Effective Management Approaches for Psychosis in Patients With Parkinson Disease

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Parkinson disease (PD) is the fastest growing neurologic disease worldwide, and the majority of patients with PD will experience symptoms of psychosis during the course of the disease. Psychotic symptoms lead to poor outcomes and increase the already heavy burden on patients with PD and their caregivers. Treatment is available but must be initiated early for optimal outcomes. Therefore, clinicians need to be familiar with and vigilant for potential signs of psychosis. Once psychotic symptoms are detected, clinicians should follow a cautious management plan that includes a medical evaluation, medication review and reduction (while trying to avoid worsening motor symptoms), and possibly the addition of an antipsychotic. However, antipsychotics must be used with caution in this population because of the risk of increased mortality in elderly patients.

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Parkinson disease (PD) has been described as a pandemic because it is the fastest growing neurologic disorder and a leading cause of global disability.[1] The global prevalence of PD is projected to more than double by 2040 as the population ages and life expectancies increase.[1] More than half of patients with PD will experience hallucinations or delusions during the course of their illness, and most of these individuals will develop Parkinson disease psychosis (PDP).[2,3]

THE BURDEN OF PSYCHOSIS IN PATIENTS WITH PARKINSON DISEASE

Psychosis in patients with PD drastically increases the burden of this disease on caregivers[4] and predicts reduced quality of life for the patient.[5] PDP increases the risk of hospitalizations and placement in long-term care facilities.[6,7] In one study[6] of all PD admissions to a neurologic hospital over a 6-year period, investigators found that 24% of patients had been admitted due to psychosis alone and 25% had been admitted due to a combination of motor and psychiatric complications. Furthermore, they found drug-induced psychosis to be the greatest contributing factor to repeated and prolonged admissions. An analysis of Medicare claims data[7] revealed that patients with PD and psychosis spent more than twice as many days in long-term care as PD patients without psychosis (179 days versus 83 days). Finally, the presence of psychosis greatly increases mortality in patients with PD.[8]

Patient Perspectives

"I also get auditory Hallucinations. Door bell, road runner BEEP-BEEP, police sirens, etc. going off.… I hear my name being called at random."[9]

"I have had hallucinations and I was told it was probably one drug interacting with another. It was very scary. I saw whole families moving into my home and trying to take over. These hallucinations lasted for several weeks and followed a storyline you wouldn't believe. I had two bouts of them and the worst part was that I knew they weren't real but they still kept recurring."[10]

"I keep seeing a shadowy female figure over my right shoulder. I have given her the identity of my estranged wife. I tried it because I got rid of her via the legal system in real life, so I thought that the identity of someone who was controllable in real life might make her controllable in the fantasy existence, and it works quite well. It normally takes a very short time, but just sometimes it can take about an hour or so on bad PD days. The important thing is to remember that it is a fantasy figure."[9]

Caregiver Perspectives

"[My husband] swears that the neighbor across the road has planted grape vines and put a row in our yard, [and] sees cows, people fishing in boats, thinks people have come and no one has."[11]

"[My wife's] fixed delusion of infidelity is at its peak … she believes I am having affair[s] with 2–3 women at one time."[12]

"Today my mom got angry at me for an argument she hallucinated happened between me and my father. She was really hurt, and I couldn't tell her it had been a hallucination without it coming off like me and my dad were conspiring against her."[13]

What Do PD Patients and Caregivers Need to Know Early on About Psychosis?

- Psychosis is common in PD as the disease progresses.
- The nonmotor symptoms the patient may begin experiencing may be related to PD.
- The Movement Disorder Society–sponsored revision of the Unified Parkinson's Disease Rating Scale[14] has a section that includes questions related to nonmotor PD symptoms.
- Psychosis symptoms are often underreported; therefore, it's necessary to make patients aware that there are available treatment options.

