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MDS COMMISSIONED REVIEW

Update on Treatments for Nonmotor Symptoms of Parkinson's Disease—An Evidence-Based Medicine Review

Seppi K, Chaudhuri KR, Coelho M, et al. *Movement Disorders*. 2019;34(2)180-198.

"Dose reductions of antiparkinsonian drugs to a level that will lead to a resolution of psychotic symptoms while maintaining sufficient symptomatic motor control is not always feasible and start of antipsychotic therapy becomes necessary."[1]

EVIDENCE-BASED MEDICINE REVIEW OF TREATMENTS FOR NONMOTOR SYMPTOMS OF PARKINSON'S DISEASE

Objective[1]

To update evidence-based medicine recommendations for treating nonmotor symptoms (NMS) in Parkinson's disease (PD).

Background[1]

- Previous recommendations reviewed studies from January 2004 to December 2010. This update included new studies up to December 31, 2016
- If new interventions were not reviewed in prior recommendations, this update made retrospective searches to include all appropriate studies

Methodology[1]

The methodology used for this update was the same as prior reports, and included literature searches using electronic databases (Medline, Cochrane Library) and systematic checking of references from review articles and other reports

- Each study was rated by at least 2 study group members using the Rating Scale for Quality of Evidence with a quality score of 75% or greater to be designated high quality

Key inclusion criteria[1,2]

The following inclusion criteria were adhered to:

- Randomized controlled trials in idiopathic PD that measured non-motor symptoms as the primary endpoint
- Interventions included pharmacological, surgical, and nonpharmacological therapies that were commercially available in at least 1 country
- In most cases, papers were only selected for review when there was:
  - an established rating scale or well-described measurement of endpoints
  - a minimum of 20 subjects that were treated for a minimum duration of 4 weeks
  - a report in full-paper format in English

Evaluation for recommendation[1]

- Each intervention was assigned an efficacy conclusion of: Efficacious, likely efficacious, unlikely efficacious, nonefficacious, or insufficient evidence—according to the level of evidence
- Safety was assessed and assigned as one of the following: Acceptable risk with no specialized monitoring, acceptable risk with specialized monitoring, unacceptable risk, or insufficient evidence
- Overall implications for clinical practice were assessed and classified as: Clinically useful, possibly useful, unlikely useful, not useful, or investigational

"...Pimavanserin is considered 'clinically useful' for the treatment of psychosis in PD."[1]

—Seppi, et al.

MDS COMMISSIONED REVIEW

Updated treatment recommendations for psychosis in PD

Interventions to treat psychosis in PD[1]

DRUG	EFFICACY	SAFETY*	PRACTICE IMPLICATIONS	FDA APPROVAL STATUS FOR PD PSYCHOSIS[3]
Pimavanserin	**Efficacious**	**Acceptable risk without specialized monitoring‡**	**Clinically useful**	**FDA approved**
Clozapine	Efficacious	Acceptable risk with specialized monitoring	Clinically useful	Not FDA approved
Quetiapine	Insufficient evidence	Acceptable risk without specialized monitoring	Possibly useful†	Not FDA approved
Olanzapine	Not efficacious	Unacceptable risk	Not useful	Not FDA approved

- This reflects the MDS commissioned review and is provided for educational purposes only. Acadia does not recommend any drug for an indication not approved by the FDA
- Comparisons of efficacy or safety between or among drugs should not be drawn or inferred in the absence of head-to-head clinical data
- Please review full Prescribing Information for specific safety monitoring required for drugs listed above

RCTs=randomized controlled trials.

*The FDA mandates that antipsychotic drug manufacturers add black box warnings to labels and prescribing information because of the link found between antipsychotics and an increased mortality risk in elderly dementia patients. Moreover, antipsychotic medication may be associated with QT interval prolongation.

