Poster # P 129-I

Retrospective Analyses Evaluating the Risk of Mortality Associated With Pimavanserin or Other Atypical Antipsychotics in Patients With Parkinson's Disease Psychosis

Stuart H. Isaacson[1], MD; Fernando Pagan[2], MD; Daniel Truong[3,4], MD; Victor Abler[5], DO; Rajesh Pahwa[6], MD

[1]Parkinson's Disease and Movement Disorders of Boca Raton, Boca Raton, FL, USA; [2]Department of Neurology, Georgetown University Medical Center, Washington, DC, USA; [3]The Parkinson and Movement Disorder Institute, Fountain Valley, CA, USA; [4]Department of Psychiatry and Neuroscience, University of California Riverside, Riverside, CA, USA; [5]Acadia Pharmaceuticals Inc., San Diego, CA, USA; [6]Department of Neurology, University of Kansas Medical Center, Kansas City, KS, USA

INTRODUCTION

- Parkinson's disease (PD) is estimated to affect approximately 1 million adults in the United States.[1]
- Although PD is primarily characterized by motor symptoms, many patients with PD also experience a range of nonmotor symptoms, including neuropsychiatric disorders such as psychosis.[2]
- Among patients with PD, the presence of symptoms of psychosis has been identified as an independent predictor of increased mortality.[3-7]
- Atypical antipsychotics used off-label to treat PD with psychosis (PDP) symptoms can increase the risk of mortality; >2-fold increases in risk have been reported.[6]
- Pimavanserin is a selective 5-HT_{2A} inverse agonist/antagonist that is currently the only FDA-approved medication for hallucinations and delusions associated with PDP.[8]
- Similar to other antipsychotics, pimavanserin also has a boxed warning for increased risk of mortality in elderly patients with dementia-related psychosis.[8]
- This narrative review summarizes the available data for mortality risk associated with PDP and pimavanserin using mortality data from an open-label extension study, 5 retrospective studies, and a postmarketing analysis.

RESULTS

Mortality Risks in PD and PDP and Current Treatment

- Independent of PDP, PD itself is associated with an increased risk for mortality compared with that of the general population (**Table 1**).[9-11]
- For PDP, an observed mortality rate of 28.2 per 100 patient-years (PY) (95% CI, 27.5–28.8) has been reported.[12]
- In a 2016 retrospective, matched cohort study of 7877 pairs of patients with PD for which patients with dementia with Lewy bodies, bipolar disorder, schizophrenia, or other causes of psychosis were actively excluded, antipsychotic use of any kind was associated with an increased hazard for mortality in the 180 days after treatment (hazard ratio 2.35; 95% CI 2.08–2.66), and the mortality rate for atypical antipsychotics ranged from 14.2–31.0 per 100 PY (**Table 1**).[6]
  - Of the antipsychotics recommended by the American Academy of Neurology for use in PDP, only quetiapine was assessed and had a hazard ratio of 2.16 (95% CI, 1.88–2.48) for increased mortality compared with no treatment.

Table 1. Mortality Rates of PD and Atypical Antipsychotic Treatment

Data Source	Mortality Per 100 PY (95% CI)
US Medicare data (2012–2015)[12]	PD: 7.31 (7.15–7.47) PDP: 28.2 (27.5–28.8)
US Veterans Administration data[6]	Olanzapine: 29.3 (24.1–35.2) Quetiapine: 18.6 (16.9–20.3) Risperidone: 31.0 (26.4–36.1) Other atypical antipsychotics: 14.2 (7.6–24.3)

PD, Parkinson's disease; PDP, Parkinson's disease psychosis; PY, patient-years.

