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# Understanding the Burden and Management of Hallucinations and Delusions Associated With Parkinson's Disease Psychosis


## PRESENTER

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Parkinson's disease (PD) affects approximately 1 million people in the United States, and more than half of patients with PD will develop Parkinson's disease psychosis (PDP) at some point in the course of their disease.[1,2] The presentation of this condition is distinct from that of other psychotic conditions.[3] It may include a range of symptoms, predominantly visual hallucinations, as well as auditory hallucinations and delusions.[4-6] Less common symptoms may include olfactory and tactile hallucinations.[4] These symptoms tend to increase in severity over time.[7]

## ESTABLISHING A DIAGNOSIS OF PDP

PDP may be related to PD progression; as a result, it is often accompanied by more severe PD and older age.[2,8,9] According to a report developed by the National Institute of Neurological Disorders and Stroke-National Institute of Mental Health working group in 2007, a diagnosis of PDP requires at least one of the following symptoms: hallucinations, delusions, illusions, or false sense of presence. Additionally, these symptoms of PDP must be recurrent or continuous for a minimum of 1 month and must be preceded by symptoms of PD, as described in the Parkinson's UK Brain Bank criteria.[3]



To establish a diagnosis, other potential causes of psychosis must be excluded. These potential causes may include any of several general medical conditions, including delirium. Other causes, including Lewy body dementia or psychiatric disorders (such as schizophrenia, schizoaffective disorder, delusional disorder, or mood disorder with psychotic features), must also be excluded before arriving at a diagnosis of PDP.[3] Even with all of these factors excluded and a PDP diagnosis firmly established, there is no specific International Classification of Diseases, Tenth Revision (ICD-10), code for PDP. Instead, ICD-10 designates individual codes for PD and psychosis, which may coexist in the same patient.[10]

## PDP: CONTRIBUTORY FACTORS

Factors contributing to PDP may be classified as intrinsic or extrinsic. Extrinsic factors may include medications and environmental factors, whereas intrinsic factors include comorbid conditions, disease progression, and neurochemical abnormalities associated with neurodegeneration.[8,11-13] In characterizing

## IMPORTANT SAFETY INFORMATION AND INDICATION FOR NUPLAZID™ (PIMAVANSERIN) 17-MG TABLETS

**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.**

**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 most 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:** Strong CYP3A4 inhibitors (eg, ketoconazole) increase NUPLAZID concentrations. Reduce the NUPLAZID dose by one-half. Strong CYP3A4 inducers may reduce NUPLAZID exposure, monitor for reduced efficacy. Increase in NUPLAZID dosage may be needed.

**Renal Impairment:** No dosage adjustment for NUPLAZID is needed in patients with mild to moderate renal impairment. Use of NUPLAZID is not recommended in patients with severe renal impairment.

**Hepatic Impairment:** Use of NUPLAZID is not recommended in patients with hepatic impairment. NUPLAZID has not been evaluated in this patient population.

**Pregnancy:** Use of NUPLAZID in pregnant women has not been evaluated and should therefore be used in pregnancy only if the potential benefit justifies the potential risk to the mother and fetus.

**Pediatric Use:** Safety and efficacy have not been established in pediatric patients.

**Dosage and Administration:** Recommended dose: 34 mg per day, taken orally as two 17-mg tablets once daily, without titration.

### INDICATION

NUPLAZID is an atypical antipsychotic indicated for the treatment of hallucinations and delusions associated with Parkinson's disease psychosis.