‡There is a lack of safety data regarding durability beyond 6 weeks. There were more serious adverse events in the pimavanserin arm (7.9%) when compared with the placebo arm (3.5%), but without a unifying pattern and as such, it is difficult to interpret these as drug related. Nevertheless, the FDA has very recently conducted an evaluation of available information about pimavanserin after the publication of reports of postmarketing adverse events. Based on the analysis of all available data, the FDA did not identify any new or unexpected safety findings with pimavanserin. After a thorough review, the FDA's conclusion remains unchanged that the drug's benefits outweigh its risks for patients with hallucinations and delusions of PD psychosis. Although the FDA did not identify any new or unexpected safety risks, there should be awareness of the possible adverse effects of pimavanserin including QT prolongation (especially with the concomitant use of other antipsychotic drugs or drugs that can cause QT prolongation) and a potential to cause a paradoxical worsening of symptoms.

†Although there is insufficient evidence for quetiapine to be rated for the treatment of psychosis in PD, the practice implication is "possibly useful." There are no high-quality RCTs available for the treatment of quetiapine for psychosis in PD, and quetiapine was similarly efficacious to clozapine in the clozapine-controlled trials.

Adapted from *Movement Disorders*, from Update on treatments for nonmotor symptoms of Parkinson's disease—an evidence-based medicine review. Seppi, et al. *Mov Disord*. 34(2);2019; permission conveyed through Copyright Clearance Center, Inc

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Important Safety Information (cont'd)

- **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.

See additional Important Safety Information, including Boxed **WARNING** on page 7.
Please read the full Prescribing Information, also available at NUPLAZIDhcp.com

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American Geriatrics Society 2023 Updated AGS Beers Criteria® for Potentially Inappropriate Medication Use in Older Adults

By the 2023 American Geriatrics Society Beers Criteria® Update Expert Panel*

*From the American Geriatrics Society, New York, New York.

2023 UPDATE OF THE AGS BEERS CRITERIA® FOR POTENTIALLY INAPPROPRIATE MEDICATION USE IN OLDER ADULTS

Background[4]

The American Geriatrics Society (AGS) Beers Criteria® (AGS Beers Criteria®) for Potentially Inappropriate Medication (PIM) Use in Older Adults are widely used by clinicians, educators, researchers, healthcare administrators, and regulators. Since 2011, the AGS has been the steward of the criteria and has produced updates on a 3-year cycle. The AGS Beers Criteria® are an explicit list of PIMs that are typically best avoided by older adults in most circumstances or under specific situations, such as in certain diseases or conditions.

Intent of criteria[4]

The primary target audience for the AGS Beers Criteria® is practicing clinicians. The criteria are intended for use in adults 65 years and older in all ambulatory, acute, and institutionalized settings of care, except for the hospice and palliative care settings. The intention of the AGS Beers Criteria® is to improve medication selection, educate clinicians and patients; reduce adverse drug events; and serve as a tool for evaluating quality of care, cost, and patterns of drug use of older adults.

The AGS Beers Criteria® are not meant to be applied in a punitive manner. Prescribing decisions are not always clear-cut, and clinicians must consider multiple factors, including discontinuation of medications no longer indicated. Quality measures must be clearly defined, easily applied, and measured with limited information and, thus, although useful, cannot perfectly distinguish appropriate from inappropriate care.

Design and methodology[4-6]

For the 2015 update, the AGS employed a well-tested framework that has long been used for development of clinical practice guidelines. Specifically, the framework involved the appointment of a 13-member interdisciplinary expert panel with relevant clinical expertise and experience and an understanding of how the criteria have been previously used. This framework also involved a development process that included a systematic literature review and evaluation of the evidence base by the expert panel. Finally, the Institute of Medicine's 2011 report on developing practice guidelines, which included a period for public comments, guided the framework.

For the 2019 update, the panel was comprised of the same 13 clinicians and methods remained similar; however, there was additional emphasis on extending the rigor of the evidence review and synthesis process. Methods were based on the Grading of Recommendations Assessment, Development and Evaluation (GRADE) guidelines for clinical practice guideline development.

Methods used for the 2023 update of the AGS Beers Criteria® were similar to those used in the 2019 update. The AGS Beers Criteria® expert panel included 12 interprofessional members drawn from medicine, nursing, and pharmacy, 10 of whom had participated in the 2019 update. The goal of this update was to update the 2019 AGS Beers Criteria®, with consideration to removing or modifying existing criteria and adding new criteria based on evidence published between 2017 and 2022.

