-up period & treatment sub-periods

- The follow-up period for each patient was from the index date until death, transition to Medicare Advantage Prescription Drug (MAPD) plan, or Dec 31, 2019, whichever occurred earlier
- Each patient's follow-up period was divided into treatment periods, with a new treatment period starting on the date of change in the treatment exposure
  - The treatment periods continued until there was evidence of a ≥60-day continuous gap of the specific treatment exposure
  - Periods with a 60-day or longer continuous gap in any antipsychotic use were categorized as no antipsychotic use treatment periods
  - The treatment periods were then further divided into sub-periods, with a new sub-period starting on the day after the date of occurrence of an outcome event (see Outcomes section below)

Outcomes

- Treatment failure was a composite outcome of psychiatric hospitalization, antipsychotic discontinuation, suicide attempts, and death
  - Antipsychotic discontinuation was defined as a continuous gap of ≥60 days after the days' supply of the most recent antipsychotic prescription was exhausted
  - Psychiatric hospitalization was defined as the presence of a medical claim for an inpatient admission with a diagnosis code of a psychiatric disorder
- Relapse was defined as the occurrence of an inpatient admission or ER visit with a diagnosis of schizophrenia

Analysis

- The primary analytic approach was within-individual Cox regressions, in which each individual served as his or her own control to remove selection bias
- In the first set of analyses, we compared outcomes across all LAIs (aripiprazole, fluphenazine, haloperidol, olanzapine, paliperidone, and risperidone) and OAPs (first-generation antipsychotics [FGA]: fluphenazine, haloperidol, and other FGA; second-generation anti-psychotics [SGA]: aripiprazole, clozapine, lurasidone, olanzapine, paliperidone, quetiapine, risperidone, and ziprasidone, and other SGA)
- In a second set of analyses we further separated the LAI agents with sufficient sample size by dosing interval: paliperidone (every month and 3 months), aripiprazole (every month and 6-8 weeks), and fluphenazine (every month and 6 weeks)
- LAI aripiprazole was used as the reference group in both sets of analyses
- 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
  - The unit of analysis was the sub-period
- Given the within-individual analyses, control variables for time invariant covariates were not required; however, we controlled for the following time varying covariates: years from the first ever schizophrenia diagnosis date in Medicare claims until the starting date of each sub-period, number of relapses within 3 months before the starting date of a sub-period, and order of exposure (number of treatments used before this sub-period)

Results

- The final sample included 152,835 beneficiaries (mean age 53.5 years, 54.0% male, 61.5% White, **Table 1**)

Treatment failure

- In the first set of agent-level analyses, clozapine (HR 0.89; 95% CI 0.84-0.94) was the only OAP associated with significantly lower hazard of treatment failure compared to LAI aripiprazole (data not shown)
  - LAI risperidone (HR 0.92; 95% CI 0.87-0.98) and LAI paliperidone (HR 0.88; 95% CI 0.83-93) were the only LAIs associated with lower hazard of treatment failure compared to LAI aripiprazole
- In the second set of analyses further breaking out LAIs by dosing intervals, LAI haloperidol every month (HR 1.14; 95% CI: 1.07-1.20), LAI fluphenazine every month (HR 1.36; 95% CI: 1.28-1.45), and LAI olanzapine primarily every month (HR 1.77; 95% CI 1.58-1.98) were associated with a significantly higher hazard of treatment failure compared to LAI aripiprazole every month (**Figure 1**)
  - LAI paliperidone every 3 months, the LAI with the longest dosing interval, had the lowest hazard of treatment failure compared to LAI aripiprazole every month (HR 0.62; 95% CI 0.55-0.71)
  - LAI fluphenazine every 1.5 month was associated with a significantly lower hazard of treatment failure compared to LAI aripiprazole LAI every month (HR 0.86; 95% CI 0.80-0.93)

Antipsychotic discontinuation

- No OAP was associated with a lower hazard of antipsychotic discontinuation compared to LAI aripiprazole every month
- Compared to LAI aripiprazole every month, the only LAIs with significantly lower hazard of antipsychotic discontinuation were LAI paliperidone every 1 month (HR 0.87; 95% CI 0.77-0.99) and LAI paliperidone every 3 months (HR 0.29; 95% CI 0.22-0.37) (**Figure 2**)