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the extrinsic and intrinsic factors associated with PDP, it is important to note that NUPLAZID™ (pimavanserin) is approved only for treatment of the hallucinations and delusions associated with PDP.[14]

Intrinsic factors such as visual processing abnormalities or deficits and neurochemical abnormalities have an important role in PDP pathogenesis. Visual processing abnormalities may include poor contrast recognition, low visual acuity, and other ocular abnormalities. These abnormalities are more common in patients with PDP experiencing hallucinations, suggesting that perceptual difficulties may have a role in producing hallucinations.[8,9,15] However, the role of neurochemical abnormalities in producing PDP symptoms is also crucial. Neurochemical changes observed in patients with PDP include increased serotonergic binding to 5-$HT_{2A}$ receptors, especially in regions of the brain involved in visual processing.[13] The hallucinogenic effects of neurochemical changes that occur in PDP may be mediated through a biochemical pathway similar to that of the illicit drug lysergic acid diethylamide, which is a potent 5-$HT_2$ agonist.[16] These data support the role of abnormal 5-$HT_{2A}$ processing and receptor binding in patients with PD who are also experiencing PDP-related hallucinations.[13]

Unlike intrinsic factors related to PDP, extrinsic factors originate from outside the body. Both medications and dim lighting conditions are extrinsic factors that may trigger PDP symptoms.[17,18] Because medications may contribute to PDP symptoms, reducing the dose of PD medications may help control symptoms in some cases. However, it is important to recognize that the use of PD medications is neither necessary nor sufficient for patients to develop PDP.[8,18] Other contributory extrinsic factors, such as time of day, may explain why PDP hallucinations tend to occur more often in the late afternoon to evening. Even so, it is important to note that PDP hallucinations may occur at any time of day and under any lighting conditions.[3,8,18]

## CHALLENGES IN ASSESSING NONMOTOR SYMPTOMS OF PD

Nonmotor symptoms of PD often affect patients to a larger degree than the motor symptoms, but patients and caregivers are often reluctant to disclose these symptoms to their treating physician.[8,19] In an international, multicenter study, researchers investigated nondeclared nonmotor symptoms in 242 patients with PD. Patients involved in this study belonged to a wide range of age groups and received treatment in a variety of settings, including outpatient offices and inpatient care facilities. In the study, researchers investigated nondeclared nonmotor symptoms using a 30-item questionnaire (NMSQuest).[19]



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**Table 1.** $K_i$ (nM) for NUPLAZID[14]

| Receptor | $K_i$ (nM) |
|---|---|
| 5-$HT_{2A}$ | 0.087 |
| 5-$HT_{2B}$ | – |
| 5-$HT_{2C}$ | 0.44 |
| $D_1$ | – |
| $D_2$ | – |
| $D_3$ | – |
| Alpha 1A | – |
| Alpha 1B | – |
| Alpha 2A | – |
| Alpha 2B | – |
| H1 | – |
| M1 | – |
| M2 | – |
| M3 | – |
| M4 | – |
| M5 | – |
| Sigma 1 | – |

Lower $K_i$ numbers indicate stronger binding.
– indicates no response, $K_i$ >100 nM.

More than one-third (41.5%) of patients who reported experiencing hallucinations in the survey did not spontaneously report the symptom to physicians, and 50% or more of patients with symptoms of daytime sleepiness, intense and vivid dreams, or dizziness failed to report the symptom to their physician. According to the survey, delusions were the nonmotor symptom least likely to be reported; nearly two-thirds (65.2%) of patients experiencing delusions failed to report this symptom. Underreporting of symptoms may occur due to several causes, including embarrassment, not realizing that nonmotor symptoms are related to PD, and time constraints.[19]

## THE PROGRESSION OF PDP

Initially, hallucinations associated with PDP may be mild and not troublesome.[20] However, over time, hallucinations may affect activities of daily living and may even progress to a severity level that leads patients to react to their hallucinations aggressively or inappropriately. In early-stage disease, patients are generally aware that the hallucinations and delusions they are experiencing are not real (ie, they retain insight), but the ability to cope with the symptoms gradually diminishes over time.[15,20,21] Loss of insight may lead to more serious sequelae associated with hallucinations and delusions, which may be associated with nursing home placement, often on a permanent basis.[22-24]

Although PD exacts a substantial toll on patients with the disorder, it is also associated with substantial caregiver burden. As symptoms progress, more than 40% of caregivers report experiencing a decline in physical health, nearly two-thirds (65%) report experiencing deterioration in their social life, and nearly half (47%) have scores from self-administered psychiatric inventories consistent with depression.[25]