2023 UPDATE OF THE AGS BEERS CRITERIA® FOR POTENTIALLY INAPPROPRIATE MEDICATION USE IN OLDER ADULTS

The American Geriatric Society 2023 update to the AGS Beers Criteria® recommendation is to avoid use of antipsychotics in older adults, except for FDA-approved indications

- AGS Beers Criteria supports use of pimavanserin in older adults for the FDA-approved indication for the treatment of hallucinations and delusions associated with PD psychosis.
- AGS Beers Criteria does not support use of other antipsychotics for the treatment of PD psychosis in older adults as they are not FDA-approved for this indication.

- This reflects the AGS criteria and is provided for educational purposes only.
- Comparisons of efficacy or safety between or among drugs should not be drawn or inferred based on this information.

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Important Safety Information (cont'd)

- **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.

See additional Important Safety Information, including Boxed **WARNING** on page 7.
Please read the full Prescribing Information, also available at NUPLAZIDhcp.com

Indication

NUPLAZID 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.**

- **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.

Please read the full Prescribing Information, including **Boxed WARNING**, also available at NUPLAZIDhcp.com

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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References: 1. Seppi K, Chaudhuri KR, Coelho M, et al; on behalf of Movement Disorders Society Evidence-Based Medicine Committee. Update on treatments for nonmotor symptoms of Parkinson's disease—an evidenced-based medicine review. *Mov Disord*. 2019;34(2):180-198. **2.** Seppi K, Weintraub D, Coelho M, et al. The Movement Disorder Society evidence-based medicine review update: treatments for the non-motor symptoms of Parkinson's disease. *Mov Disord*. 2011;26(suppl 3):S42-S80. **3.** US Food and Drug Administration. FDA approves first drug to treat hallucinations and delusions associated with Parkinson's disease. https://www.fda.gov/newsevents/newsroom/pressannouncements/ucm498442.htm. Updated March 1st, 2019. Accessed September 12, 2023. Accessed April 3, 2019. **4.** By the 2023 American Geriatrics Society Beers Criteria® Update Expert Panel. American Geriatrics Society 2023 updated AGS Beers Criteria® for potentially inappropriate medication use in older adults. *J Am Geriatr Soc*. 2023;71(7):2052-2081. doi:10.1111/jgs.18372 **5.** The 2019 American Geriatrics Society Beers Criteria® Update Expert Panel. American Geriatrics Society 2019 updated AGS Beers Criteria® for potentially inappropriate medication use in older adults. *J Am Geriatr Soc*. 2019;67(4):674-694. doi:10.1111/jgs.15767 **6.** The 2015 American Geriatrics Society Beers Criteria® Update Expert Panel. American Geriatrics Society 2015 updated AGS Beers Criteria® for potentially inappropriate medication use in older adults. *J Am Geriatr Soc*. 2015;63(11):2227–2246. doi:10.1111/jgs.13702

ONCE-DAILY NUPLAZID® (pimavanserin) 34mg capsules

ACADIA

Acadia Pharmaceuticals Inc. Announces Positive Label Update for NUPLAZID® (pimavanserin)

ONCE-DAILY
NUPLAZID®
(pimavanserin) 34mg capsules

See Important Safety Information, including **Boxed WARNING** below.

As requested by Acadia, the FDA has made 2 positive changes to the NUPLAZID label, clarifying that its **use in patients with Parkinson's disease–related hallucinations and delusions, with or without dementia, is consistent with the current indication**[1]

- No other findings or changes are included as part of the label update

Why did Acadia request this label change?

According to recent market research*:

<50% of healthcare professionals in Community and LTC settings were aware that NUPLAZID is approved for use in patients with Parkinson's disease–related hallucinations and delusions who also have dementia[2]

*Based on market research conducted April 21-May 2, 2023.