Pimavanserin Clinical Trial Mortality Data

- In pre-marketing placebo-controlled trials in patients with PDP, the crude mortality rate was 1.5% for pimavanserin vs 0.4% for placebo.[13]
- The long-term mortality data for pimavanserin comes from an open-label extension study that included patients with PDP who completed 1 of 3 previous placebo-controlled studies or participated in a previous open-label extension study.[14]
- In an analysis of 459 patients conducted over an 11-year period, an estimated 55.8% of patients continued pimavanserin treatment for 1 year, and 18.1% continued pimavanserin treatment for 4 or more years.
- The overall observed mortality rate was 6.45 deaths per 100 PY.
  - Most deaths (76.3%) occurred in patients aged ≥70 years.
  - The most common adverse events with fatal outcomes were cardiac disorders (3.7%) and respiratory disorders (2.6%) at the organ level (**Table 2**).[14]
  - Independent medical review of 61 patient deaths did not find any to be drug related and instead were consistent with patients' age, advanced stage of illness, and comorbidities.

Table 2. Most Common AEs With Fatal Outcomes in an Open-Label Extension Study

AE		Patients (%) (N=459)
System	Cardiac disorders	3.7
	Respiratory disorders	2.6
Preferred Term	Pneumonia	1.1
	PD	1.1
	Acute respiratory failure	0.9
	Acute myocardial infarction	0.7
	Dementia	0.7
	Cardiac arrest	0.7

AE, adverse event; PD, Parkinson's disease.

- The observed mortality rate was 6.45 deaths per 100 PY (**Table 3**).[13]

Retrospective Studies of Mortality With Pimavanserin

- In addition to the data from the open-label extension study, several retrospective analyses have investigated the mortality risk associated with pimavanserin treatment in patients with PDP (**Table 3**).

Table 3. Studies of Pimavanserin Mortality in Patients With PD

Study	Design	No. of Patients	Primary Objective	Mortality Findings	Study Limitations
Ballard et al. 2020[14]	Open-label extension study	PIM: 459	Assess the long-term safety and tolerability of PIM in patients with PDP	Observed mortality rate: 6.45 per 100 PY	Given the nature of the study, there is a lack of a comparison group, a high likelihood of informative missing data, and an inability to assess patients long-term after discontinuation
Longardner et al. 2020[15]	Retrospective study of patients with PD; April 2016–April 2019	PIM: 40 Quetiapine: 188 Both agents: 74 Untreated: 2681	Review of clinical, iatrogenic, and demographic factors associated with increased mortality in patients with PDP	Mortality OR (95% CI) vs untreated PDP controls: • PIM: 1.2 (0.35–3.13); *P*=0.75 • Quetiapine: 3 (1.90–4.65); *P*<0.001 • Both agents: 3.4 (1.72–6.30); *P*<0.001	Direct comparisons cannot be made between quetiapine and pimavanserin or treated and untreated patients with PDP
Mosholder et al. 2020[16]	Retrospective new-user cohort study of patients with PD in Medicare; April 2016–March 2019	PIM: 3227 Atypical APs: 18,448	All-cause mortality with PIM vs atypical APs	PIM vs atypical APs: HR, 0.78 (95% CI, 0.67–0.91) • Risk of mortality was similar between PIM and atypical AP groups post 180 days (HR, 1.07; 95% CI, 0.84–1.36)	• Because of the observational nature of this study, results may be subject to confounding factors • A diagnosis of psychosis was not required
Brown et al. 2020[17]	Retrospective analysis of AE case reports submitted to the FAERS; 2016–Q3/2019	NA	PRR lower (95% CI) for all-cause death in PIM-treated patients; comparison with clozapine, quetiapine, and other APs	PRR lower (95% CI) for PIM: • Full FAERS population: 2.08 • PD treated with levodopa: 1.15 • PD treated with multiple medications: 1.63 PIM similar to quetiapine in patients with PD	• For any given report, there is no certainty that a suspected drug caused the reaction • Since analysis of FAERS data is the lowest level of evidence for AE reports, this analysis is subject to underreporting as well as lack of information and medical confirmation
Gupta et al. 2019[18]	Retrospective chart review of patients with PDP; June 2016–September 2018	PIM: 107	Safety and efficacy of PIM in patients with PDP	PIM: 20 per 100 PY	These results can only determine association with mortality rate not direct treatment causation of death
Hwang et al. 2021[19]	Retrospective cohort study of patients with PD in long-term care using Medicare data; November 2015–December 2018	PIM users: 2186 Nonusers: 18,212	Risk of hospitalization and death with PIM use	Higher mortality with users vs nonusers: • 90-day adjusted HR, 1.20 • 180-day adjusted HR, 1.28 • 1-year adjusted HR, 1.56	• Comparing patients that are pimavanserin users with nonusers introduces selection bias that needs to be accounted for through study design or other selection criteria imposed on the nonuser group • Pimavanserin users had more severe disease characteristics at baseline than nonusers, and risks of 30-day hospitalization and 90-day mortality were not significantly different between users and nonusers when patients were matched for baseline characteristics • Confounding factors were not adjusted for and may explain the findings observed in this analysis

