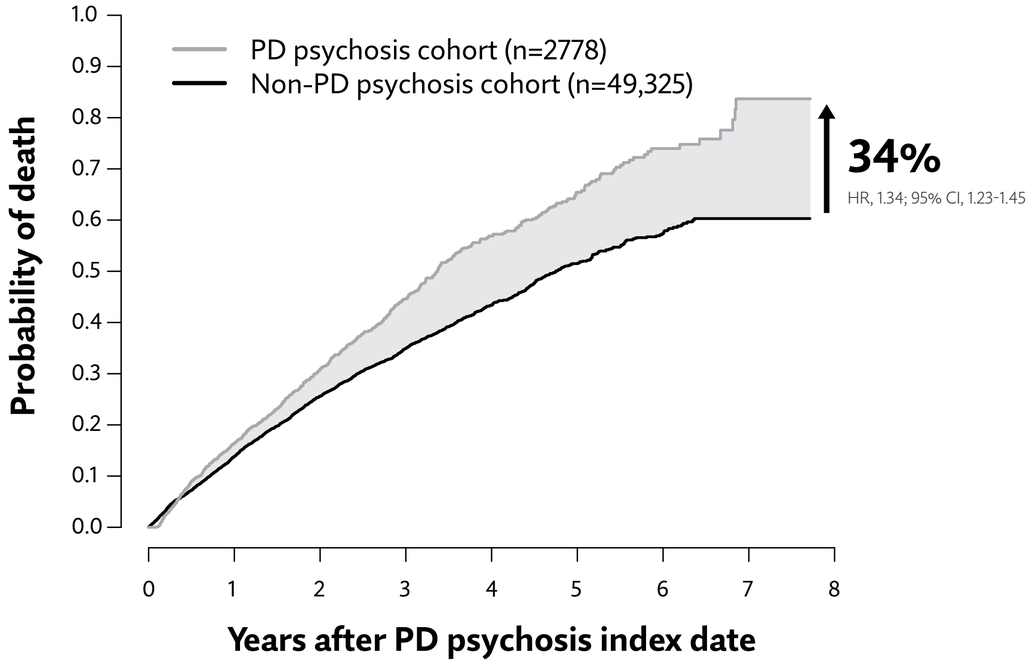
Treatment of Parkinson's Disease Psychosis and Mortality Risk: Review of Retrospective Analyses

Psychosis is an important risk factor for all-cause mortality in PD.

In a retrospective study evaluating the association of death in PD vs PD psychosis cohorts using Medicare data (20% random sample; 2007-2015), mortality risk was 34% greater when psychosis was present.[1]



Study Limitations[1]:

- Observational study; causality of death cannot be inferred
- Approach to identifying PD and PD psychosis has not been validated; some degree of misclassification is likely and under-ascertainment is possible
- Development of psychosis in patients with PD was assumed to be attributable to the disease itself
- Only US patients with Medicare were studied; results cannot be generalized

Overall, 24.2% of the PD psychosis cohort were receiving antipsychotics.[2]

HR, hazard ratio; PD, Parkinson's disease; US, United States.

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Indication

NUPLAZID® (pimavanserin) is indicated for the treatment of hallucinations and delusions associated with Parkinson's disease psychosis.

Important Safety Information

WARNING: INCREASED MORTALITY IN ELDERLY PATIENTS WITH DEMENTIA-RELATED PSYCHOSIS

- **Elderly patients with dementia-related psychosis treated with antipsychotic drugs are at an increased risk of death.**
- **NUPLAZID is not approved for the treatment of patients with dementia who experience psychosis unless their hallucinations and delusions are related to Parkinson's disease.**

Mortality Findings From Placebo-controlled Studies

In the NUPLAZID 6-week, placebo-controlled, clinical studies at approval, 3 (1.5%) deaths were reported among patients with PD psychosis treated with NUPLAZID 34 mg (N=202) versus 1 (0.4%) death in a patient treated with placebo (N=231).[3]