Unfavorable outcomes were highlighted by a community-based study conducted in Norway in which 230 patients with PD were followed from 1993 to 2005. Mortality rates over 10 years in this study were approximately 40% higher in patients with PD experiencing psychosis than in patients with PD who did not experience psychosis.[26] Similarly, in a retrospective study conducted in Israel assessing reasons for hospital admissions in 143 patients with PD over the course of 6 years, psychosis symptoms were identified as a reason for nearly 1 in 4 (24%) of hospital admissions in patients with PD. Other reasons for admission included motor and psychiatric problems (25%), motor complications of PD (37%), and general medical problems (14%).[27] Once placed in a nursing home, patients with PD are unlikely to leave the nursing home and are at high risk for mortality.[22,23]

## NUPLAZID FOR TREATMENT OF PDP

NUPLAZID is the only FDA-approved therapy for the treatment of the hallucinations and delusions associated with PDP. Importantly, this medication carries a boxed warning for increased risk of mortality in elderly patients with dementia-related psychosis. According to the warning, elderly patients treated with antipsychotic drugs may be at increased risk of death. NUPLAZID is not approved for treatment of patients with dementia-related psychosis that is not related to the hallucinations and delusions of PDP.[14]

## MECHANISM OF ACTION

NUPLAZID has a high binding affinity to 5-$HT_{2A}$ receptors and lower binding affinity to 5-$HT_{2C}$ receptors, with no appreciable dopaminergic muscarinic, histaminergic, or adrenergic activity.[14] In terms of $K_i$ values determined through in vitro assays, with lower $K_i$ values indicating stronger binding affinity, the active ingredient in NUPLAZID has been found to have a $K_i$ value (reported as a nanomolar concentration) of 0.087 to 5-$HT_{2A}$ receptors and 0.44 to 5-$HT_{2C}$ receptors (**Table 1**[14]).[14,28] These in vitro data indicate high binding affinity to serotonin 5-$HT_{2A}$ receptors, lower binding affinity to 5-$HT_{2C}$ receptors, low binding affinity to sigma 1 receptors ($K_i$ value, 120 nM), and no appreciable affinity ($K_i$ value >300 nM) for other known receptors assessed through in vitro assays. It is important to note that the effect of NUPLAZID in patients with PDP may be mediated through a combination of inverse agonist and antagonist activity at 5-$HT_{2A}$ receptors and (to a lower degree) 5-$HT_{2C}$ receptors. However, the precise mechanism of action of NUPLAZID in the treatment of hallucinations and delusions associated with PDP remains unknown.[14]

The selective serotonin inverse agonist (SSIA) activity of NUPLAZID may be understood in terms of receptor activity (**Figure 1**[29]).[14] Whereas traditional agonists stimulate a receptor and antagonists block a receptor but permit basal activity, inverse agonists act to suppress basal activity.[29] By suppressing basal activity, NUPLAZID inhibits the ability of receptors to initiate a signal when an agonist is not bound to the

**Figure 1.** Conceptual Representation of Agonists, Antagonists, and Inverse Agonists[29]

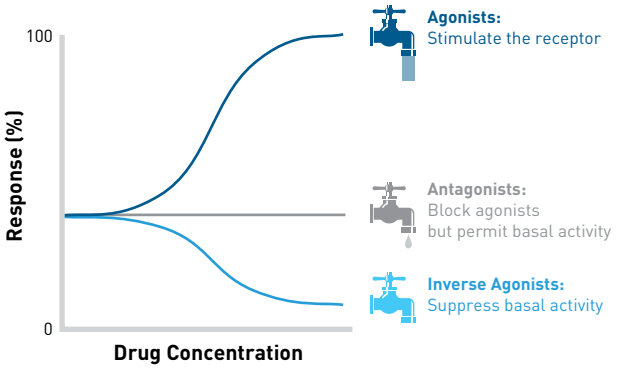



**Table 2.** Components of SAPS-PD[5]

| SAPS-PD | |
|---|---|
| Hallucinations | Visual |
| | Somatic/tactile |
| | Auditory |
| | Voices conversing |
| | **Global hallucinations** |
| Delusions | Persecutory |
| | Jealousy |
| | Reference |
| | **Global delusions** |