RECOGNITION OF PSYCHOSIS IN PATIENTS WITH PARKINSON DISEASE

Clinicians often underrecognize the nonmotor symptoms of PD; this is particularly true of psychosis.[15] A major contributor to the underrecognition of nonmotor symptoms, including PDP, is the failure of patients and caregivers to report these issues to their health care providers. Chaudhuri and colleagues[16] conducted a study in which 242 patients with PD were asked to complete a 30-item self-report screening tool designed to detect nonmotor symptoms. This tool, the NMSQuest, assesses for a host of nonmotor symptoms, ranging from hallucinations and delusions to sleep and urinary problems. After completing the NMSQuest, patients were asked if any identified symptoms had previously been discussed during an appointment with their physician, and if not, why. The investigators found that hallucinations/delusions was the symptom domain most frequently not declared to physicians, with 41.5% of the patients experiencing hallucinations and 65.2% experiencing delusions not reporting these symptoms to their physicians.[16]

Although patients would admit to these symptoms on the survey, they would not report them to their physicians. Patients cited 3 explanations for not spontaneously declaring their nonmotor symptoms: (1) they did not realize the symptoms were related to PD, (2) they were embarrassed, and/or (3) their consultation time was focused on motor symptoms.[16] The results of this study indicate several steps clinicians can take to improve the recognition of psychotic symptoms in patients with PD, including educating patients and caregivers early in the disease process about psychiatric symptoms, as well as screening patients for PDP symptoms at each visit.[17,18] Furthermore, due to the sensitive nature of these symptoms, physicians should inquire about these issues in a non-threatening manner.[19]

Symptoms and Features

Psychosis associated with PD has a distinct clinical profile from other forms of psychosis.[20] The National Institutes of Neurologic Disorders and Stroke and the National Institute of Mental Health formed a work group that developed diagnostic criteria for PDP (**Table 1**).[20] A central criterion is a primary PD diagnosis rendered prior to the onset of psychotic symptoms. In addition, because PDP is stable and progressive, diagnosis requires that the psychotic symptoms be recurrent or continuous for at least 1 month. Other medical or psychological causes of the symptoms must also be ruled out. The psychosis can occur with or without insight, PD treatment, or dementia.[20] The characteristic symptoms required for a diagnosis of PDP include at least one of the following: hallucinations, illusions, a false sense of presence, or delusions.[20]

Hallucinations. A hallucination is an abnormal perception involving any sensory modality that occurs in the absence of external stimuli. Visual hallucinations are the most common symptoms in PDP. These can be simple or well formed, they often consist of people or animals, and the content is frequently recurrent.[20] Auditory hallucinations are also common in PDP, but unlike the auditory hallucinations common in schizophrenia that tend to be perceived as threatening, those in PD are often vague and consist of music or sounds such as footsteps or whispers.[21–23] Patients with PDP can also experience olfactory, gustatory, or somatic hallucinations, but these are less common (**Figure 1**).[23] Often, patients with PDP will experience multimodal hallucinations. For example, they may both see and hear or be touched by a person who is not there. Hallucinations are usually brief and are more common at night, in low light, or in instances of compromised vision.[21,22]

Illusions. In PDP, illusions are considered a type of minor hallucination. Illusions are unique in that patients are misperceiving actual objects or stimuli.[21] For example, a patient might see trees as people or a chair as a dog.

False sense of presence. The false sense of presence commonly experienced by patients with PDP is the vivid sensation that someone is nearby when nobody is actually there. This sensation is also sometimes called a *presence hallucination*.[20] The presence is usually perceived to be a human or an animal generally in the same room as the patient. Some patients perceive the identity of the presence, recognizing it, for example, to be a deceased loved one or pet, but for others the presence is unidentified.[22,24] The false sense of presence most commonly occurs in combination with a hallucination of a different sensory modality, frequently visual.[23]

Delusions. Delusions are false, firmly held beliefs that the patient holds with no evidence, or with evidence to the contrary.[20] These delusions can focus on jealousy, paranoia, or themes of abandonment, theft, or spousal infidelity.[21] Delusions have a negative nature and can be far more disruptive and distressing to the patient than hallucinations.[25]

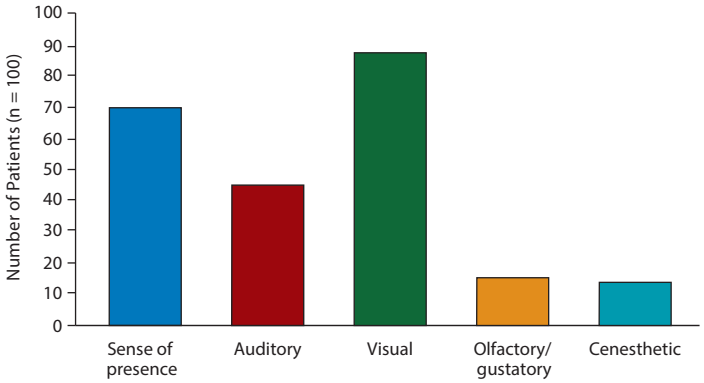
Table 1. NINDS-NIMH Diagnostic Criteria for Parkinson Disease (PD) Psychosis[a]

