CME/CE OUTSERT

EARN ★CME/CE★ CREDITS

IMPROVING THE QUALITY OF LIFE OF PATIENTS WITH PARKINSON DISEASE PSYCHOSIS AND THEIR CAREGIVERS

Original Release: October 1, 2019 **Expiration: October 31, 2020**

Faculty

George T. Grossberg, MD *(Chair)*

Marc E. Agronin, MD

Pratap Chand, MD, FRCP

Dana Saffel, PharmD

Visit https://tinyurl.com/QoLinPDP for online testing and instant CME/CE certificate.

This continuing medical education activity is jointly provided by the American Association for Geriatric Psychiatry and MedEdicus LLC.

AAGP American Association for Geriatric Psychiatry

MedEdicus LLC

This continuing medical education activity is supported through an unrestricted educational grant from ACADIA Pharmaceuticals Inc.

ACTIVITY DESCRIPTION

Psychotic symptoms occur during the course of Parkinson disease in up to 60% of patients. These progressive symptoms range in severity from mild hallucinations to disruptive delusions that might drastically affect the quality of life of patients and their caregivers alike and increase the likelihood of patient institutionalization. Patients with severe symptoms are often prescribed antipsychotics that lack evidence of efficacy for Parkinson disease psychosis and might have adverse effects that jeopardize patient safety. The efficacy and adverse effects associated with many commonly used antipsychotics, such as quetiapine, clozapine, and risperidone, can be explained by examining their broad receptor-binding profile. Pimavanserin, a newer agent used to treat Parkinson disease psychosis, binds specifically to the 5-hydroxytryptamine 2A and 2C receptors, minimizing the risk of adverse effects. The desired outcome of this activity is for psychiatrists, neurologists, physician assistants, nurses, and psychologists to recognize psychosis in Parkinson disease as part of the progressive disease process and to treat symptoms effectively while maintaining safety and quality of life for patients residing at home or in long-term care facilities.

TARGET AUDIENCE

This activity intends to educate psychiatrists, neurologists, physician assistants, nurses, and psychologists caring for patients with Parkinson disease psychosis.

LEARNING OBJECTIVES

Upon completion of this activity, participants will be better able to:

- Discuss the clinical features of Parkinson disease psychosis and effect on quality of life
- Describe the pathophysiologic basis of psychotic symptoms in Parkinson disease
- Develop management strategies for patients with Parkinson disease who present with mild-to-severe symptoms of psychosis
- Relate safety and efficacy data for antipsychotics to their individual receptor-binding characteristics
- Use current evidence to select an antipsychotic for patients with Parkinson disease psychosis that minimizes adverse effects

TO OBTAIN CME/CE CREDIT

To obtain CME/CE credit for this activity, read the material in its entirety and consult referenced sources as necessary. Please take this post test and evaluation online by going to https://tinyurl.com/QoLinPDP. Upon passing, you will receive your certificate immediately. You must score 70% or higher to receive credit for this activity, and may take the test up to 2 times. Upon registering and successfully completing the post test, your certificate will be made available online and you can print it or file it. There are no fees for participating in and receiving credit for this activity.

Physicians CME: This activity has been planned and implemented in accordance with the accreditation requirements and policies of the Accreditation Council for Continuing Medical Education (ACCME) through the joint providership of Amedco and the American Association for Geriatric Psychiatry. Amedco is accredited by the ACCME to provide continuing medical education for physicians. Amedco designates this enduring activity for a maximum of 1.5 *AMA PRA Category 1 Credits*™. Physicians should claim only the credit commensurate with the extent of their participation in the activity.

Continuing Education credit for this program is awarded by Commonwealth Educational Seminars (CES) for the following professions:

Nursing Continuing Education: Upon completion of this course, nurses are eligible for CE contact hours. As an American Psychological Association (APA) approved provider, CES programs are accepted by the American Nurses Credentialing Center (ANCC). These courses can be utilized by nurses to renew their certification and will be accepted by the ANCC. Every state Board of Nursing accepts ANCC approved programs except California and Iowa, however CES is also an approved Continuing Education provider by the California Board of Registered Nursing (Provider # CEP15567) which is also accepted by the Iowa Board of Nursing.

Psychology Education: Commonwealth Educational Seminars (CES) is approved by the American Psychological Association (APA) to offer continuing education credit programs. CES maintains responsibility for this program and its content. Psychologists receive continuing education credit upon completing this program.

