Mortality in Patients With Parkinson's Disease Psychosis Using Pimavanserin Versus Other Antipsychotics

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BACKGROUND

- Pimavanserin is the only medication approved in the United States (US) to treat hallucinations and delusions associated with Parkinson's disease psychosis (PDP).
- All US antipsychotic labels include boxed warnings of mortality risk in elderly patients with dementia-related psychosis.
- This follow-up study was conducted as part of continued safety monitoring of pimavanserin[1] to evaluate mortality risk.

OBJECTIVES

- To compare mortality risk after initiation of pimavanserin or a comparator atypical antipsychotic among older adults with PDP in the general population and in a subcohort of older patients with PDP residing in long-term care (LTC) or skilled nursing facilities (SNFs)
- To evaluate if the mortality risk varied over time and in subgroups of interest (for the primary PDP and LTC/SNF subcohort)

METHODS

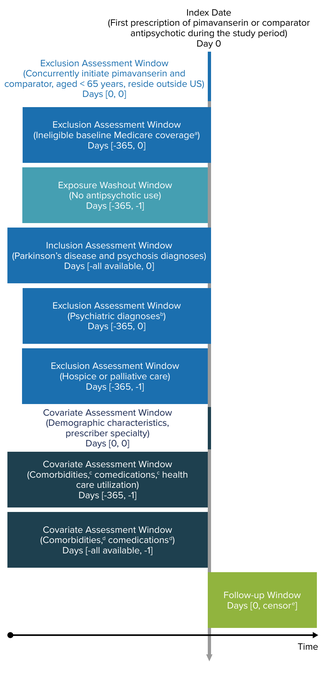
Study Setting

- Data source: US Medicare claims and assessment data
- Study population: Adults (aged ≥ 65 years at the time of treatment initiation) with PDP
- Study period: 1 April 2016 (US launch of pimavanserin) through 31 December 2021 (most recent Medicare data available)
- Treatment groups:
  - Treatment: Initiation of pimavanserin
  - Comparator: Initiation of an atypical antipsychotic
  - Index date: Date of antipsychotic treatment initiation
- Study design details and eligibility criteria are shown in Figure 1.

Statistical Analysis

- Pimavanserin initiators were matched 1:1 to a comparator initiator without replacement using propensity scores (PS).[2-4]
  - Covariate distributions and absolute standardized differences were evaluated before and after matching to ensure balance of confounders.
- Cumulative incidence, incidence rates, hazard ratios (HRs), and corresponding 95% confidence intervals (CIs) of mortality during follow-up were estimated.
  - To describe the changing risk more granularly, time period–specific risk ratios (RRs) and absolute risk differences (RDs) were estimated at days 30, 90, 180, and 365.
- Subgroup analyses were conducted by sex (male/female), age group (65 to < 75 years, 75 to < 85 years, ≥ 85 years) and dementia diagnosis (present/not present in 365 days before index date).
- Sensitivity analyses included:
  - Disregard of treatment discontinuation (intent to treat analysis)
  - Not requiring a psychosis diagnosis
  - Alternative comparator groups (a) quetiapine alone and (b) other nonquetiapine comparators
  - Condition on requiring Parkinson's disease (PD) treatment at baseline
  - Inclusion of prior users of other antipsychotics

Figure 1. Study Design Schematic Illustrating Cohort Eligibility and Inclusion Criteria



[a] Initial Medicare enrollment entitlement not due to age (≥ 65 years); enrollment in a managed care plan; incomplete or intermittent enrollment in Medicare Parts A, B, and/or D.

[b] Bipolar disorder, schizophrenia, schizoaffective disorder, or major depressive disorder with psychotic symptoms.

[c] The 365-day lookback window applies to all comorbidities and comedications other than those listed in footnote d.

[d] Myocardial infarction, congestive heart failure, cerebrovascular disease, diabetes mellitus, malignancy, HIV/AIDS, chronic cardiovascular disease, tobacco use, drugs used in tobacco dependence.

[e] Death, end of the study period, disenrollment from eligible Medicare plan, end of continuous use period of index medication, switching to or adding a different study medication.

RESULTS

- The study identified 32,426 patients with PDP initiating atypical antipsychotic treatment; 4,384 initiated pimavanserin and 28,042 initiated a comparator atypical antipsychotic (67.2% of comparators initiated quetiapine).
  - PS matching retained 4,381 patients in each treatment group in the primary PDP cohort and 905 patients in the LTC/SNF subcohort.
- Select baseline characteristics before matching are shown in Table 1.
  - Pimavanserin users presented with lower frequency of certain comorbidities, more frequently received treatment for PD, and were more likely to be prescribed by a neurologist.
  - After PS matching, all patient characteristics were well balanced.

