Association of Antipsychotic Medication Nonadherence With All-Cause Mortality in Newly Treated Adults With Schizophrenia: A Retrospective Healthcare Claims Study

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Introduction

- Patients with schizophrenia have a shorter life expectancy than the general population[1,2]
- Excess mortality in schizophrenia is observed starting early in the course of disease[3,4]
- Mortality risk is influenced by modifiable factors such as lifestyle behaviors, access to care, and use of antipsychotic medication[3]
- Adherence to antipsychotic medication is a known challenge in schizophrenia, and nonadherence is a risk factor for relapse and hospitalization[5–7]
- Relapse is strongly associated with all-cause mortality risk;[8] however, the influence of nonadherence on mortality is not well characterized

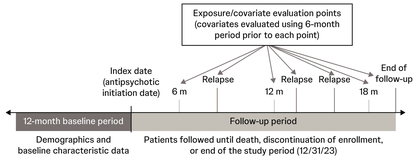
Objective

- To quantify the impact of antipsychotic medication adherence level on all-cause mortality in adults with schizophrenia

Methods

- This retrospective, non-interventional study utilized data from Optum's de-identified Clinformatics® Data Mart Database reflecting events from 01/01/11 to 12/31/23
- Patient inclusion criteria
  - Initiated or re-initiated any antipsychotic medication during the cohort identification period (01/01/12 to 12/31/22)
  - Had ≥2 outpatient claims on separate dates or ≥1 inpatient claim with a schizophrenia diagnosis between 01/01/12 and 12/31/22
  - Had ≥12 months of continuous pre-index enrollment
  - Aged ≥18 years at index (defined as the antipsychotic initiation date)
- Patient exclusion criteria
  - Antipsychotic prescription during the 12-month baseline period
  - Healthcare claim with a bipolar disorder diagnosis code during the 12-month baseline period
  - Death record prior to the index date
- The exposure of interest was level of adherence, and the primary outcome was all-cause mortality
- Month and year of death were captured from claims with a discharge status of "expired," coverage discontinuation due to death, electronic health record data indicating death, the Death Master File maintained by the Social Security Office, Center for Medicare and Medicaid Services data, and obituary data
- Adherence levels were defined by cumulative proportion of days covered (PDC):
  - High adherence (≥0.8)
  - Low/moderate adherence (≥0.2 to <0.8)
  - Nonadherence (<0.2)
- Covariate values and adherence level were evaluated whenever the following driver events occurred: (1) index date, (2) relapse, (3) every 6 months post-index, (4) administrative censoring (i.e., plan disenrollment or end of the study period), or (5) all-cause mortality (**Figure 1**)
- A marginal structural model adjusting for baseline (age on the index date, sex, race) and time-varying (relapse, healthcare resource utilization, medication use, clinical characteristics) confounding factors was used to estimate hazard ratios (HRs) and 95% CIs for mortality at different adherence levels

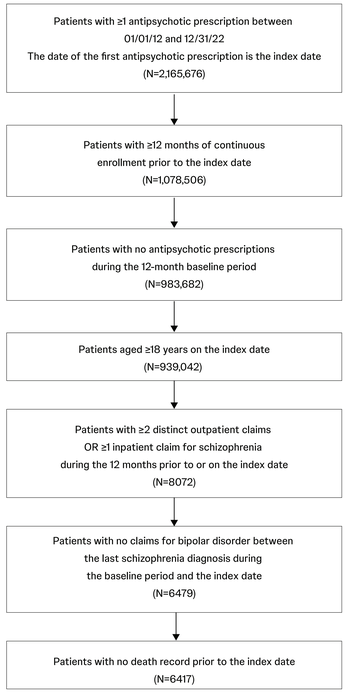
Figure 1: Study design



Results

- The study population included 6,417 patients with schizophrenia newly treated with or re-initiating antipsychotic treatment (**Figure 2**)

Figure 2: Patient attrition



Demographics and baseline characteristics

- Mean age at index was 55.3 ± 20.5 years; the majority of patients (54.0%) were male and 51.0% of patients were White (**Table 1**)
- Most patients (81.7%) were prescribed a second-generation oral antipsychotic at index
- Use of first- or second-generation long-acting injectable antipsychotics was low (<7.0%)

Table 1: Demographics and baseline characteristics

Parameter	Study population[a] (N = 6,417)
Age on index date, mean ± SD	55.3 ± 20.5
Male sex	3,464 (54.0)
Race	
White	3,275 (51.0)
Black	1,512 (23.6)
Other	1,630 (25.4)
Mental health-related medication use	
First-generation oral antipsychotic	667 (10.4)
Second-generation oral antipsychotic	5,241 (81.7)
First-generation LAI antipsychotic	444 (6.9)
Second-generation LAI antipsychotic	176 (2.7)
Clozapine	61 (1.0)
Lithium	92 (1.4)
Benzodiazepines	1,158 (18.0)
Antidepressant	3,244 (50.6)
Concomitant medications	
Antidiabetic	1,152 (18.0)
Antihyperlipidemic	1,992 (31.0)
Antihypertensive	2,132 (33.2)
Beta blocker	1,574 (24.5)
Anticoagulant	849 (13.2)
Narcotics/opioids	695 (10.8)
Healthcare resource utilization in past 6 months	
All-cause hospitalization, median (IQR)	0.5 (0–1.0)
All-cause emergency department visit, median (IQR)	0.5 (0–1.0)
All-cause ICU visit, median (IQR)	0 (0–0)
All-cause outpatient visit, median (IQR)	4.5 (2.0–9.0)

ICU, intensive care unit; IQR, interquartile range; LAI, long-acting injectable.
[a]Data are n (%) unless otherwise specified.