Professional Counselors/Licensed Mental Health Counselors: Commonwealth Educational Seminars (CES) is entitled to grant continuing education credit for LCPCs/LMHCs in the following states: AZ, AR, CA, CO, CT, DE, DC, FL, GA, HI, ID, IL, IN, IA, KS, KY, ME, MA, MO, NE, NH, NJ, NM, NC, OR, PA, RI, SC, SD, TN, UT, VT, VA, WA, WI, WY. CES maintains responsibility for this program. LCPCs/LMHCs completing the program will receive continuing education hours of credit.

GRANTOR STATEMENT

This continuing medical education activity is supported through an unrestricted educational grant from ACADIA Pharmaceuticals Inc.

DISCLOSURES

Marc E. Agronin, MD, had a financial agreement or affiliation during the past year with the following commercial interest in the form of *Consultant:* Axsome Therapeutics, Inc.

Pratap Chand, MD, FRCP, had a financial agreement or affiliation during the past year with the following commercial interests in the form of *Scientific/Medical Advisory Board Member:* US WorldMeds, LLC; *Speakers Bureau:* Adamas Pharmaceuticals, Inc; Neurocrine Biosciences, Inc; and Teva Pharmaceuticals USA, Inc.

George T. Grossberg, MD, had a financial agreement or affiliation during the past year with the following commercial interests in the form of *Scientific/Medical Advisory Board Member/Consultant:* ACADIA Pharmaceuticals Inc; Alkahest, Inc; Allergan; Avanir Pharmaceuticals, Inc; Axovant Sciences Ltd; BioXcel Therapeutics; F. Hoffmann-La Roche Ltd; Genentech, Inc; H Lundbeck A/S; Novartis Pharmaceuticals Corporation; Otsuka America Pharmaceutical, Inc; and Takeda Pharmaceutical Company Limited; *Contracted Research:* F. Hoffmann-La Roche Ltd; and Janssen Global Services, LLC; *Other Financial or Material Support:* EryDel SPA; Merck & Co., Inc; and Newron Pharmaceuticals SPA.

Dana Saffel, PharmD, had a financial agreement or affiliation during the past year with the following commercial interests in the form of *Scientific/Medical Advisory Board Member:* ACADIA Pharmaceuticals Inc; and Sunovion Pharmaceuticals Inc; *Consultant:* ACADIA Pharmaceuticals Inc; Astellas Pharma Europe Ltd; Axovant Sciences Ltd; Mylan NV; and Sunovion Pharmaceuticals Inc; *Speakers Bureau:* ACADIA Pharmaceuticals Inc; and Sunovion Pharmaceuticals Inc.

EDITORIAL SUPPORT DISCLOSURES

Carrie Noriega, MD; Erika Langsfeld, PhD; Cynthia Tornallyay, RD, MBA, CHCP; and **Michelle Ong** have no relevant commercial relationships to disclose.

DISCLOSURE ATTESTATION

The contributing physicians and instructors listed above have attested to the following:

1) that the relationships/affiliations noted will not bias or otherwise influence their involvement in this activity;
2) that practice recommendations given relevant to the companies with whom they have relationships/affiliations will be supported by the best available evidence or, absent evidence, will be consistent with generally accepted medical practice; and
3) that all reasonable clinical alternatives will be discussed when making practice recommendations.

OFF-LABEL DISCUSSION

This educational activity might contain discussion of evidence-based and/or investigational uses of agents that are not indicated by the FDA. For additional information about approved uses, including approved indications, contraindications, and warnings, please refer to the official prescribing information for each product.

DISCLAIMER

The views and opinions expressed in this educational activity are those of the faculty and do not necessarily represent the views of the American Association for Geriatric Psychiatry, MedEdicus LLC, ACADIA Pharmaceuticals Inc, or *The American Journal of Geriatric Psychiatry.*

Faculty

George T. Grossberg, MD *(Chair)*
Samuel W. Fordyce Professor
Director, Geriatric Psychiatry
Department of Psychiatry and Behavioral Neuroscience
Saint Louis University School of Medicine
St Louis, Missouri

Marc E. Agronin, MD
Senior Vice President for Behavioral Health
Miami Jewish Health
Affiliate Associate Professor of
Psychiatry and Neurology
University of Miami Miller School of Medicine
Miami, Florida