The 2 label changes include[1]:

1. Updated language in the Clinical Studies section restating that the phase 3 study supporting approval of NUPLAZID included patients with Parkinson's disease–related hallucinations and delusions, with or without dementia
2. Revised **Boxed WARNING** clarifying that NUPLAZID is approved to treat patients with Parkinson's disease–related hallucinations and delusions who also have dementia

The new language in the **Boxed WARNING** is underlined below[1]:

- 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

This is a positive change, as it clarifies the appropriate patient population for NUPLAZID.

— Feedback from practicing neurologists and psychiatrists

For more information about this update, visit Acadia.com

Indication

NUPLAZID 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.**

See additional Important Safety Information below. Please read the full Prescribing Information, including **Boxed WARNING**, also available at NUPLAZIDhcp.com.

Important Safety Information (cont'd)

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.

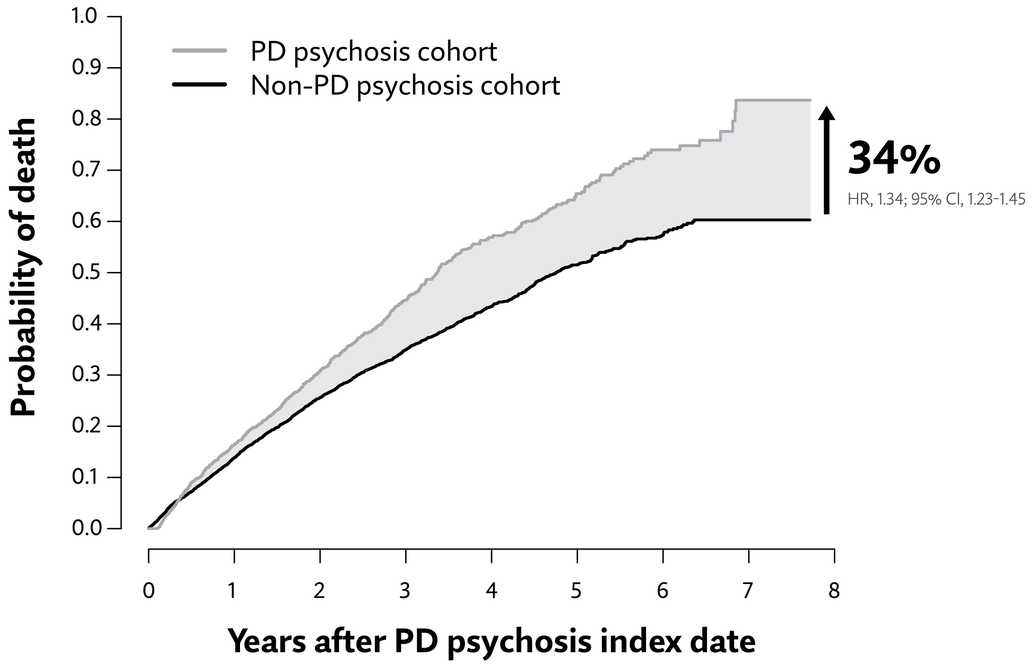
Please read the full Prescribing Information, including **Boxed WARNING**, also available at NUPLAZIDhcp.com.

References: 1. Acadia Pharmaceuticals Inc. NUPLAZID® [package insert]. San Diego, CA; 2023. **2.** Acadia Pharmaceuticals Inc. Market Research_2023.

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

Psychosis is an important risk factor for mortality in PD.

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



Study Limitations:

- Observational study; causality 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

NEXT

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

*Patients with PD: n=49,325.
Patients with PD psychosis: n=2778.

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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-related psychosis unrelated to the hallucinations and delusions associated with Parkinson's disease psychosis.**

Preapproval Mortality Findings

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).[2]

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
- 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 of relative differences in mortality between NUPLAZID and off-label atypical antipsychotics should not be drawn based on the findings
- Direct causation between a drug and reported mortality in patients with PD cannot be established
- 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

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FDA, Food and Drug Administration.

Multiple retrospective analyses investigating the risk of all-cause mortality associated with NUPLAZID® (pimavanserin) and off-label atypical antipsychotics have been conducted. See below and next section for select studies' details and key findings.