Important Considerations

- Information from the retrospective analyses presented here has not been reviewed by the US FDA and is not meant to rebut the current risk information, including the **Boxed WARNING**, for NUPLAZID or other atypical antipsychotics as described in each product's FDA-approved labeling
- This communication does not include findings from all retrospective analyses evaluating the comparative risk of all-cause mortality associated with NUPLAZID vs off-label atypical antipsychotics in patients with PD psychosis
- Two retrospective analyses presented here are based on the following considerations: a data source appropriate for capturing patients with PD psychosis and for measuring mortality as an endpoint; large, comprehensive studies with broad representation of the treatment population; and sound study methodology and statistical approach, including appropriate patient selection criteria and matching/weighting to address potential confounding
- NUPLAZID is the only FDA-approved treatment for hallucinations and delusions associated with PD psychosis. By providing this information, Acadia Pharmaceuticals Inc. is not recommending or suggesting that an off-label use of other atypical antipsychotics for the treatment of PD psychosis is appropriate

The following key limitations of retrospective analyses should be considered when interpreting the authors' findings presented here:

- Definitive conclusions regarding any differences or lack thereof in mortality rates between or among antipsychotics, including NUPLAZID, should not be drawn based on these findings
- Direct causation between a drug and reported mortality rates in patients with PD cannot be established, which includes not only the risk of mortality but also, conversely, any impact on overall survival of the patient population
- The potential exists for selection bias, unknown prognostic factors, underreporting of adverse events, and residual confounding
- Heterogeneity in characteristics of NUPLAZID users may have arisen over the study period. Heterogeneity may also have been present in indications for atypical antipsychotics, which have been used off-label for insomnia or agitation

FDA, Food and Drug Administration.

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The retrospective analyses below investigated the risk of all-cause mortality among Medicare beneficiaries with PD or PD psychosis (100% sample) associated with NUPLAZID® (pimavanserin) and off-label atypical antipsychotics. See below for study details and next section for key findings.

Study	Objective	Design	Comparisons	Select Inclusion/Exclusion Criteria	Follow-up
Mosholder et al 2022[4] FDA Center for Drug Evaluation and Research **Data source:** Medicare beneficiaries (Parts A, B, and D), April 2016-March 2019 *The findings reflect the views of the authors and should not be construed to reflect the FDA's views or official position.*	To evaluate all-cause mortality risk in patients with PD treated with NUPLAZID compared with off-label atypical antipsychotics	Retrospective, new-user, cohort analysis. Propensity score weighting was used to balance multiple baseline characteristic differences across the 2 cohorts • After weighting, the 2 cohorts were well balanced on all covariates, including chronic medical conditions, healthcare utilization, and dispensed medications	Atypical antipsychotics (grouped) (n=3251) vs NUPLAZID (n=3227)	**Included:** Aged ≥65 years; ≥1 PD diagnosis; ≥1 levodopa prescription **Excluded:** Use of multiple antipsychotics on the index date or diagnosis of schizophrenia, schizoaffective disorder, or schizophreniform disorder during baseline	Follow-up ended on the first of the following: • All-cause mortality (study outcome) • Censoring: —Disenrolling from Medicare —Stopping treatment (ie, gap of >14 days between study drug prescriptions) —Dispensing of nonstudy antipsychotic —Switching between NUPLAZID and an off-label atypical antipsychotic —End of study period
Layton et al 2022[5] RTI Health Solutions **Data source:** Medicare beneficiaries (Parts A, B, and D) and MDS 3.0 assessment, April 2016-December 2019[5]	To compare all-cause mortality risk in patients with PD psychosis initiating NUPLAZID with those initiating off-label atypical antipsychotics and to evaluate whether the mortality risk varies over time or in clinically meaningful subgroups, including those in LTC or SNF settings[5]	Retrospective, active-comparator, new-user cohort analysis. Propensity score matching was used to account for confounding arising from differences between characteristics across the 2 cohorts[5] • After matching, the 2 cohorts were well balanced on all covariates, including demographic characteristics, psychiatric diagnoses, comorbidities, comedication use, and healthcare utilization[6]	Atypical antipsychotics (grouped) (n=2891) vs NUPLAZID (n=2891)[5]	**Included:** Aged ≥65 years; PD diagnosis; psychosis diagnosis (ICD-10: F06.0 or F06.2; or MDS 3.0-reported hallucinations or delusions)[5,6] **Excluded:** Use of multiple antipsychotics on the index date or diagnosis of bipolar disorder, schizophrenia, schizoaffective disorder, or major depressive disorder with symptoms of psychosis[5]	Follow-up ended on the first of the following[5]: • All-cause mortality (study outcome) • Censoring: —Disenrolling from Medicare —Discontinuing index antipsychotic —Adding on or switching to another study medication —End of study period

ICD-10, International Classification of Diseases, 10th Revision; LTC, long-term care; MDS, Minimum Data Set; SNF, skilled nursing facility.