Pratap Chand, MD, FRCP
Professor of Neurology
Director, Movement Disorders
Director, Division of General Neurology
Department of Neurology
Saint Louis University
St Louis, Missouri

Dana Saffel, PharmD
President and CEO
PharmaCare Strategies, Inc
Santa Rosa Beach, Florida

IMPROVING THE QUALITY OF LIFE

OF PATIENTS WITH PARKINSON DISEASE PSYCHOSIS AND THEIR CAREGIVERS

OVERVIEW

Parkinson disease (PD) psychosis (PDP) is part of the spectrum of neuropsychiatric disorders affecting many patients with PD. It is increasingly recognized as a major factor in poor quality of life, nursing home placement, and caregiver stress.[1] Treating PDP is challenging because many antipsychotics are dopaminergic, adrenergic, or histaminic antagonists and can worsen a patient's motor symptoms, increase the risk of falls, and cause sedation.[2] A safe and effective treatment for PDP that can improve psychosis symptoms while still maintaining a patient's motor function is needed to reduce the burden of PDP.

This CME/CE monograph reviews new information presented at a recent CME/CE symposium on early diagnosis and treatment of PDP. Emphasis is placed on how treatment approaches can be tailored to individuals through a better understanding of the pathophysiology of the disease and the individual characteristics of the drugs used to treat psychosis.

CLINICAL PRESENTATION OF PARKINSON DISEASE PSYCHOSIS

PDP ranges from mild illusions to hallucinations to frank delusions,[1] with most patients developing more severe symptoms over the course of their disease.[3] Minor hallucinations can precede development of more severe hallucinations and include visual hallucinations that occur in the peripheral visual field (passage hallucinations) and vivid sensations that someone is present nearby (presence hallucinations).[1] Other types of hallucinations that can occur include the following[4]:

- Auditory
- Tactile
- Olfactory
- Gustatory

Patients who have normal cognitive function are frequently aware they are having hallucinations. When insight is retained, patients are often able to cope with their symptoms without behavioral disturbances[4,5]; but patients with dementia or more advanced psychosis tend to lose this awareness and their ability to cope with symptoms, triggering behavioral disturbances.[4]

Delusions are not as common as hallucinations.[6] Although delusions can occur in isolation, they often accompany hallucinations, particularly in the setting of delirium or advanced disease. Types of delusions seen in PDP include, but are not limited to, the following[1,4]:

- Persecutory
- Jealousy
- Misidentification syndromes

DIAGNOSIS

Initially, psychosis was thought of as an advanced disease phenomenon beginning an average of 10 or more years after the initial diagnosis of PD,[7] but research now suggests that patients with PD can experience hallucinations early in their disease course, even in the premotor phase.[8] This observation advances knowledge of the natural history of PDP, and is not reflected in current diagnostic criteria. A study by Pagonabarraga and colleagues reported that 42% of 50 newly diagnosed, drug-naïve patients with PD (disease duration of 19.5 ± 15 months) experienced minor hallucinations.[8] An unexpected finding in the study was that 33.3% of patients had minor hallucinations manifest as a premotor symptom beginning 7 months to 8 years before onset of the first parkinsonian motor symptoms.

The criteria for diagnosing PDP have differed over the years. To create standardized criteria, the National Institute of Neurological Disorders and Stroke and the National Institute of Mental Health sponsored a working group in 2007. The proposed criteria require at least 1 of the following: illusions, false sense of presence, hallucinations, delusions. These features should occur after onset of PD and should be recurrent or continual for at least 1 month. Other causes of psychosis—including medical, neurological, or psychiatric causes and acute delirium—should be excluded before diagnosing PDP.[9]

FREQUENCY OF UNDETECTED PARKINSON DISEASE PSYCHOSIS AND EFFECT ON PATIENT OUTCOMES

Using the National Institute of Neurological Disorders and Stroke and the National Institute of Mental Health criteria, prevalence of PDP can be as high as 60% in patients with PD.[1] However, few patients will spontaneously discuss their psychosis symptoms with their medical providers.[6,8] In the study by Pagonabarraga and colleagues, only 19% of patients experiencing hallucinations spontaneously reported them to their medical provider.[8] Because of the multifaceted and complex nature of PD, nonmotor symptoms of PD, including hallucinations, are often overlooked during visits in favor of discussing the more noticeable motor symptoms.[6] Patients frequently neglect to bring up these psychosis symptoms during medical visits for various reasons, including a lack of awareness that the symptoms are related to PD, and embarrassment/fear of stigma.[6]

Symptoms of PDP often affect both the patient and the caregiver. When patients suffer from confusion, hallucinations, and falls, the quality of life of the caregiver is significantly affected.[10] Schrag and colleagues found that these symptoms have a greater effect on caregiver quality of life than do bladder problems and motor symptoms.[10] For the patient, PDP is associated with increased morbidity and mortality, impairment in quality of life, placement in skilled nursing facilities, and approximately one-quarter of PD-related hospital admissions.[1,11] All told, these adverse events (AEs) highlight the need to identify PDP symptoms early in the course of the disease.