0 None 1 2 3 4 5 Severe

SAPS-PD indicates Scale for the Assessment of Positive Symptoms adapted for Parkinson's disease.

receptor. Although it is recognized that the inverse agonist activity of NUPLAZID may suppress basal activity of 5-$HT_{2A}$ and 5-$HT_{2c}$ receptors, NUPLAZID may also act as an antagonist at these 2 receptor sites.[14]

## ASSESSING THE SYMPTOMS OF PD

Researchers assessed PD severity using an adapted form of a scale that was previously used in schizophrenia, known as the Scale for the Assessment of Positive Symptoms (SAPS). The original SAPS includes 5 domains to assess positive symptoms: behavioral disorders (5 items), positive formal thought disorders (9 items), inappropriate affect (1 item), delusions (13 items), and hallucinations (7 items). Using items from the latter 2, researchers developed the Scale for the Assessment of Positive Symptoms adapted for Parkinson's disease (SAPS-PD), which is a 9-item scale designed to assess the severity of hallucinations and delusions associated with PDP.[5,14] A change of 2.33 points on the SAPS-PD scale is associated with a 1-point change on the Clinical Global Impressions of Improvement scale. Each item on the SAPS-PD is rated from 0 (no symptoms) to 5 (severe and frequent symptoms), for a highest possible score of 45, with higher scores reflecting greater illness severity (**Table 2**[5]). The 5 items on the hallucinations subscore of the SAPS-PD total score are auditory, voices conversing, somatic/tactile, visual, and global rating on the severity of hallucinations. The 4-item SAPS-PD delusions subscore consists of persecutory, jealousy, reference, and global rating on the severity of delusions.[5] From baseline, a negative change in the SAPS-PD indicates symptom improvement.[14]

## THE PIVOTAL PHASE 3 CLINICAL STUDY FOR NUPLAZID: STUDY DESIGN

Researchers conducted a placebo-controlled, randomized, parallel-group study of patients with PDP randomized to receive either placebo (n = 90) or NUPLAZID 34 mg daily (n = 95) over a 6-week course of therapy, with assessment at screening, baseline, and weeks 2, 4, and 6.[14,30] Researchers designated the change in total SAPS-PD score from baseline as the primary end point and changes in the United Parkinson's Disease Rating Scale Parts II+III (UPDRS Parts II+III) as a secondary end point.[30] Of note, SAPS-PD scores were measured by central, independent, blinded raters.[14,30] Before study entry, patients were screened for delusions and/or hallucinations on the neuropsychiatric inventory, with a qualifying score being a combined score of at least 6 or an individual score of at least 4 on either delusions or hallucinations.[30]

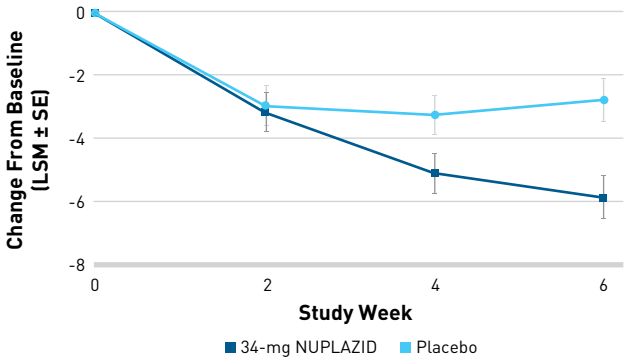
All patients included in the trial were 40 years or older, had a diagnosis of PD for at least 1 year prior to study entry, and had PD with psychotic symptoms, such as hallucinations or delusions that developed after the diagnosis of PD was established. Patients taking PD-specific medications were required to receive a stable dose of medication for a minimum of 30 days before study entry and throughout the study.[14,30]