Study	Objective	Design	Comparisons	Select Inclusion/Exclusion Criteria	Follow-up	Key Findings
Mosholder et al 2022[3] 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	**Lower risk of mortality was reported in patients treated with NUPLAZID vs off-label atypical antipsychotics for the first 180 days of treatment (HR, 0.65; 95% CI, 0.53-0.79), and no additional mortality advantage thereafter. See pages 4-5 for more details**
Layton et al 2022[4] RTI Health Solutions **Data source:** Medicare beneficiaries (Parts A, B, and D) and MDS 3.0 assessment, April 2016-December 2019[4]	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[4]	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[4] • After matching, the 2 cohorts were well balanced on all covariates, including demographic characteristics, psychiatric diagnoses, comorbidities, comedication use, and healthcare utilization[5]	Atypical antipsychotics (grouped) (n=2891) vs NUPLAZID (n=2891)[4]	**Included:** Aged ≥65 years; PD diagnosis; psychosis diagnosis (ICD-10: F06.0 or F06.2; or MDS 3.0-reported hallucinations or delusions)[4,5] **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[4]	Follow-up ended on the first of the following[4]: • All-cause mortality (study outcome) • Censoring: —Disenrolling from Medicare —Discontinuing index antipsychotic —Adding on or switching to another study medication —End of study period	**Overall, lower risk of mortality was reported in primary PD psychosis cohort treated with NUPLAZID vs off-label atypical antipsychotics (HR, 0.78; 95% CI, 0.67-0.91).[4] See page 6 for more details**
Nguyen et al 2022[6] University of Pennsylvania, Perelman School of Medicine **Data source:** Optum® Clinformatics® Data Mart, May 2016-March 2021	To evaluate the risk of all-cause mortality with NUPLAZID, preferred DRBA off-label atypical antipsychotics, or other off-label atypical antipsychotics	Retrospective, new user, cohort study. Propensity score matching and other matching methods were used • When censoring upon discontinuation or switching was included in the analytical model, the sample could not be well balanced on baseline characteristics with multiple matching methods	Preferred DRBA (clozapine and quetiapine) (n=4563) and nonpreferred DRBAs (all others) (n=1297) vs NUPLAZID (n=775) Comparisons were based on index antipsychotic.	**Included:** PD diagnosis; aged ≥40 years at initial diagnosis **Excluded:** Atypical and drug-induced parkinsonism, amyotrophic lateral sclerosis, dementia with Lewy bodies, and bipolar disorder	Follow-up ended on the first of the following: • All-cause mortality (study outcome) • Censoring: —Loss of insurance coverage —End of study period Switching between antipsychotics was allowed.	**No difference in risk of mortality between NUPLAZID and off-label atypical antipsychotics**

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

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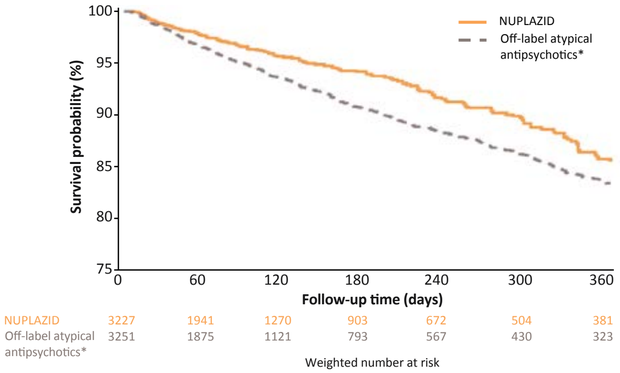
Mortality Among Parkinson's Disease Patients Treated With Pimavanserin or Atypical Antipsychotics: An Observational Study in Medicare Beneficiaries

MOSHOLDER ET AL 2022[3]