Comorbidities

- Mental health-related comorbidities were present in 89.8% of patients (**Table 2**)
- Common non–mental-health-related comorbidities included hypertension (57.9%), other neurologic disorder (41.2%), and deficiency anemia (23.2%)

Table 2: Comorbidities at baseline

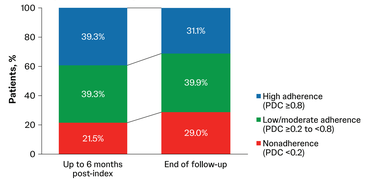
Parameter	Study population[a] (N = 6,417)
QCCI, mean ± SD	1.87 ± 2.38
Mental health-related comorbidities[b]	
Any mental health-related disorder	5,762 (89.8)
Depressive disorders	3,203 (49.9)
Anxiety disorders	2,879 (44.9)
Substance-related and addictive disorders	2,554 (39.8)
Other clinical focus areas	2,147 (33.5)
Neurocognitive disorders	1,894 (29.5)
Sleep-wake disorders	1,551 (24.2)
Trauma and stress-related disorders	925 (14.4)
Other mental disorders	750 (11.7)
Comorbidities[b]	
Hypertension[c]	3,718 (57.9)
Other neurologic disorder	2,642 (41.2)
Deficiency anemia	1,488 (23.2)
Diabetes[c]	1,290 (20.1)
Hypothyroidism	1,046 (16.3)
Obesity	824 (12.8)
Weight loss	704 (11.0)

QCCI, Quan-Charlson comorbidity index.
[a]Data are n (%) unless otherwise specified.
[b]Comorbidities occurring in 10% or more of the overall study population.
[c]Most cases were uncomplicated/did not have chronic complications.

Adherence during follow-up

- Median follow-up was 17.3 months (interquartile range, 6.2–36.7)
- Within 6 months of antipsychotic initiation, mean cumulative PDC was 0.59 ± 0.33 and only 39.3% of patients had high adherence (**Figure 3**)

Figure 3: Proportion of patients in each cumulative PDC group up to 6 months post-index and by end of follow-up



PDC, proportion of days covered.
Median duration to end of follow-up was 17.3 months. PDC is cumulative; hence, end of follow-up includes up to 6 months post-index data.

Adherence and outcomes

- By the end of 96 months, Kaplan-Meier survival curve analysis indicated a mortality rate of approximately 40%, after accounting for censoring
- After adjustment for covariates, nonadherence and low/moderate adherence patients had significantly higher all-cause mortality hazard than high-adherence patients (**Table 3**)

Table 3: Hazard ratios for all-cause mortality comparing different adherence levels[a]

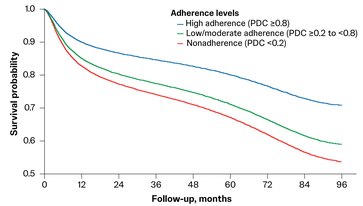
Adherence level (cumulative PDC)	Hazard ratio (95% CI)
High adherence (<0.8) (reference)	1.00
Low/moderate adherence (≥0.2 to <0.8)	1.53 (1.25–1.89)
Nonadherence (≥0.2)	1.80 (1.43–2.27)

PDC, proportion of days covered.
[a]Adjusted for (1) all baseline covariates with a proportion ≥2%, and (2) the time-varying covariates: non-antipsychotic psychiatric medication use and comorbidities over time.

Predicted survival

- Survival curves among adherence groups diverged rapidly and continued to separate over time (**Figure 4**)
- Five-year estimated survival rates were 80%, 71%, and 67% for high-adherent, low/moderate-adherent, and nonadherent patients, respectively

Figure 4: Predicted survival curves by cumulative antipsychotic adherence level



PDC, proportion of days covered.

Limitations

- Administrative claims data are limited by the potential for coding errors and inconsistencies and missing clinical or laboratory data
- Residual confounding may exist for information that is not available within claims data (e.g., traumatic events, socioeconomic status, etc.)
- The presence of a claim for a dispensed prescription does not indicate that the medication was taken as prescribed
- Although multiple sources were used to identify patient deaths, it is possible that not every death was captured in the database, which could lead to outcome misclassification, especially in the form of underreporting
- Given the limited lookback time window, it was not possible to distinguish patients who were newly treated versus those who were re-initiating antipsychotic treatment
- Results may not be generalizable to all patients with schizophrenia due to regional or national differences in patient demographics, healthcare delivery, and schizophrenia treatment

Key Takeaway

Suboptimal adherence in patients with schizophrenia who were newly treated with or re-initiating antipsychotic therapy significantly increased risk of all-cause mortality

Conclusions

- In this study, patients with suboptimal adherence to antipsychotic therapy were at greater risk of all-cause mortality than high-adherence patients
- The difference in survival curves among adherence groups showed divergence as early as 12 months after starting treatment in this population of patients newly treated with or re-initiating an antipsychotic
- These data add to a growing body of evidence demonstrating that elevated mortality risk occurs early in the course of schizophrenia
- There is a need for interventions that support early and sustained antipsychotic adherence to reduce mortality risk in patients with schizophrenia

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Disclosures
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