Patients were excluded from the clinical trial if they experienced psychosis secondary to toxic or metabolic disorders, psychosis following ablative stereotaxic surgery, dementia concurrent to or before PD, uncontrolled serious mental illness, or were taking medications that may affect the action or potentiate the toxicity of NUPLAZID, including antipsychotic drugs, centrally acting anticholinergics, or drugs that cause QT prolongation.[30] Additionally, at study entry, patients were required to have a mini-mental state examination (MMSE) score of at least 21 and to be able to self-report symptom severity.[14,30]

A total of 314 patients met screening criteria and entered a 2-week lead-in period during which the nonpharmacologic Brief Psychosocial Therapy adapted for Parkinson's disease was performed. This 2-week lead-in period was intended both to ensure that only patients who required treatment received it and to elicit a placebo response before the baseline assessment.[30] After the lead-in period, 199 patients were randomized to receive treatment in the pivotal trial, and 185 patients who had not discontinued treatment before the first postbaseline visit were included in the full analysis set.[14,30]

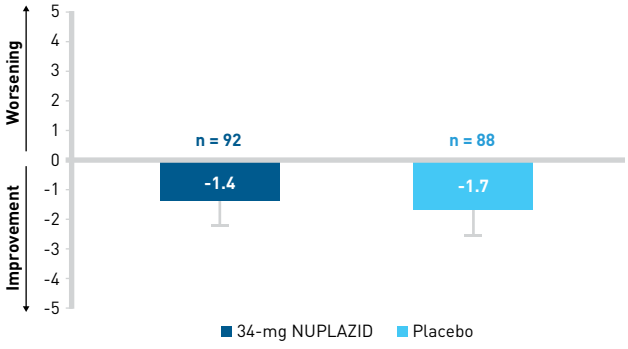
At baseline, patients receiving NUPLAZID had a SAPS-PD mean score of 15.9 (standard deviation: 6.12), and patients taking a placebo had a mean SAPS-PD score of 14.7 (standard deviation: 5.55).[14] On the primary outcome of least-square mean change from baseline to Week

**Figure 2.** SAPS-PD Change From Baseline Through 6 Weeks Total Study Treatment[14]




LSM indicates least-squares mean; SAPS-PD, Scale for the Assessment of Positive Symptoms adapted for Parkinson's disease; SE, standard error.

**Figure 3.** Motor Function Changes From Baseline to Week 6 UPDRS Parts II+III (LSM, SE)[14,a]




LSM indicates least-squares mean; SE, standard error; UPDRS, United Parkinson's Disease Rating Scale.
[a]The error bars extend one SE below the LSM.

6, patients receiving NUPLAZID experienced a 5.79-point reduction versus a 2.73-point reduction in SAPS-PD score with placebo at Week 6, which was a significantly greater improvement ($P = 0.0014$). The placebo-subtracted difference between groups was −3.06 (95% unadjusted CI: −4.91 to −1.20). Expressed as a percentage, these results equate to a 37% improvement in the least-square mean change from baseline score on the SAPS-PD scale in patients receiving NUPLAZID versus a 14% improvement in patients receiving placebo. Changes from baseline to Week 6 are described in **Figure 2**[14].[14,30]

On the secondary end point, researchers assessed changes in the UPDRS Parts II+III, which are intended to assess motor function, and the impact of motor function on activities of daily living. On this end point, there was not a significant difference between NUPLAZID and placebo. In 92 patients receiving NUPLAZID 34 mg daily, least-squares mean changes of a 1.4-point reduction on the UPDRS Parts II+III scores versus a 1.7-point reduction in 88 patients receiving placebo were observed (**Figure 3**[14]). Although patients in both the placebo and active treatment groups experienced improvements in motor function as measured by the UPDRS Part II+III scores, from baseline to Week 6, the difference between groups was not statistically significant, establishing that NUPLAZID does not negatively affect motor function compared with placebo.[14]

## ADVERSE REACTIONS

Researchers assessed the frequency of adverse reactions in placebo-controlled studies of NUPLAZID versus placebo over 6 weeks of treatment and reported adverse reactions occurring in at least 2% of patients receiving active medication and with a greater frequency than in patients receiving placebo. In 202 patients receiving NUPLAZID 34 mg daily and 231 patients receiving placebo, these adverse reactions included nausea, peripheral edema, confused state, hallucination, constipation, and gait disturbance. Comparative rates of common adverse reactions are reported in **Table 3**[14].[14]