Symptoms of PDP often affect both the patient and the caregiver. When patients suffer from confusion, hallucinations, and falls, the quality of life of the caregiver is significantly affected.[10]

RISK FACTORS FOR PARKINSON DISEASE PSYCHOSIS

A number of intrinsic risk factors associated with PDP have been identified, including disease duration and severity, comorbidities, visual processing defects, metabolic changes in the brain, serotonergic dysfunction, and genetic predisposition **(Table 1)**.[4,7,12-15] Extrinsic and environmental factors also play a role in PDP pathogenesis, with medications at the forefront **(Table 2)**.[16,17]

Table 1. Intrinsic Risk Factors Associated With Parkinson Disease Psychosis

Parkinson disease progression, severity, duration, and older age[4,7,12]
Akinetic rigid variety[12]
Gait abnormalities or freezing gait[12]
Psychiatric conditions[4,7,12-14] • Cognitive impairment • Depression/Anxiety • Rapid eye movement sleep behavior disorder • Excessive daytime sleepiness
Visual acuity/Processing deficits[4]
Neurotransmitter abnormalities[15] • Increased 5-HT_{2A} receptor binding
Metabolic changes in multiple brain regions[4]
Genetic SNCA and LRRK2 mutations[12]

Abbreviations: 5-HT_{2A}, 5-hydroxytryptamine 2A; LRRK2, leucine-rich repeat kinase 2; SNCA, α-synuclein.

Table 2. Secondary Causes of Parkinson Disease Psychosis[16,17]

P	Parkinson disease medications
SY	Systemic illness or infection
C	Centrally acting medications (eg, dopaminergic, anticholinergic)
H	Hepatic, renal, or other metabolic dysfunction
O	Overdose of medications or intoxication
S	Sensory deprivation (eg, hearing and visual impairment)
I	Infection (eg, urinary tract infection and pneumonia)
S	Structural lesions (eg, stroke, subdural hematoma, and trauma)

NEW UNDERSTANDING OF THE PATHOPHYSIOLOGYOF PSYCHOTIC SYMPTOMS IN PARKINSON DISEASE

The exact pathophysiology of PDP is still unclear. Classically, it was thought that psychosis among patients with PD arose secondary to use of dopaminergic agents, identified through a correlation between dopaminergic therapy and symptoms of psychosis, with symptom improvement accompanying dose reduction.[1] For some vulnerable patients with PD and other risk factors, use of dopaminergic therapy to alleviate motor symptoms resulting from a loss of signaling from the substantia nigra to the dorsal striatum can hypothetically cause a relative overdose of dopamine in the ventral striatum, precipitating symptoms of psychosis **(Figure 1)**.[15]

Although common PD medications such as levodopa might contribute to development of psychosis, several studies have now demonstrated an absence of correlation between PDP symptom severity and levodopa dose.[4,18] The progressive nature of PDP, with patients experiencing more frequent and more fully formed hallucinations over time with loss of insight, has been found to be independent of the levodopa-equivalent dose.[4,19] Furthermore, hallucinations have been documented among patients with treatment-naïve PD.[8]

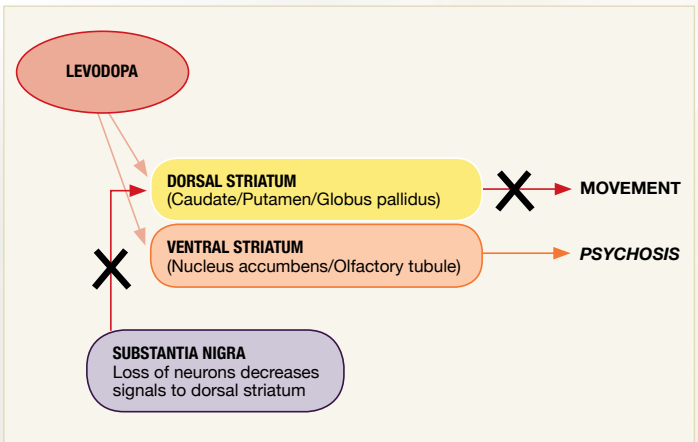

Figure 1. Dopamine pathway hypothesis as cause of Parkinson disease psychosis

Figure courtesy of Marc E. Agronin, MD, based in part from information from Stahl[15]