Psychiatric hospitalization

- Compared to LAI aripiprazole every month, all LAIs had significantly lower hazard of psychiatric hospitalization (HRs 0.84 to 0.93) except LAI fluphenazine (HR 1.00, 95% CI 0.91-1.09), LAI aripiprazole every 1.5-2 months (HR 1.12; 95% CI 0.88-1.44), and LAI olanzapine primarily every month (HR 1.97; 95% CI 1.74-2.22) (**Figure 3**)
- Most OAPs were significantly higher hazard of psychiatric hospitalization (HRs 1.08 to 1.24) compared to LAI aripiprazole every month with the exception of oral clozapine (HR 0.85; 95% CI 0.79-0.91), oral olanzapine (HR 1.03; 95% CI 0.96-1.09), oral paliperidone (HR 1.04; 95% CI 0.97-1.12), and oral fluphenazine (HR 1.05; 95% CI 0.98-1.12)

Relapse

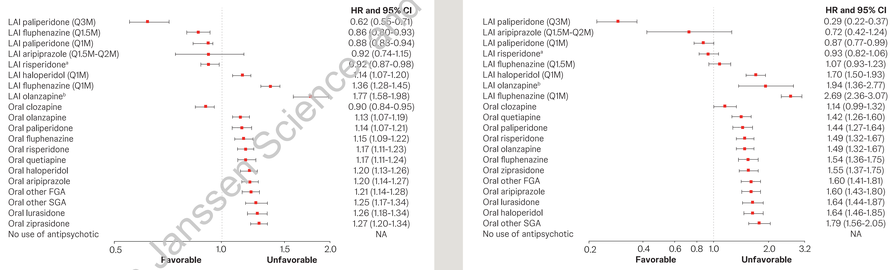
- Paliperidone LAI every 3-months (HR 0.84; 95% CI 0.74-0.94) had the lowest hazard of relapse relative to LAI aripiprazole every month (**Figure 4**)

Table 1. Patient Characteristics

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		
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%

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

FIGURE 1: Within-individual Cox regressions using once-monthly LAI aripiprazole as reference [Endpoint: treatment failure]



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 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).

[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 (i.e., Q1M).

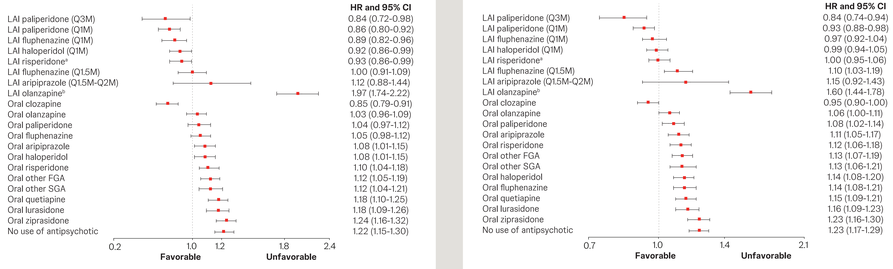
FIGURE 2: Within-individual Cox regressions using once-monthly LAI aripiprazole as reference [Endpoint: antipsychotic discontinuation]

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 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).

[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 (i.e., Q1M).

FIGURE 3: Within-individual Cox regressions using once-monthly LAI aripiprazole as reference [Endpoint: psychiatric hospitalization]



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 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).

[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 (i.e., Q1M).

FIGURE 4: Within-individual Cox regressions using once-monthly LAI aripiprazole as reference [Endpoint: relapse]

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 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).

[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 (i.e., Q1M).

Limitations

- Our study is only generalizable to the fee-for-service Medicare population with standalone Part D coverage and not other insurance types (Medicaid, commercial, etc.)
- Our within-individual Cox regressions controlled for observed and unobserved time-invariant confounders as well as observed time-varying confounders, but we cannot rule out the possibility of unobserved time-varying confounders that could bias our results

Conclusions

- This real-world study found that all OAPs except clozapine had a higher risk of treatment failure relative to aripiprazole LAI
- Several LAIs showed a greater benefit with paliperidone LAI every-3-months having the lowest risk of treatment failure

Disclosures

PL received personal fees from Cobbs Creek Healthcare and SKB Consulting Inc., all unrelated to the submitted work. ZG reported no conflicts of interest. CB and CP are employees of Janssen Scientific Affairs, LLC and stockholders of Johnson & Johnson, Inc. JAD received grants from Janssen Scientific Affairs, LLC during the conduct of the study, personal fees from AbbVie, Acadia, Janssen, Merck, Otsuka, and Takeda, and grants from Merck and Spark Therapeutics unrelated to the submitted work.

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