Adverse reactions leading to discontinuation of treatment occurred in 8% of 202 patients receiving NUPLAZID 34 mg and 4% of 231 patients receiving placebo. Adverse reactions leading to discontinuation that occurred in more than 1 patient and with an incidence at least twice that of placebo included hallucination (2% NUPLAZID vs <1% placebo), urinary tract infection (1% NUPLAZID vs <1% placebo), and fatigue (1% NUPLAZID vs 0% placebo). In a subgroup analysis, no differences in the incidence of adverse reactions in patients of varying age groups (ie, those ≤75 years vs >75 years), males versus females, or in patients with high (≥25) and low (<25) MMSE scores at entry were observed.[14]

**Table 3.** Adverse Reactions in Placebo-Controlled Studies of 6-Week Treatment Duration and Reported in ≥2% and With a Greater Frequency Than in Patients Receiving Placebo[14]

| Percentage of Patients Reporting Adverse Reaction | | |
|---|---|---|
| | NUPLAZID 34 mg n = 202 | Placebo n = 231 |
| **Gastrointestinal disorders** | | |
| Nausea | 7% | 4% |
| Constipation | 4% | 3% |
| **General disorders** | | |
| Peripheral edema | 7% | 2% |
| Gait disturbance | 2% | <1% |
| **Psychiatric disorders** | | |
| Hallucination[a] | 5% | 3% |
| Confusional state | 6% | 3% |

[a]Hallucination includes visual, auditory, tactile, and somatic hallucinations.

## DOSING AND ADMINISTRATION

NUPLAZID is an oral tablet administered at a starting and maintenance dose of 34 mg daily, supplied as 2 tablets of 17 mg each. It can be taken either with or without food once daily at any time of day, without a titration period. In patients taking NUPLAZID with a strong CYP3A4 inhibitor, such as ketoconazole, the daily dose should be reduced to a single 17-mg tablet daily. Patients should be monitored for reduced efficacy if NUPLAZID is used concomitantly with strong CYP3A4 inducers; an increase in NUPLAZID dosage may be needed.[14]

In clinical studies, NUPLAZID has been administered with a variety of PD medications.[30] Additionally, based on pharmacokinetic studies, no dosage adjustment of carbidopa/levodopa is required in patients receiving NUPLAZID. However, it should be noted that NUPLAZID prolongs the QT interval and should be avoided in patients with QT prolongation syndromes, as well as with medications that prolong the QT interval, such as certain antiarrhythmic drugs, antipsychotic medications, or antibiotics, and in patients with certain comorbid medical conditions, such as cardiac arrhythmias, symptomatic bradycardia, hypokalemia, hypomagnesemia, or the presence of congenital prolongation of the QT interval.[14]

## CONCLUSIONS

Over the course of illness, more than half of patients with PD develop PDP.[2] Symptoms of PDP generally worsen with an increasing duration of illness.[3] This burdensome condition adversely affects both patients and caregivers and may be associated with increased risk of nursing home placement.[22,23]

Pharmacologically, NUPLAZID is an SSIA that also demonstrates antagonist activity at serotonergic receptors. Importantly, NUPLAZID has no appreciable activity at muscarinic, histaminergic, or adrenergic receptors, or calcium channels. Each 34-mg dose, supplied as two 17-mg tablets, should be taken once daily at any time of day, without any titration.[14] From baseline to Week 6, patients receiving NUPLAZID experienced a 5.79-point reduction versus a 2.73-point reduction in SAPS-PD score with placebo at Week 6, which was a significantly greater improvement ($P = 0.0014$). Patients receiving NUPLAZID experienced a 37% improvement in hallucinations and delusions as measured by the SAPS-PD from baseline versus a 14% improvement in patients receiving placebo, and they did not have worsened motor function relative to placebo.[14,30] For patients with PDP, NUPLAZID is a unique option for treatment of hallucinations and delusions that has a manageable adverse event profile and clinically important benefits.