Diagnostic Criteria
Presence of at least 1 of the following psychotic symptoms, with or without retained insight:
Illusions
False sense of presence
Hallucinations
Delusions
Primary diagnosis of PD, which was received prior to the onset of psychotic symptoms
Duration of psychotic symptoms of at least 1 month
Absence of other potential causes of psychosis

[a]Based on Ravina et al.[20]

Abbreviations: NIMH = National Institute of Mental Health, NINDS = National Institute of Neurological Disorders and Stroke.

Figure 1. Prevalence of Different Types of Hallucinations Experienced by Patients with Parkinson Disease[a]



[a]Data from Llorca et al[23]

Table 2. Risk Factors for Parkinson Disease (PD) Psychosis[a]

Endogenous Risk Factors	Exogenous Risk Factors
Advanced age	Dopaminergic PD medications
Longer duration of illness	Anticholinergic medications
Greater severity of illness	Medications used to treat other issues such as pain, sleep disturbance, anxiety, or bladder issues
Cognitive impairment or dementia	
Sleep disturbance	
Psychiatric symptoms	
Vision problems or abnormalities	

[a]Based on Fénelon et al,[22] Jakel and Stacy,[26] and Morgante et al[27]

Risk Factors

Not every patient with PD will develop psychosis. Certain risk factors may help physicians recognize patients that warrant close observation for signs of PDP. These factors can be both endogenous and exogenous (**Table 2**).[22,26,27]

Endogenous factors. Individuals who have experienced a late onset of PD have been found to be at a higher risk of developing psychotic symptoms.[26] In addition, the prevalence of hallucinations can increase with the duration of and severity of motor impairments.[22,26] Cognitive impairments are also associated with PDP risk. The presence and severity of cognitive symptoms have been found to be positively correlated with psychotic symptoms,[26] and psychotic symptoms are experienced by as many as 70% of PD patients with dementia.[22] Although PDP is extremely common in patients with dementia, it can also occur in patients without dementia. Clinicians must therefore screen all patients for signs of psychosis regardless of their cognitive status.

Other endogenous risk factors include the presence of psychiatric symptoms, particularly depression and anxiety, and sleep disturbance.[22,27] In a study of 423 patients with newly diagnosed PD, Barrett and colleagues[28] found that the patients who screened positive for REM sleep behavior disorder or excessive daytime sleepiness at baseline were significantly more likely to later screen positive for psychotic symptoms ($P = .021$ and $P = .003$ respectively). Interestingly, individuals who are blind can experience visual hallucinations, and, in patients with PD, visual abnormalities or visual deterioration may increase the risk of developing hallucinations.[22] Patients with PD who experience hallucinations may have difficulties perceiving spatial relations, color and contrast discrimination, and object perception. They also commonly experience double vision.[29] The hallucinations in PD may be a result of the brain attempting to make sense of defective visual information, or they may stem from the same underlying pathology.[29]

Exogenous risk factors. The main exogenous risk factor for psychosis is the medication used to treat the symptoms of PD. Initially, psychosis was thought to be caused by a surplus of dopamine as a result of treatment with common PD medication such as levodopa and dopamine agonists.[21] However, as new research has been conducted, the pathophysiology of PDP is now understood to be more complex than simply an excess of dopamine. Although dopamine pathways are certainly involved, alterations in the serotonergic and cholinergic systems are known to also play a role in the development of psychosis.[21] In one study,[30] neither levodopa nor dopamine agonists were found to carry a significant risk of psychosis, but the risk associated with anticholinergic drugs was considerable (hazard ratio, 19.7 [95% CI, 2.39–1.63]; $P = .006$). Thus, the medications that can increase patients' risk of psychosis will not only be those that are prescribed for their PD. They may, for example, have consulted their primary care doctor about pain, sleep issues, or bladder problems and received a prescription that is contributing to hallucinations.