An additional, complementary theory for the development of PDP that takes into account patients who develop PDP independent of dopaminergic treatment describes a serotonin-dopamine imbalance arising from accumulation of Lewy bodies in the cerebral cortex **(Figure 2)**.[15] Although PD is considered to be a dopamine-deficient syndrome affecting the dorsal striatum through loss of substantia nigra neurons, theoretically it can also cause a superimposed serotonin-dopamine excess in the cerebral cortex and ventral striatum, which leads to PDP.

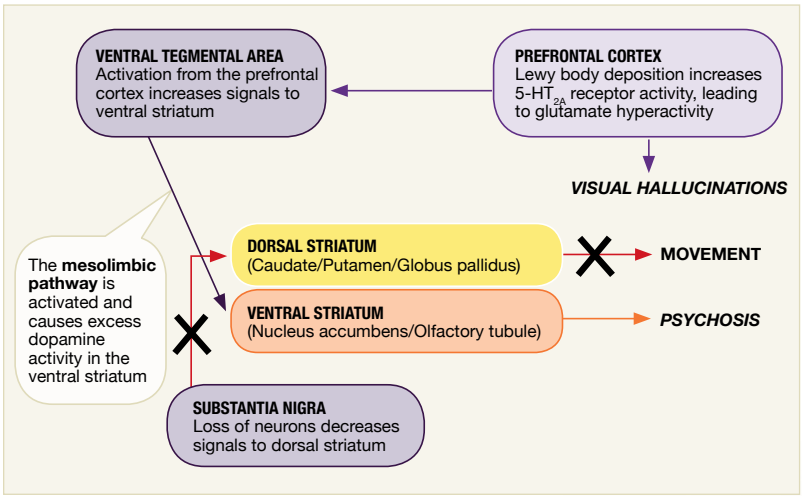

Figure 2. Serotonin/Glutamate hypothesis as cause of Parkinson disease psychosis

Abbreviation: 5-HT_{2A}, 5-hydroxytryptamine 2A.

Figure courtesy of Marc E. Agronin, MD, based in part from information from Stahl[15]

For some patients, as their PD progresses and Lewy bodies accumulate in the cerebral cortex, neurons containing serotonin receptors degenerate. Through upregulation, the number of 5-hydroxytryptamine 2A (5-HT_{2A}) receptors increases in the remaining neurons. This upregulation of 5-HT_{2A} receptors might result in excessive receptor activation in the prefrontal and visual/temporal cortex areas. Along with an increase in raphe serotonin levels, the upregulation also causes visual hallucinations. Upregulation of 5-HT_{2A} receptors in the prefrontal cortex also hypothetically leads to downstream changes in areas of the brain that regulate dopamine release in the ventral striatum. This enhanced dopamine release can lead to delusions and auditory hallucinations.

A careful patient history that begins with open-ended questions can help determine which of the 2 pathways could be contributing to the PDP. The history might also help identify secondary sources that are contributing to or are the main cause of the psychosis.

MANAGEMENT STRATEGIES FOR SYMPTOMS OF PSYCHOSIS

Treatment of PDP should be done using a series of sequential steps, with a multidisciplinary reassessment of both motor and psychotic symptoms after each trial period. A careful evaluation to assess for potential secondary causes should be done first **(Table 2)**.[7,9,12,16,17] This is followed by adjustment of the doses or, in some cases, discontinuation or switching of medications used to treat nonmotor symptoms of PD, if advisable, and, finally, treatment with an antipsychotic agent if none of the aforementioned interventions resolves symptoms.