## ASK THE PRESENTER

Editors from *The American Journal of Managed Care®* interviewed Dr Kremens to gain additional insight on the impact of PDP.

### Q & A WITH DANIEL E. KREMENS, MD, JD

***AJMC®*: How do you see the standard of care evolving for patients with hallucinations and delusions associated with PDP as a result of the approval of NUPLAZID™ (pimavanserin), and why?**

**Dr Kremens:** We should hopefully see a paradigm shift in the treatment of hallucinations and delusions associated with PDP as a result of the approval of NUPLAZID. Until now, we've been in a Hobson's choice of treating PDP because atypical antipsychotics tend to block dopamine, but PD patients don't have enough dopamine; therefore, if we attempt to treat their psychosis, we end up worsening their motor function. NUPLAZID does not interfere with the motor function of patients. Now, with NUPLAZID, we'll be able to treat the psychosis associated with PD without worsening the motor function.

***AJMC®*: What are the risks that can lead a patient with PD to develop PDP?**

**Dr Kremens:** A number of risks, both intrinsic and extrinsic factors, can lead to the development of psychosis in patients with PD. On the intrinsic side, comorbid medical and psychiatric conditions are associated with developing PDP. In addition, the PD itself has elements that are risk factors, including the severity of the underlying disease, the duration of the disease, and the fact that older patients tend to be at greater risk for developing PDP. In addition, the underlying neurodegenerative process in PD is implicated in the development of PDP. In PD, there is a loss of various neurotransmitters. Typically, we think of dopamine, but other neurotransmitters are altered in PD; a growing body of evidence suggests that serotonin plays a significant, or even primary, role in the development of PDP. We know that there is loss of serotonin in PD but increased activity at serotonin receptors, and it is thought that this may be one of the reasons why we see PDP.

Another intrinsic factor is visual processing deficit; people with PD have issues with lower visual acuity and contrast. In addition, there are extrinsic factors. Even though we believe serotonin may be the main neurotransmitter involved in PDP, it's not the only neurotransmitter. Dopamine likely does play a role, and in some patients, the dopaminergic medicine that we use to treat PD may worsen PDP. In addition, there are medicines for conditions other than PD that can worsen PDP, such as anticholinergics that are used to treat medical conditions such as urinary incontinence. And environmental factors, such as dim lighting, can contribute to visual hallucinations.

***AJMC®*: How likely is it for a patient with PD to develop psychosis?**

**Dr Kremens:** Probably greater than 50% of patients with PD will experience PDP at some time during the course of their disease.[2]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***AJMC®*: What symptoms point to the likelihood of a patient with PD being diagnosed with PDP?**

**Dr Kremens:** The main symptoms in PDP are hallucinations and delusions. Hallucinations are the perception of a stimulus in the absence of a physical stimulus. Typically, in PDP, it's a visual hallucination, but the hallucinations are not exclusively visual; they can be tactile, gustatory, or auditory. There are so-called minor hallucinations, which include illusions, which are a misperception of a physical stimulus. A classic one is if someone throws a belt or a tie on their bed and they see a snake. In addition, there are delusions, which are false fixed beliefs in the presence of evidence to the contrary. The most common that we see in PDP are delusions of spousal infidelity. Often with male patients, they believe their wife is engaging in sexual relationships with others. Also, delusions of persecution are not uncommon; for example, people believe that someone is trying to steal their money. So, the main symptoms are hallucinations and delusions, in the absence of any other underlying condition that could cause them, such as delirium, an infection, or another underlying psychiatric condition, such as schizophrenia.