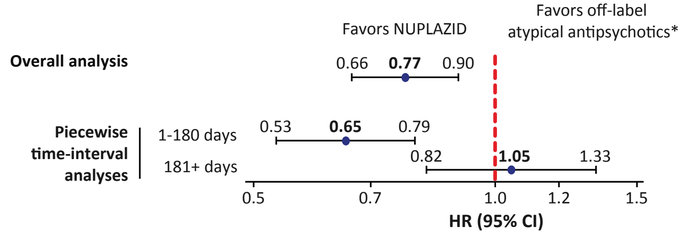
Probability of survival among the weighted cohort of patients with PD treated with NUPLAZID or off-label atypical antipsychotics



Mortality was 23% lower over 360 days in patients treated with NUPLAZID vs off-label atypical antipsychotics*

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 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 (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:

- 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
- Probability of survival results should be interpreted with caution due to patient attrition over time
- 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.
Figures adapted with permission.

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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[3]

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:

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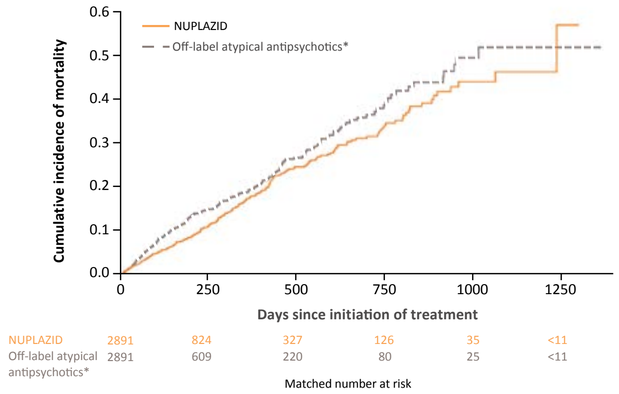
- Probability of survival results should be interpreted with caution due to patient attrition over time
- Due to study design differences, cross-study comparisons should not be made
- Please see additional important considerations and also review the publications for other study limitations

*Quetiapine, risperidone, olanzapine, and aripiprazole.

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

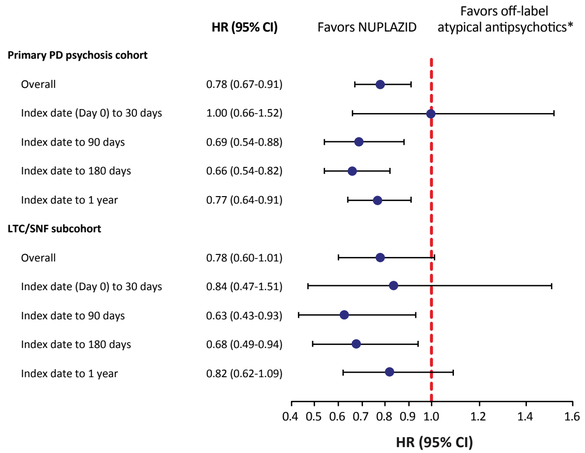
LAYTON ET AL 2022[4]

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



Overall cumulative mortality was 22% lower in patients treated with NUPLAZID vs off-label atypical antipsychotics*

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:

- The first 180 days of treatment showed the largest difference in mortality in patients treated with NUPLAZID vs off-label atypical antipsychotics*
- Cumulative mortality at 1 year was 23% lower in patients treated with NUPLAZID vs off-label atypical antipsychotics*

Important Considerations:

- 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
- Cumulative incidence of mortality results should be interpreted with caution due to patient attrition over time
- 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 with dementia-related psychosis unrelated to the hallucinations and delusions associated with Parkinson's disease psychosis.**

- **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 including Class 1A antiarrhythmics or Class 3 antiarrhythmics, certain antipsychotic medications, and certain 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 common 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 (e.g., ketoconazole) 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.

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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2. Acadia Pharmaceuticals Inc. NUPLAZID advisory committee briefing document: sponsor background information for a meeting of the Psychopharmacologic Drugs Advisory Committee; March 29, 2016.
3. 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.
4. 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. *Drug Safety.* Published online December 14, 2022. doi:10.1007/s40264-022-01260-6.
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6. Nguyen TPP, Thibault D, Hamedani AG, Weintraub D, Willis AW. Atypical antipsychotic use and mortality in Parkinson disease. *Parkinsonism Relat Disord.* 2022;103:17-22.

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