AE, adverse event; AP, antipsychotic; FAERS, US Food and Drug Administration Adverse Event Reporting System; HR, hazard ratio; NA, not applicable; OR, odds ratio; PD, Parkinson's disease; PDP, Parkinson's disease psychosis; PIM, pimavanserin; PRR, proportional reporting ratio; PY, patient-years.

Pimavanserin Postmarketing Data

- In the postmarketing analysis, the overall cumulative mortality rate of pimavanserin was 15.40 per 100 PY (95% CI, 14.97–15.85), with a minimum of 41,218 patients (30,426 PY) exposed (**Table 4**).[20]
  - Reported causes of death reflect common comorbidities and underlying conditions of an elderly PDP population (eg, PD, disease progression, dementia, pneumonia, and respiratory and cardiac events).

Table 4. Postmarketing Analysis of Pimavanserin Mortality in Patients With PDP

Time Period	Deaths	Minimum[a] Patients Exposed (PY)	Mortality Rate Per 100 PY (CI 95%)
April 2016–April 2021	4687	41,218 (30,426)	15.40 (4.97–15.85)

[a]Based on unique patients tracked through Acadia reimbursement hub and specialty distribution channel.
PDP, Parkinson's disease psychosis; PY, patient-years.

LIMITATIONS

- Study design and limitations should be considered when interpreting mortality findings from retrospective cohort analyses, postmarking safety data, and US Food and Drug Administration Adverse Event Reporting System database analysis.
- Furthermore, using data from hospital-admitted PDP patients causes confounding factors because 74% of hospitalized PD patients experience interruptions in their medication or receive inappropriate PD medication.[21]

CONCLUSIONS

- **Mortality risk in PD is compounded by the presence of hallucinations and/or delusions and treatments currently used for PDP; therefore, long-term monitoring of treatment-emergent fatal events is imperative.**
- **Although increased mortality has been reported to be associated with pimavanserin in a recent publication[19] and with atypical antipsychotic treatment, the mortality risk associated with pimavanserin has remained consistent over time, supporting the established benefit/risk profile of pimavanserin for the treatment of PDP.**
- **Physicians should assess the risk-benefit ratio related to the impact on symptoms of psychosis, mortality, caregiver burden, and quality of life when initiating any antipsychotic treatment in patients with PDP.**
- **Further studies with long-term mortality rates for antipsychotic treatments in this frail, elderly population are warranted to continue to monitor drug safety.**