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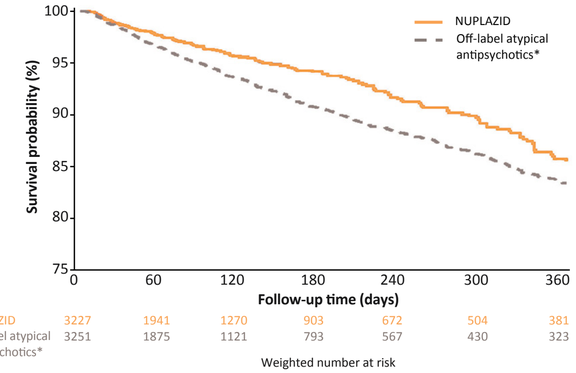
Mortality Among Parkinson's Disease Patients Treated With Pimavanserin or Atypical Antipsychotics: An Observational Study in Medicare Beneficiaries

MOSHOLDER ET AL 2022[4]

Probability of survival among the weighted cohort of patients with PD treated with NUPLAZID or off-label atypical antipsychotics



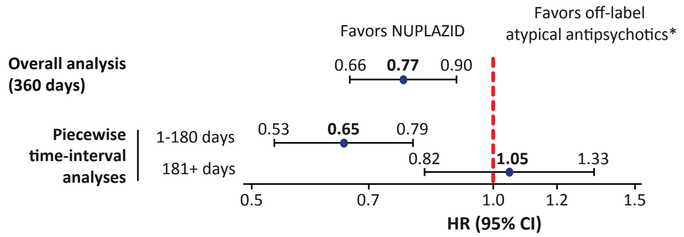
NUPLAZID	3227	1941	1270	903	672	504	381
Off-label atypical antipsychotics*	3251	1875	1121	793	567	430	323

Weighted number at risk

Through 360 days of follow-up, patients treated with NUPLAZID had a 23% lower mortality risk compared to patients treated with off-label atypical antipsychotics* (HR, 0.77; 95% CI, 0.66-0.90)

Note: A statistical evaluation showed that the proportional hazard assumption was violated in this analysis. The authors subsequently performed 2 separate piecewise time-interval analyses for Days 1-180 and Days 181+. These segmented analyses satisfied the proportional hazard assumption.

All-cause mortality among patients with PD, overall and in 2 separate piecewise analyses



First time-interval analysis (1-180 days): 35% lower mortality risk observed in patients treated with NUPLAZID vs off-label atypical antipsychotics*

Second time-interval analysis (181+ days): No additional mortality advantage was seen with NUPLAZID

Results driven by patients in the community setting

- Nursing home residents subgroup (15% of the study population):
  - 1-180 days – HR, 1.05; 95% CI, 0.73-1.52
  - 181+ days – HR, 1.54; 95% CI, 0.91-2.63

Important Considerations (cont'd):

- The findings from the retrospective analyses presented here are descriptive and should be interpreted with caution as the studies were not designed or powered to make direct safety comparisons between antipsychotics and due to high patient attrition over time. The data are not intended to show an independent treatment effect of product on survival
- Due to study design differences, cross-study comparisons should not be made
- Please see additional important considerations and also review the publications for other study limitations

*Quetiapine, risperidone, olanzapine, and aripiprazole.
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Mortality Among Parkinson's Disease Patients Treated With Pimavanserin or Atypical Antipsychotics: An Observational Study in Medicare Beneficiaries (cont'd)

MOSHOLDER ET AL 2022[4]