Improving Recognition and Educating Patients

Because symptoms of psychosis are underreported by patients and caregivers,[16] it is incumbent upon health care professionals to improve the recognition of PD psychosis. To facilitate this process, patients should receive education about PDP and available treatments early in the disease course.[31] This can be done in a gentle, non-threatening manner using language such as the following:

> *"At some point in your disease process, particularly as the disease advances or as we change medication, you might experience some strange symptoms, such as hallucinations. You may see things that aren't there, and this is a common symptom in advancing Parkinson disease. There are treatments and ways to manage these symptoms, so I don't want you to be frightened, but it is important for you to know what to expect and for you to discuss these things with me if they begin to occur."*

Patients and caregivers must also be asked direct questions about the possible experience of psychotic symptoms at every visit. These questions should cover all types of sensory hallucinations, illusions, senses of presence, and delusions (**Table 3**).[32] Direct but non-threatening inquiries will help physicians identify the earliest possible signs of psychosis and initiate treatment.

Table 3. Questions to Assess for Symptoms of Parkinson Disease Psychosis[a]

Hallucinations	Illusions	Sense of Presence	Delusions
Do you see people, animals, or objects that are not really there?	Do you ever see something different than a real object, such as seeing a person instead of a tree or a spider instead of a spot on the floor?	Do you ever have the distinct sense that someone is nearby, perhaps right behind you, but no one is there?	Do you feel that anybody wants to harm you or steal from you?
Do you hear sounds or voices that others don't?	Do you ever have the impression of someone or something passing through your peripheral vision when nothing is there?		Do you believe that someone close to you is being deceitful with you?
Do you feel things touching you or moving on you with no visible cause?			Do you believe that your spouse or partner is being unfaithful?
Do you smell odors with no source?			
Do you experience tastes with no source?			
Do you ever feel like your mind is playing tricks on you?			

[a]Based on Fénelon et al[32]

Case Practice Questions

Discussion of best responses can be found at the end of the activity.

Case 1. Mr Smith is a 78-year-old man diagnosed with PD 15 years ago. His disease is now moderately advanced although he is otherwise in good health and shows no signs of dementia. Over the years, you have developed a good therapeutic relationship with Mr Smith and his visits are generally cordial. On his most recent visit, Mr Smith confides in you that he suspects his wife is having an affair and he believes that when she says she is going to visit their grandchildren, she is actually going to the neighbor's house with whom she is having the affair.

What should you do?

a. Because Mr Smith shows no signs of dementia, you have no reason to suspect that his fears are unfounded. You should assume that he is confiding in you as a friend and suggest he discuss these concerns with his wife.

b. Recognize that Mr Smith is suffering from a delusion and alert him immediately that he has developed PDP.

c. Ask Mr Smith if he has ever experienced sights, sounds, or other sensations that were not there, or if he ever has the impression that someone is nearby when no one is there.

Case 2. Mrs Juarez is an 82-year-old woman who was diagnosed with PD 10 years ago. This is her first visit to your clinic, and she is accompanied by her daughter, Lisa. During Mrs Juarez's examination, Lisa tells you that her mother recently saw her dead husband, Lisa's father, standing by her bed. Mrs Juarez admits that this occurred but says she was too embarrassed to bring it up herself and she thinks that it was just her eyes playing tricks on her. Although Mrs Juarez is very dismissive of what she saw, the incident is clearly very distressing to her daughter.

Which of the following is the *best* way to address Mrs Juarez's potential hallucination during this visit?

a. Because the incident only occurred once and it was at night, tell Mrs Juarez that she probably was not experiencing a true hallucination. Rather, the low light might have tricked her eyes, or she may even have been dreaming.

b. Ask if Mrs Juarez and her daughter are familiar with Parkinson disease psychosis, and if not, tell them that it is very common to experience some hallucinations in the course of PD. Assess Mrs Juarez for additional symptoms and provide information on what to expect and available treatments.

c. Reassure both women that Mrs Juarez's hallucination could have been caused by something as simple as being overtired or dehydrated and that they have no cause to worry unless the hallucinations recur.