Nonpharmacologic approaches for managing PDP involve coping strategies and environmental modifications. Teaching patients how to use coping strategies to manage their response

to hallucinations might help improve their reaction to the hallucinations. Strategies include the following[5]:

- Visual techniques, such as taking time to better focus on the hallucinatory object or focusing on a different object
- Cognitive techniques, such as turning on a light to better focus on the objects around them, consciously noting that the hallucinatory object is not real, or self-reassurance that the object is not real
- Interactive techniques with family or caregivers to gain comfort and reassurance that the hallucinatory object is not real

Environmental modifications and social interaction might also help. Removing triggers from the person's surroundings and installing bright lights or nightlights might help the person better identify the surrounding objects and reduce the potential for confusion or misidentification of objects.[20]

Another good practice for treating PDP is to review all medications a patient is taking, specifically looking for any psychoactive medications, such as anticholinergics, opioids, or benzodiazepines. These agents should be reduced to their minimum effective dose or, if possible, discontinued.[21] If PDP symptoms persist after making these changes, then careful reductions in medications used to treat motor symptoms of PD should be tried next.[22] However, reducing the dosage of dopaminergic medications is a balancing act and at some point will likely result in worsening motor function.

There is no set algorithm to follow when reducing or discontinuing PD medications and no strong evidence to support reducing or removing one drug over another. Removing amantadine is generally accepted as the starting point.[21] This can be followed by adjustments to monoamine oxidase B inhibitors and then to dopamine agonists. Because catechol-*O*-methyltransferase inhibitors do not work directly in the brain, discontinuing this class of drug is not likely to improve psychosis. For this reason, removing catechol-*O*-methyltransferase inhibitors is not done until all other medications have been removed. Changes to levodopa dosing generally occur after ***all*** other medication adjustments have been made. No matter the order in which medications are reduced or discontinued, adjustments should be done slowly and systematically, taking into consideration the individual patient's symptoms. If these initial treatment approaches fail to improve psychosis symptoms, then adding an antipsychotic medication should be considered.[22]

CASE 1: ASSESSMENT AND MANAGEMENT OF MILD PARKINSON DISEASE PSYCHOSIS

From the Files of Marc E. Agronin, MD

An 80-year-old man with a 3-year history of PD was being managed with levodopa to treat his mild motor symptoms. During a routine visit to his neurologist, he said he thought his wife was having an affair. He had occasionally "seen" a strange man in his house who, he believed, was his wife's new lover. He also reported feeling the "presence" of other people in the house who, he also believed, were helping the man have the affair with his wife and hide it from him.

Upon further questioning, the patient reported not sleeping well and having to get up to use the bathroom multiple times at night. His wife, who provided most of his care, said that she started giving him an over-the-counter (OTC) sleeping pill approximately 3 to 4 weeks ago to try to improve his sleep.

Discussion

All the following should be considered when evaluating the cause of this patient's concern about the affair:

1. His wife is having an affair
2. Side effects of levodopa
3. Anticholinergic activity of the sleeping pill
4. Urinary tract infection (UTI)
5. PDP

Case Continuation

The patient's laboratory tests confirmed a UTI, and an antibiotic was prescribed to treat it. Discontinuation of the OTC sleeping pill and decreasing the patient's levodopa dose slightly was recommended. Several nonpharmacologic strategies, including coping mechanisms and environmental modifications, were also recommended.

When the patient returned 2 weeks later, his psychosis had improved, but his motor symptoms had slightly worsened. His son reported that redirecting the patient when he started having hallucinations seemed to be helping. The patient still felt that his wife was having an affair, although he seemed to be less angry about it in the presence of his family. When his family left the room, however, he reported he was going to ask his wife for a divorce.

Discussion

Treating the patient's UTI; discontinuing the OTC sleeping pill, which might have contained diphenhydramine and would have resulted in both antihistaminic and anticholinergic AEs; and teaching the family how to use coping strategies with the patient could all help treat his probable PDP. Reducing the levodopa dosage has the benefit of improving psychosis, but can be associated with worsening motor symptoms. Thus, when planning to reduce medications that treat PD, the patient and family should be warned about the potential for worsening motor function.

Yet even when all nonpharmacologic approaches for treating PDP are used effectively, patients might still require more aggressive treatment. For this reason, treatment must be tailored to the individual patient. For this specific patient who still experiences psychotic delusions after receiving all initial treatment options, treatment will likely need to be escalated to include an antipsychotic agent.