Select sensitivity analyses

Comparison	Days 1-180	Days 181+
NUPLAZID vs quetiapine	HR, 0.69; 95% CI, 0.57-0.85	HR, 1.09; 95% CI, 0.85-1.40
NUPLAZID vs non-quetiapine antipsychotics	HR, 0.54; 95% CI, 0.37-0.78	HR, 1.24; 95% CI, 0.75-2.07

- Before weighting, 78% (14,463) of the atypical antipsychotics cohort were taking quetiapine; 79% of that cohort were taking quetiapine ≤50 mg

Additional sensitivity analyses included: 2-prescriptions analysis; NUPLAZID 34-mg dose analysis; neurologist visit within 90 days; death or hospice admission outcome; censoring for entry to SNF; 30-day gap allowance; time-varying QT-prolonging drug analysis; unweighted unadjusted Cox; unweighted covariate-adjusted Cox; and unweighted LASSO covariate-adjusted Cox. The results were consistent with those of the main analysis.

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Important Considerations (cont'd):

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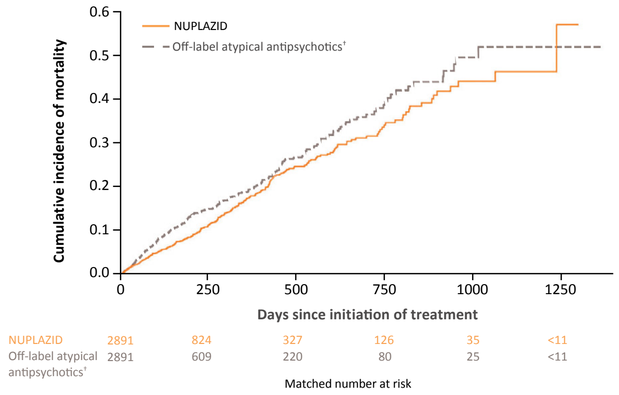
*Quetiapine, risperidone, olanzapine, and aripiprazole.

Mortality in Patients With Parkinson's Disease-Related Psychosis Treated With Pimavanserin Compared With Other Atypical Antipsychotics: A Cohort Study

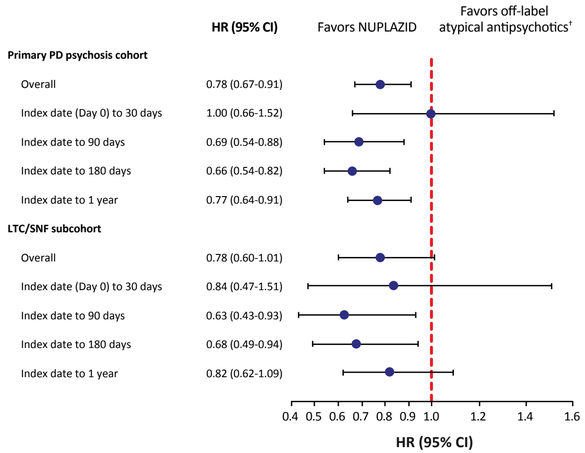
LAYTON ET AL 2022[5]

Cumulative incidence of mortality since atypical antipsychotic initiation in patients with PD psychosis after propensity score matching



Overall, patients treated with NUPLAZID had a 22% lower cumulative mortality risk compared to patients treated with off-label atypical antipsychotics* (HR, 0.78; 95% CI, 0.67-0.91)

All-cause mortality among patients with PD psychosis, overall and by follow-up period



- In the matched cohort, ~86% were taking quetiapine

In the primary PD psychosis cohort after propensity score matching:

- For the first 180 days of treatment, cumulative mortality risk was 34% lower in patients treated with NUPLAZID vs off-label atypical antipsychotics*
- Cumulative mortality risk at 1 year was 23% lower in patients treated with NUPLAZID vs off-label atypical antipsychotics*

Important Considerations (cont'd):

- The findings from the retrospective analyses presented here are descriptive and should be interpreted with caution as the studies were not designed or powered to make direct safety comparisons between antipsychotics and due to high patient attrition over time. The data are not intended to show an independent treatment effect of product on survival
- Due to study design differences, cross-study comparisons should not be made
- Please see additional important considerations and also review the publications for other study limitations

*Clozapine, quetiapine, risperidone, olanzapine, aripiprazole, and brexpiprazole.
Figures adapted with permission.