TREATMENT OF PARKINSON DISEASE PSYCHOSIS

Psychosis associated with PD is typically progressive; therefore, clinicians must decide both when and how to treat these symptoms. For most patients, the earliest signs of psychosis will be visual hallucinations, and initially patients will retain insight and be able to distinguish these symptoms from reality. These symptoms may occur occasionally, may not be too distressing to patients, and can often be managed with coping strategies.[33] The hallucinations experienced at this stage of the disease process have sometimes been referred to as benign, but this term is misleading because it can be misunderstood as indicating a positive prognosis.[17] A study by Goetz and colleagues[17] found that after 3 years, 96% of PD patients (n = 48) with "benign" hallucinations at baseline had progressed to either hallucinations with loss of insight or delusions, signifying that the experience of hallucinations, even with retained insight, should not be considered benign. Indeed, the majority of patients who experience mild hallucinations will eventually develop more severe psychotic symptoms, which contribute to negative outcomes and therefore necessitate treatment.[26]

Implications of PD Pathology for Treatment

In PD, motor symptoms such as rigidity, bradykinesia, and tremor are thought to result from degeneration of dopamine neurotransmission within the nigrostriatal pathway, whereas behavioral symptoms such as psychosis are believed to originate from overactivation of the ventral dopaminergic pathway.[34] This creates a treatment conundrum because medications that are intended to reduce motor symptoms by providing the brain with extra dopamine may induce or exacerbate psychosis, and medications that attempt to alleviate psychosis by blocking dopamine can worsen motor symptoms.

The serotonergic system (5-HT) is also involved in PD pathology and treatment. Patients with PD have been found to have decreased serotonin function,[34] and patients with PD and psychosis have been found to have lower cerebral serotonin levels than those without.[21] There is up-regulation of the 5-HT_{2A} receptors in the cerebral cortex due to loss of serotonin signaling from medial raphe. Up-regulated 5-HT_{2A} receptors on the glutamate neurons are presumed to increase signaling to the ventral dopaminergic pathways, which results in delusions and hallucinations.[35] Hallucinogenic effects of drugs such as LSD are known to be mediated through serotonin receptors,[36] providing further evidence of the role of the

serotonergic system in the pathology of PDP and another potential pathway for treatment.

Initial Assessment

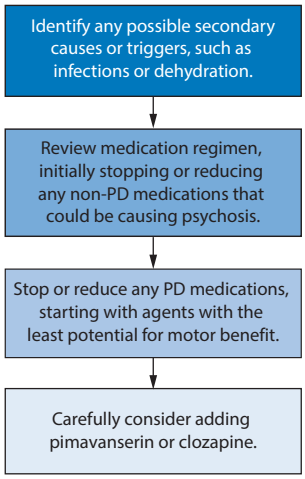
All patients with PD who exhibit symptoms of psychosis should first be given a complete medical evaluation to rule out other potential causes or triggers (**Figure 2**).[18,26] Relatively minor medical issues such as dehydration or urinary tract infections can contribute to psychotic symptoms. Therefore, patients should receive routine blood work, a urinalysis, and an assessment of their vitamin B_{12} and folate levels. Any issues identified should be treated and the patient monitored to see if the psychotic symptoms persist.[26]

Medication Review and Adjustment

Medications that a patient is taking for a variety of non-PD related issues can contribute to symptoms of psychosis. If a patient continues to experience symptoms of psychosis after a medical evaluation, the patient's medications should be reviewed. Polypharmacy is common in PD, and patients may, for example, be taking sedatives, anxiolytics, antidepressants, narcotic pain medications, antihistamines, or anticholinergics.[18,25,26] These medications should be reduced, or discontinued, if possible.

If psychotic symptoms persist, clinicians should attempt to reduce the patient's PD medications without worsening the patient's motor symptoms. The recommended strategy is to reduce or eliminate the drugs that hold the least potential for clinical benefit or are most likely to cause hallucinations.[18] Thus, clinicians should adjust anticholinergics, amantadine, dopamine agonists, monoamine oxidase B inhibitors, and catechol-O-methyltransferase (COMT) inhibitors. Finally, if psychotic symptoms persist, clinicians should attempt to adjust the patient's levodopa dose. These treatment adjustments will often lead to an exacerbation of motor symptoms.[18,25,26] Patients must decide if they believe the improvement in psychosis is an acceptable trade-off for the decline in motor symptoms.[25]

Figure 2. Recommendations for Treating Parkinson Disease Psychosis[a]



[a]Based on Martinez-Ramirez et al[18] and Jakel and Stacy[26]