REFERENCES

1. Marras C, et al. *NPJ Parkinsons Dis*. 2018;4:21.
2. Jankovic J. *J Neurol Neurosurg Psychiatry*. 2008;79(4):368-376.
3. Macleod AD, et al. *Mov Disord*. 2014;29(13):1615-1622.
4. Forsaa EB, et al. *Neurology*. 2010;75(14):1270-1276.
5. Wetmore JB, et al. *Parkinsonism Relat Disord*. 2019;68:95-101.
6. Weintraub D, et al. *JAMA Neurol*. 2016;73(5):535-541.
7. Lo RY, et al. *Arch Neurol*. 2009;66(11):1353-1358.
8. NUPLAZID (pimavanserin) [package insert]. San Diego, CA: Acadia Pharmaceuticals Inc.; 2020.
9. Driver JA, et al. *Neurology*. 2008;70(16 Pt 2):1423-1430.
10. Rong S, et al. *Neurology*. 2021;97(20):e1986-e1993.
11. de Lau LM, Breteler MM. *Lancet Neurol*. 2006;5(6):525-535.
12. Weintraub D, Mari Z. 2019. https://www.touchneurology.com/wp-content/uploads/sites/3/2019/03/private_articles_12493_pdf_IAPRD-Spotlight-Debate-Supplement-US-Neuro-15.1_EPUB.pdf?_ga=2.221041624.1950398314.1639608424-1003862124.1639608424. Accessed March 25, 2022.
13. Mathis MV, et al. *J Clin Psychiatry*. 2017;78(6):e668-e673.
14. Ballard CG, et al. *Parkinsonism Relat Disord*. 2020;77:100-106.
15. Longardner K, et al. Poster presented at the American Neurological Association (ANA) Annual Virtual Meeting; October 4–9, 2020. Poster 502.
16. Mosholder A, et al. Poster presented at the International Parkinson and Movement Disorder Society (IPMDS) Annual Virtual Conference; September 12–18, 2020. Abstract 1039.
17. Brown JD, et al. *J Manag Care Spec Pharm*. 2021;27(6):785-790.
18. Gupta H, et al. Poster presented at the American Academy of Neurology (AAN). May 4–10, 2019; Philadelphia, PA. Poster P2.8-020.
19. Hwang YJ, et al. *Neurology*. 2021;97(13):e1266-e1275.
20. Acadia Pharmaceuticals Inc. Data on File. Periodic adverse drug experience report (PADER No.14). April 28, 2021.
21. Gerlach OH, et al. *Mov Disord*. 2011;26(2):197-208.

ACKNOWLEDGMENTS

Medical writing support for the development of this poster, under the direction of the authors, was provided by Meghan Jones, PhD, and Kirill Yulin of Ashfield MedComms, an Ashfield Health company, and funded by Acadia Pharmaceuticals Inc. (San Diego, CA, USA).

DISCLOSURES

SI has received honoraria for CME, and has served as consultant, received research grants, and/or acted as promotional speaker on behalf of AbbVie, Acadia, Acorda, Adamas, Addex, Allergan, Amarantus, Axovant, Biogen, Britannia, Eli Lilly, Enterin, GE Healthcare, Global Kinetics, Impax, Intec Pharma, Ipsen, Kyowa, Lundbeck, the Michael J. Fox Foundation, Neurocrine, Neuroderm, the Parkinson Study Group, Pharma2B, Roche, Sanofi, Sunovion, Teva, UCB, US WorldMeds, and Zambon. **FP** serves as speaker and consultant for Acorda Therapeutics Inc., Acadia Pharmaceuticals Inc., Adamas Pharmaceuticals, Amneal Pharmaceuticals Inc., AbbVie Inc., Abbott Laboratories, Kyowa Kirin Co. Ltd., Merz Pharma GmbH & Co. KGaA, Sunovion Pharmaceuticals Inc., Teva Pharmaceutical Industries Ltd., and US WorldMeds LLC; is founder of and advisor for KeifeRx LLC; and receives research funding from NIH/NIA, Sun Pharmaceutical Industries Ltd., and Alzheimer's Research Foundation. **DT** has received research funding from Abbvie, Aeon, Biogen, Bukwang, Cerevel, Eli Lilly, Enterin, Ipsen, Kyowa, Lundbeck, Merz, National Institute of Neurological Disorders and Stroke, Neurocrine, Neuroderm, Parkinson's Foundation, Revance, and Sunovion. He has received honoraria for consulting and speaker activities from Acorda, Amneal, Neurocrine, and US Worldmed. **VA** is an employee of Acadia Pharmaceuticals Inc. **RP** has received consulting fees from AbbVie, Acadia, Acorda, Adamas, Cynapses, Global Kinetics, Lundbeck, Neurocrine, Pfizer, Sage, Sunovion, Teva Neuroscience and US World Meds. He has received research grants from AbbVie, Adamas, Avid, Biotie, Boston Scientific, Civitas, Cynapses, Kyowa, National Parkinson Foundation, NIH/NINDS, and Parkinson Study Group.

To receive a copy of this poster, scan QR code via barcode reader application.

By requesting this content, you agree to receive a one-time communication using automated technology. Message and data rates may apply. Links are valid for 30 days after the congress presentation.

ACADIA