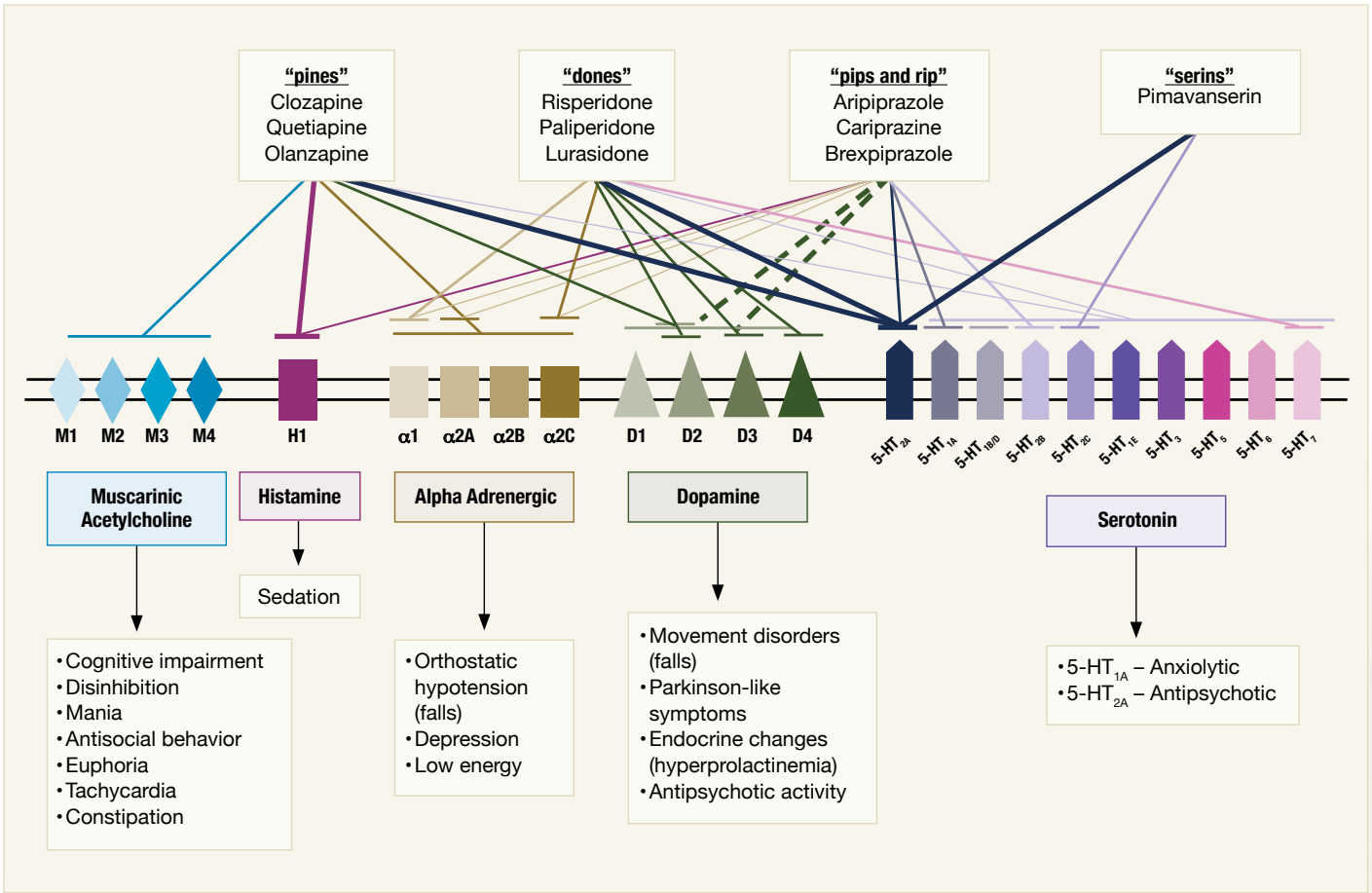

Figure 3. Relative receptor binding affinity and physiologic effects of various antipsychotics.[2,23,24] Relative strength of antagonist activity for each receptor type is indicated by the thickness of the line. The dashed line indicates partial antagonism.

Abbreviation: 5-HT, 5-hydroxytryptamine.

RELATIONSHIP BETWEEN RECEPTOR-BINDING CHARACTERISTICS OF ANTIPSYCHOTICS AND ADVERSE EVENTS

So-called "conventional" antipsychotic agents developed in the 1950s worked primarily because they blocked dopamine receptors.[2] However, blocking dopamine receptors to treat PDP is problematic because doing so can worsen motor symptoms. Newer "atypical" serotonin/dopamine-antagonizing antipsychotics, although effective, tend to block multiple receptors, which can lead to a number of distinct AEs, ranging from minor tolerability problems to life-threatening AEs. When selecting agents to treat PDP, all these factors must be considered and carefully balanced to provide patients with a safe and effective treatment.