Nonpharmacologic Management

Patients may find nonpharmacologic strategies helpful for dealing with symptoms of psychosis, particularly early in the disease process while insight is still retained. Clinicians should educate patients on helpful coping strategies.[18] A study[33] by Barnes et al identified a number of coping strategies frequently used by patients with PD who were experiencing psychotic symptoms. The most common strategy was an action-oriented approach. Patients would blink, rub their eyes, or turn on a light to make hallucinations or illusions go away. They would also try to interact with the things they saw by trying to touch or talk to them. Additionally, many patients used a cognitive approach in which they rationalized the symptoms, told themselves they were not real, and tried to inspect them more closely. Emotional coping was common as well and involved the patients discussing their feelings and fears with others to relieve the emotional burden. Humor was an effective coping strategy, too; many patients found the best way to deal with their hallucinations was to laugh and joke about them with friends and family.[37] Psychosocial treatments have not been well studied in PDP, but they may be considered early in the disease process before insight is lost.[18]

Pharmacologic Treatment

If a patient has been assessed for medical issues, had non-PD medications discontinued, and had PD treatments reduced as much as possible yet psychotic symptoms persist, the clinician should consider treatment with an antipsychotic. This must be done carefully because all atypical antipsychotics are associated with a risk of increased mortality,[38] especially in elderly patients with dementia-related psychosis.[21,39] The receptor binding profiles of antipsychotics are an important consideration in PD patients because the symptom profiles of these patients are quite complex and the pharmacology of antipsychotic treatment can have serious clinical implications (**Table 4**).[40–42] Namely, the dopamine-blocking action of antipsychotics will often exacerbate motor symptoms. The degree of motor

Table 4. Receptor Binding Profiles and Clinical Implications of Antipsychotics Used to Treat Parkinson Disease Psychosis[a]

	Comparative Strength of Receptor Binding Affinity				
Receptor	Risperidone	Quetiapine	Clozapine	Pimavanserin	Clinical Implication
Dopaminergic	High	Low	Low	Negligible	Antagonism is associated with antipsychotic effects, motor symptoms, and endocrine effects
Serotonergic					
5-HT_{1A}	Low	Low	Low	Negligible	Agonism is associated with antidepressant and anxiolytic effects, weight changes, and improvements in cognition and motor symptoms
5-HT_{1D}	Low	Negligible	Negligible	Negligible	Antagonism is associated with antidepressant effects
5-HT_{2A}	Very high	Low	High	Very high	Antagonism is associated with antipsychotic effects and improved motor symptoms Inverse agonism is associated with antipsychotic effects
5-HT_{2C}	High	Negligible	Moderate	Moderate	Antagonism is associated with antipsychotic effect and weight gain
Muscarinic	Negligible	Moderate	High	Negligible	Antagonism is associated with memory impairment, gastrointestinal symptoms, dry mouth, blurry vision, and improved motor symptoms
Histamine	Moderate	High	High	Negligible	Antagonism is associated with sedation and weight gain

[a]Data from Casey and Zorn,[40] Pahwa and Lyons,[41] and Vanover et al[42]

Case Practice Questions

Discussion of best responses can be found at the end of the activity.

Case 3.1 Mr Cohen is a 73-year-old man with PD who has been having visions of dogs running around his house. These visions initially occurred only once a week, but he now has them daily. He has even started buying food to feed the dogs and is putting food in a bowl on the ground. Mr Cohen's caregiver is upset and is arguing with him that there are no dogs. Mr Cohen's primary care doctor checked his laboratories and urine, which were normal, and asked him to follow up with his neurologist.

What would be the best line of treatment?

a. Start the patient on haloperidol.
b. Reduce PD medications.
c. Start risperidone.
d. Do nothing.

Case 3.2 Mr Cohen's treatment regimen consisted of 1 mg of pramipexole 3 times a day and 25/100 mg of carbidopa/levodopa, also 3 times a day. To treat his hallucinations, Mr Cohen's pramipexole dose was reduced to 0.5 mg/3 times a day. His motor symptoms increased and he could not sleep. His pramipexole dose was brought back up, and his hallucinations were unchanged.