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Indication

NUPLAZID® (pimavanserin) is indicated for the treatment of hallucinations and delusions associated with Parkinson's disease psychosis.

Important Safety Information

WARNING: INCREASED MORTALITY IN ELDERLY PATIENTS WITH DEMENTIA-RELATED PSYCHOSIS

- **Elderly patients with dementia-related psychosis treated with antipsychotic drugs are at an increased risk of death.**
- **NUPLAZID is not approved for the treatment of patients who experience psychosis unless their hallucinations and delusions are related to Parkinson's disease.**

- **Contraindication:** NUPLAZID is contraindicated in patients with a history of a hypersensitivity reaction to pimavanserin or any of its components. Rash, urticaria, and reactions consistent with angioedema (e.g., tongue swelling, circumoral edema, throat tightness, and dyspnea) have been reported.

- **Warnings and Precautions:** QT Interval Prolongation
  - NUPLAZID prolongs the QT interval. The use of NUPLAZID should be avoided in patients with known QT prolongation or in combination with other drugs known to prolong QT interval (e.g., Class 1A antiarrhythmics, Class 3 antiarrhythmics, certain antipsychotics or antibiotics).
  - NUPLAZID should also be avoided in patients with a history of cardiac arrhythmias, as well as other circumstances that may increase the risk of the occurrence of torsade de pointes and/or sudden death, including symptomatic bradycardia, hypokalemia or hypomagnesemia, and presence of congenital prolongation of the QT interval.

- **Adverse Reactions:** The adverse reactions (≥2% for NUPLAZID and greater than placebo) were peripheral edema (7% vs 2%), nausea (7% vs 4%), confusional state (6% vs 3%), hallucination (5% vs 3%), constipation (4% vs 3%), and gait disturbance (2% vs <1%).

- **Drug Interactions:**
  - Coadministration with strong CYP3A4 inhibitors increases NUPLAZID exposure. Reduce NUPLAZID dose to 10 mg taken orally as one tablet once daily.
  - Coadministration with strong or moderate CYP3A4 inducers reduces NUPLAZID exposure. Avoid concomitant use of strong or moderate CYP3A4 inducers with NUPLAZID.

Dosage and Administration

Recommended dose: 34 mg capsule taken orally once daily, without titration, with or without food.

NUPLAZID is available as 34 mg capsules and 10 mg tablets.

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ONCE-DAILY
NUPLAZID®
(pimavanserin) 34mg capsules

acadia connect®

Acadia Connect® helps ensure that it's easy for your patients to start and continue taking NUPLAZID. Acadia Connect offers support for you and your enrolled patients, including access, insurance, affordability, and prescription assistance. Learn more at **NUPLAZIDhcp.com/acadia-connect**

Comprehensive coverage and financial assistance support

With comprehensive coverage and financial assistance support from Acadia Connect, your patient's NUPLAZID prescription may be more affordable than you think.

Less than $10

9 in 10 patients pay less than $10 as final out-of-pocket costs for their prescription*

100%

100% of Medicare Part D plans cover NUPLAZID†

$0 co-pay

$0 co-pay for qualifying commercially covered patients‡

*Around 10% of patients pay more than $10 for their prescription (as reported by 4 specialty pharmacy organizations; Q4 2020 and Q1 2021 data).
†Managed Markets Insight & Technology. Formulary Lookup website. https://formularylookup.com. Accessed August 4, 2020.
‡Acadia Connect patient eligibility and terms and conditions apply.

References

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4. Mosholder AD, Ma Y, Akhtar S, et al. Mortality among Parkinson's disease patients treated with pimavanserin or atypical antipsychotics: an observational study in Medicare beneficiaries. *Am J Psychiatry.* 2022;179(8):553-561.
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6. Layton JB, Forns J, McQuay LJ, et al. Mortality in patients with Parkinson's disease-related psychosis treated with pimavanserin compared with other atypical antipsychotics: a cohort study. Supplementary material. Online resource. *Drug Saf.* 2023;46(2):195-208. Accessed August 29, 2023. https://static-content.springer.com/esm/art%3A10.1007%2Fs40264-022-01260-6/MediaObjects/40264_2022_1260_MOESM1_ESM.pdf

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