***AJMC®*: When do symptoms of PDP begin in patients with PD, and what triggers the initiation of pharmacologic treatment?**

**Dr Kremens:** PDP can occur at any point in the disease, although it's typically associated with later disease. However, a recent study suggested that a large number of patients may experience some minor hallucinations before they're even diagnosed with disease, as a sort of pre-motor symptom of PD, such as an illusion, where there is a misperception in the presence of a physical stimulus. But, in general, PDP tends to occur with longer duration of disease.[31]

When we decide to treat PDP is an interesting question, as well. I think that has to be a discussion between the physician, the patient, and the caregiver. Early in the course of PDP, hallucinations may not be terribly distressing to the patient; for example, the patient may see a small child or animals that aren't there. Nonetheless, this may be quite distressing to the caregiver, who sees the patient interacting or speaking to people who aren't there; that can be socially isolating and disturbing. Even though the patient may not be especially bothered, if it's sufficiently distressing to the family and isolating to the patient, you may want to consider beginning treatment at that time. Certainly when hallucinations or delusions are distressing to the patient, it's really important to begin treatment. Another point to keep in mind is that even so-called benign hallucinations are generally harbingers of bad things to come, so it's important to at least begin a discussion.

***AJMC®*: How likely is it that a patient with PD will need to be hospitalized or institutionalized in a long-term care setting because of PDP?**

**Dr Kremens:** PDP is a significant risk factor for both hospitalization and institutionalization of PD patients. One study suggested that 24% of all hospital admissions of PD patients were for PDP.[27] Patients who are admitted to the hospital with PDP are 2.5 times more likely to end up in nursing homes, and nursing homes are associated with an increased risk of mortality.[22-24] One study suggested a mortality rate of 40% after 10 years of follow-up in patients with PDP.[26]

***AJMC®*: How are caregivers affected by caring for patients with PDP?**

**Dr Kremens:** There is a tremendous burden on caregivers. A study showed that over 40% of caregivers reported declines in their physical health, 65% reported that their close relationships suffered, and nearly half (47%) have increased scores on depression scales.[25] The inability to care for a patient who becomes delusional or has disturbing hallucinations often leads to nursing home placement.[22]

***AJMC®*: How would you describe the mechanism of action of NUPLAZID, which is a selective serotonin inverse agonist?**

**Dr Kremens:** NUPLAZID is a selective serotonin inverse agonist. To understand this, you have to understand how receptors in the brain work. Many receptors in the brain are capable of initiating signals even when they are not being stimulated, even when you don't have an agonist bound to that receptor. Signaling can occur without an agonist; that is called basal activity. If you have an agonist, that stimulates a receptor and increases the activity of that receptor. Then there are drugs called antagonists. Antagonists block the agonist, but they permit the ongoing basal activity. Then you have inverse agonists. Inverse agonists suppress basal activity. So, with NUPLAZID, you are suppressing the basal activity of some serotonin receptors in the brain. It's thought that the effect of NUPLAZID is a result of a combination of an inverse agonist and antagonist activity at serotonin receptors.

***AJMC®*: What role do primary care physicians, neurologists, and psychiatrists play in the care of patients with PDP?**

**Dr Kremens:** Primary care physicians, neurologists, and psychiatrists all can play a role in the care of patients with PDP. The key thing for primary care physicians and, to a lesser extent, neurologists and psychiatrists is first to recognize PDP. We do a pretty poor job of identifying patients with PDP. The patients themselves often are embarrassed by their symptoms. They're concerned that if they report that they're seeing things, someone is going to call them crazy and they're going to get locked up. So, patients don't share the fact that they're having psychotic symptoms. In one study, symptoms weren't disclosed to the physicians by 41.5% of patients who were experiencing hallucinations and 65.2% of patients experiencing delusions, but then they later reported it in an anonymous survey.[19]

Primary care physicians and neurologists may be so focused on the motor symptoms of PD that they don't get around, by the time the visit has ended, to asking about nonmotor symptoms such as PDP. Physicians need to ask patients if they are experiencing hallucinations or delusions, and they need to do it in a way that's not threatening and not judgmental. Once PDP has been identified, make sure there are no extrinsic factors, such as a urinary tract infection and the addition of

an anticholinergic medicine, that might be causing psychosis. When PDP has been established, the primary care physician should get that patient into a neurologist, particularly a movement disorder specialist, or a psychiatrist, someone who has special training in the treatment of psychosis, to better manage the patient.

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