What should be the next line of treatment?

a. Add 34 mg/d of pimavanserin.
b. Add 17 mg/d of pimavanserin.
c. Add 1 mg of risperidone at bedtime.
d. No medication change.

symptom worsening generally corresponds with the degree to which an antipsychotic blocks dopamine. Thus, the agents with the greatest dopamine blocking properties,[43] including typical antipsychotics such as haloperidol and atypical antipsychotics such as risperidone, have the greatest risk of exacerbating motor symptoms.[21] Clozapine is used off-label to treat PDP and has the most available evidence of efficacy,[39] but pimavanserin is the only agent approved for use in PDP.[44] Although quetiapine is often used off-label, this use is based more on clinical experience rather than strong evidence suggesting its efficacy.[39]

Clozapine is a serotonergic receptor antagonist and a weak dopamine receptor antagonist that has consistently been shown in double-blind, placebo-controlled trials to effectively treat PDP without worsening motor symptoms.[41] Because of the risk of agranulocytosis, regular blood testing is required. The risk of agranulocytosis is actually minimal, but the required blood tests limit this treatment's use. Quetiapine has a similar structure to clozapine, but regular blood tests are not required. Quetiapine is not a recommended treatment strategy because controlled trials have failed to find that the medication is any more effective than placebo for controlling PDP.[39] In some instances, patients experienced worsening motor symptoms.

Pimavanserin was approved based on the results of a 6-week, placebo-controlled study of 199 patients with PDP.[44,45] All patients went through a 2-week lead-in phase during which they received psychosocial treatment adapted for PD in order to elicit a placebo response prior to baseline. Once treatment was initiated, the active treatment group received 40 mg (equivalent to 34 mg of the active drug) of pimavanserin daily.[45] The groups were evaluated after 15, 29, and 43 days of treatment. Primary outcomes were assessed using the PD-adapted Scale for Assessment of Positive Symptoms (SAPS-PD),[46] which is a 9-item scale that covers individual symptoms as well as global hallucinations and delusions. After 6 weeks of treatment, the patients receiving pimavanserin had experienced a 37% improvement in psychotic symptoms from baseline compared with a 14% improvement in the placebo group ($P = .0006$).

Several secondary outcome measures, including Clinical Global Impressions-Severity (CGI-S) and -Improvement (CGI-I) scores, caregiver burden, sleep quality, and daytime wakefulness, significantly improved compared to the placebo group ($P \leq .0446$ for all measures).[45] Pimavanserin was generally well-tolerated; serious adverse events occurred in 11% of the pimavanserin group and 4% of the placebo group. The most common treatment-emergent adverse events were urinary tract infections, falls, hallucinations, peripheral edema, nausea, and confusional states.[45]

One of the most promising findings of this study was that the patients who were treated with pimavanserin experienced a reduction in their psychotic symptoms without any worsening in motor function.[45] Pimavanserin is a selective 5-HT_{2A} inverse agonist that lacks activity at dopaminergic, muscarinic, adrenergic, and histaminergic receptors.[47] This agent's action at serotonergic receptors is noteworthy because the binding of 5-HT_{2A} receptors is increased in the neocortex of patients with PD, and visual hallucinations are thought to be associated with an increased number of 5-HT_{2A} receptors in visual processing areas.[41] As an inverse agonist, pimavanserin binds to and decreases the activity of 5-HT_{2A} receptors, thereby improving symptoms of psychosis. Additionally, because dopaminergic receptors are not affected, motor symptoms should remain unchanged.[47]

Pimavanserin 34-mg capsules and 10-mg tablets are approved to treat delusions and hallucinations associated with PD.[48,49] The lower dose should be used when pimavanserin is coadministered with strong CYP3A4 inhibitors (eg, ketoconazole). After reports raised concerns regarding the safety of pimavanserin, the US Food and Drug Administration evaluated the evidence[50] but did not add new warnings. Post-approval adverse effects that have been reported include somnolence, rash, urticaria, and reactions consistent with angioedema.[49] Current clinical trial database evidence suggests that patients with PDP are about 5 times more likely to respond (according to the SAPS-PD) to pimavanserin than to discontinue it due to an adverse event.[51] Small studies reporting patient experience so far indicate that about half have improved,[52,53] but more evidence is needed. With any pharmacologic agent, clinicians, patients, and caregivers must discuss potential benefits and risks before deciding to initiate treatment.

Clinical Points

- Ask all patients with PD about possible signs of psychosis at every visit.
- Be sensitive to the fact that patients and caregivers may find the topic of psychosis embarrassing or distressing.
- Give all patients with PDP a complete medical evaluation to eliminate other potential causes of psychosis prior to changing or adding medications.
- Reduce or eliminate all non-essential PD medications prior to starting a trial of an antipsychotic.
- Select an antipsychotic that is likely to alleviate psychosis without worsening motor symptoms.