Table 1. Select Baseline Characteristics of Patients With PDP Who Initiated Treatment With Atypical Antipsychotics, Before Propensity Score Matching

	Primary PDP cohort		LTC/SNF subcohort	
Patient characteristic	Pimavanserin N = 4,384	Comparator antipsychotics N = 28,042	Pimavanserin N = 921	Comparator antipsychotics N = 7,963
Mean age at treatment initiation, years (SD)	79.3 (6.15)	81.1 (6.72)	81.3 (6.34)	82.5 (6.70)
Female sex, N (%)	1,964 (44.8)	13,253 (47.3)	495 (53.7)	4,205 (52.8)
Race and/or ethnicity, N (%)				
Black	159 (3.6)	1,091 (3.9)	34 (3.7)	349 (4.4)
White	3,821 (87.2)	24,398 (87.0)	811 (88.1)	7,036 (88.4)
Other or unknown	404 (9.2)	2,553 (9.1)	76 (8.3)	578 (7.3)
Antipsychotic prescriber specialty, N (%)				
Geriatrics/gerontology	85 (1.9)	1,143 (4.1)	62 (6.7)	629 (7.9)
Neurology	2,704 (61.7)	7,060 (25.2)	163 (17.7)	231 (2.9)
Primary care	1,128 (25.7)	14,949 (53.3)	570 (61.9)	6,048 (76.0)
Psychiatry	159 (3.6)	2,007 (7.2)	70 (7.6)	421 (5.3)
Other	308 (7.0)	2,883 (10.3)	56 (6.1)	634 (8.0)
Treatments for PD, N (%)	4,172 (95.2)	21,473 (76.6)	870 (94.5)	5,623 (70.6)
Dementia, N (%)	3,033 (69.2)	21,891 (78.1)	784 (85.1)	7,116 (89.4)
Myocardial infarction,a N (%)	759 (17.3)	6,812 (24.3)	220 (23.9)	2,247 (28.2)
Congestive heart failure,[a] N (%)	1,520 (34.7)	12,730 (45.4)	471 (51.1)	4,484 (56.3)
Diabetes mellitus,a N (%)	1,589 (36.2)	12,280 (43.8)	431 (46.8)	3,946 (49.6)
Renal disease, N (%)	887 (20.2)	8,102 (28.9)	249 (27.0)	2,855 (35.9)

SD = standard deviation.

[a] Defined using all available lookback data. All other comorbidities and medications were defined using a 365 day lookback window.

Table 2. Incidence Rates and HRs of Mortality in Patients With PDP Who Initiated Treatment With Atypical Antipsychotics

Study cohort and treatment group	Patients	Events	Person-years	Incidence rate per 100 person-years (95% CI)	Hazard ratio (95% CI)
Primary PDP cohort					
Unmatched cohort					
Pimavanserin	4,384	604	2,926.1	20.64 (19.03-22.36)	0.65 (0.60-0.70)
Comparator atypical antipsychotic	28,042	4,914	15,089.3	32.57 (31.66-33.49)	--
Matched cohort					
Pimavanserin	4,381	603	2,925.1	20.61 (19.00-22.33)	0.76 (0.68-0.85)
Comparator atypical antipsychotic	4,381	638	2,367.2	26.95 (24.90-29.13)	--
LTC/SNF subcohort					
Unmatched cohort					
Pimavanserin	921	186	515.7	36.07 (31.07-41.64)	0.81 (0.70-0.94)
Comparator atypical antipsychotic	7,963	1,897	4,245.8	44.68 (42.69-46.74)	--
Matched cohort					
Pimavanserin	905	182	504.8	36.06 (31.01-41.69)	0.90 (0.74-1.10)
Comparator atypical antipsychotic	905	194	487.1	39.83 (34.42-45.85)	--