Discussion of Case Practice Questions

Case 1:

Preferred response is c. Ask Mr Smith if he has ever experienced sights, sounds, or other sensations that were not there, or if he ever has the impression that someone is nearby when no one is there

Mr Smith's concerns about his wife may be legitimate or may be a delusion, but a clinician probably cannot definitively determine this during an office visit without more information. Although PDP is more common in patients with dementia, the presence of dementia is not required and Mr Smith's cognitive status, therefore, cannot exclude him from the diagnosis. Because delusions usually develop later in the course of PDP, the best action for the clinician to take is to question Mr Smith about other symptoms required for a diagnosis of PDP such as hallucinations, illusions, or sense of presence that he may not have reported during his visits.

Case 2:

Preferred response is b. Ask if Mrs Juarez and her daughter are familiar with Parkinson disease psychosis and, if not, tell them that it is very common to experience some hallucinations in the course of PD. Assess Mrs Juarez for additional symptoms and provide information on what to expect and available treatments

Because of the prevalence of PDP, clinicians should never be dismissive of any potential psychotic symptoms a patient experiences, as the options b. and c. suggest. All patients should receive education about PDP early in the course of illness, but because of the sensitive nature of psychotic symptoms, this topic should be approached gently, as presented in option b.

Case 3.1:

Preferred response is b. Reduce PD medications

Because Mr Cohen's hallucinations are upsetting to his caregiver and have become disruptive, doing nothing is no longer an option. Neither haloperidol nor risperidone would be the best line of treatment because both of these medications are strong dopamine blockers and would, therefore, lead to worsening motor symptoms. Reducing Mr Cohen's PD medications is the best choice because his hallucinations may resolve without the need for adding any additional treatments.

Case 3.2:

Preferred response is a. Add 34 mg/d of pimavanserin

As in Mr Cohen's previous visit, doing nothing or adding risperidone are not viable options because the hallucinations have become disruptive, and risperidone is likely to lead to a worsening of motor symptoms. Pimavanserin is the only antipsychotic approved to treat psychosis in patients with PD, and the recommended dose is 34 mg/d.

Disclosure of off-label usage: The chair has determined that, to the best of his knowledge, haloperidol, risperidone, quetiapine, and clozapine are not approved by the US Food and Drug Administration for the treatment of Parkinson disease psychosis.

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1. **When assessing patients with Parkinson disease (PD), which of the following strategies is least effective for recognizing PD psychosis?**
   a. Educate patients and caregivers early in the illness course about possible PDP
   b. Talk about both motor and nonmotor symptoms at each visit
   c. Ask nonthreatening questions about specific psychotic symptoms
   d. Let patients bring up psychotic symptoms on their own because they may be embarrassed if asked

2. **Ms Simmons is a 75-year-old woman who was diagnosed with PD 8 years ago. She is currently taking 25/100 mg of carbidopa/levodopa 4 times daily, 6 mg/d of rotigotine patch, and 1 mg/d rasagiline. She recently developed hallucinations, ie, seeing little children and animals, primarily in the evening. Ms Simmons has insight that these visions are hallucinations and is not bothered by them. Otherwise, she complains of some urinary urgency. What would be the most appropriate next step to address the hallucinations?**
   a. Reduce or stop her rotigotine patch as dopamine agonists may contribute to PDP
   b. Start an antipsychotic such as pimavanserin, quetiapine, or clozapine to treat her PDP
   c. Check a urine analysis to assess for a urinary tract infection
   d. Do nothing because Ms Simmons has insight and is not bothered by her hallucinations

3. **Mr Williams is a 77-year-old man who was diagnosed with PD 10 years ago. He presented 2 months ago complaining of seeing men coming in his bedroom at night. He called the police to report intruders, but when no break-in evidence was found, his daughter brought him to visit you. No laboratory results were abnormal. His only PD medication was carbidopa-levodopa, and when you tried to reduce it, Mr Williams had increased falls and said he felt too slow. He now presents for follow-up and says he continues to hallucinate. Mr Williams also notes that it is harder for him to get to appointments since he is not able to drive any longer. The most appropriate step is to:**
   a. Once again, try to reduce his carbidopa-levodopa dose
   b. Initiate treatment with olanzapine
   c. Initiate treatment with pimavanserin
   d. Initiate treatment with clozapine and tell him to ask someone to drive him for regular laboratory testing