- In the primary PDP cohort after matching, mortality risk was lower in the pimavanserin group compared with other atypical antipsychotics group (Table 2).
  - Results were consistent across most subgroup analyses and all sensitivity analyses (Figure 2 and Figure 3).
  - Cumulative incidence curves demonstrated a reduced risk of mortality in the pimavanserin group throughout the first year of follow-up; the curves began to converge and became less precise after approximately 3 years of follow-up due to low sample sizes and increasing mortality rates with older age (Figure 4).
  - Time period–specific RRs and RDs estimates demonstrated pimavanserin to be associated with a sustained lower risk of mortality; on the relative scale (RR), the largest benefit of pimavanserin was seen at day 90 and day 180; on the absolute scale (RD), the largest benefit of pimavanserin was seen from day 180 through day 365 (Figure 5).
- After matching, in the LTC/SNF subcohort, no difference in mortality risk was seen between the treatment groups; results were consistent across most sensitivity analyses, all subgroup analyses, and all time period–specific RR and RD analyses.

Figure 2. Matched HRs from the Overall PDP Cohort, Primary and Subgroup Analyses

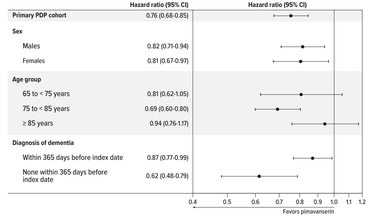


Figure 3. Matched HRs from the Overall PDP Cohort, Primary and Sensitivity Analyses

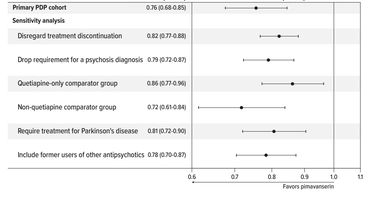
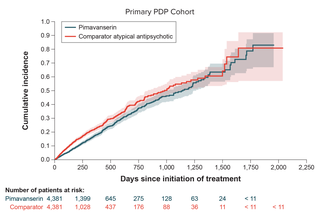


Figure 4. Cumulative Incidence of Mortality by Time Since Atypical Antipsychotic Initiation Among Patients With PDP, After Matching



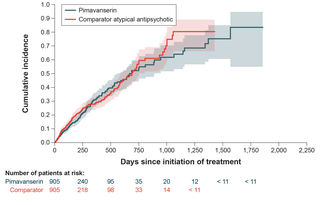
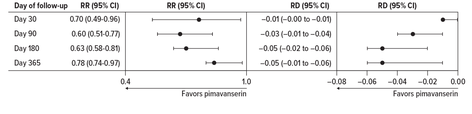


Figure 5. Matched Relative Risk and Risk Difference of Mortality Comparing Patients With PDP Using Pimavanserin With Patients Using Comparator Atypical Antipsychotics



DISCUSSION

- This active-comparator, new-user cohort study suggests an overall lower mortality risk among elderly patients with PDP treated with pimavanserin compared with that among patients treated with other atypical antipsychotic drugs through at least the first year of treatment.
- No meaningful differences in mortality risk were observed between treatment groups in the older LTC/SNF subcohort with higher overall underlying mortality risk possibly due to advanced age and larger comorbidity burden compared with the primary PDP cohort.
- Additionally, this study showed that regardless of treatment group, mortality was higher in the LTC/SNF subcohort than the primary PDP cohort.
- Mortality rates in the current analyses (which included time periods during the coronavirus disease 2019 [COVID-19] pandemic of 2020-2021), especially for LTC/SNF residents, were higher than those in first interim analyses,[1] potentially due to increased mortality rates due to COVID-19.

CONCLUSIONS

We observed (1) a consistently decreased overall mortality risk associated with pimavanserin compared with other atypical antipsychotics across subgroups and sensitivity analyses in the primary PDP population and (2) no signal of increased mortality risk with pimavanserin use in patients residing in LTC/SNFs.

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DISCLOSURES

- This study was conducted by researchers at RTI Health Solutions (RTI-HS), an independent nonprofit research organization. Funding for the research was received from Acadia Pharmaceuticals, Inc., the manufacturer of pimavanserin. The contract between RTI-HS and Acadia Pharmaceuticals, Inc., includes independent publication rights.
- SR, JBL, and JF contributed to the conceptualization, investigation, methodology, visualization, and writing of the original draft. HED and RM contributed to the resources, project administration, investigation, and writing for the review and editing drafts of the manuscript. LJM contributed to the methodology, software, formal analysis, data curation, and writing for the review and editing drafts of the manuscript. DD and VA contributed to the investigation and writing for the review and editing drafts. MSA contributed to the conceptualization, supervision, investigation, methodology, funding acquisition, and writing of the review and editing drafts.

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