Antipsychotic agents are not site specific and so can act on histamine, muscarinic acetylcholine, alpha-adrenergic, serotonin, and dopamine receptors, leading to both wanted (ie, antipsychotic effects) and unwanted effects (ie, AEs).[2] But receptor binding is only part of what needs to be considered when selecting an antipsychotic. The degree of receptor binding, length of time the drug binds to the receptor, pharmacokinetics of the drug, and an individual's ability to metabolize the drug (pharmacogenomics) also play a role in how a drug affects an individual person.

An awareness of a drug's receptor activity can help predict both the efficacy of a drug and its associated AEs. **Figure 3** shows antipsychotic receptor-binding activities and physiologic effects associated with blocking each type of receptor.[2,23,24]

A common feature of atypical antipsychotics used to treat PDP is their antagonist activity against 5-HT_{2A} receptors, which occurs with varying degrees, depending on the drug **(Figure 3).**[2,23,24] However, many of these drugs also bind to the dopamine D2 receptor, which can lead to worsening of PD symptoms. The "pines" (eg, asenapine, clozapine, olanzapine, and quetiapine) tend to have a higher binding affinity for the 5-HT_{2A} receptor than for the D2 receptor.[2] In particular, clozapine and quetiapine have a higher binding affinity for some subtypes of 5-HT_{2A} than for D2 receptors. The "dones" (risperidone, paliperidone, and lurasidone) bind to 5-HT_{2A} with varying degrees, but, compared with the other dones, risperidone has a higher affinity for 5-HT_{2A} than for D2. Of the 2 "pips" and the "rip" (aripiprazole,

brexpiprazole, and cariprazine), aripiprazole binds to the 5-HT_{2A} receptor, but it has a higher binding affinity for the D2 receptor. The only antipsychotic agent to bind to the 5-HT_{2A} receptor without meaningful D2 activity is the "serin" drug pimavanserin.

A better understanding of the AEs of antipsychotic drugs can be developed when all the receptors an antipsychotic agent binds to are taken into consideration. Only the pines (eg, clozapine, quetiapine, and olanzapine) have an affinity for muscarinic receptors, whereas all other antipsychotics essentially have no binding affinity for muscarinic receptors.[2] These same pines also have a higher affinity for histamine than for dopamine receptors. All atypical antipsychotics have at least a moderate binding affinity for alpha-adrenergic receptors; the most potent in relation to their D2 binding are clozapine, quetiapine, and risperidone. These differences in receptor-binding affinities can explain the differences in the AEs patients experience with the various drugs.

Understanding a drug's level of binding affinity for the 5-HT_{2A} and D2 receptors can allow treatment to be tailored, depending on whether a serotonin or a dopamine effect is needed. From a pharmacokinetic and pharmacologic perspective, this information can be used when a drug change is needed because of tolerability problems or a lack of effectiveness. In such circumstances, an agent from another class with a different dopamine/serotonin binding profile would be warranted.

Practical Tip: *Using the receptor-binding information for antipsychotic drugs can be clinically useful. For example, a patient who has known hypotension or who has a high fall risk should avoid drugs with a higher binding affinity for the alpha-adrenergic receptor, which is associated with hypotension and potential falls. Therefore, it would be ideal to avoid clozapine, quetiapine, and risperidone. These same drugs should also be avoided if a patient is complaining of excessive daytime somnolence.* ***– Dana Saffel, PharmD***

Not only does the degree of receptor blocking determine the AE profile, but so does the length of time the drug interacts with the receptor. There is also a close relationship between a drug's half-life and the length of time it binds to the receptor. An example of how this works clinically can be seen with quetiapine, which has a large dose range. At low doses (50 mg), this drug has a hypnotic effect and predominantly binds to the histamine receptors.[2] At middle-of-the-range doses (300 mg), it functions as an antidepressant, with more selective binding patterns mostly affecting dopamine and serotonin receptors. At higher doses (800 mg), quetiapine can be used as an antipsychotic and has a wide binding profile, interacting with most of the neurotransmitter receptor types. Despite this wide binding profile, quetiapine is well tolerated because it interacts with the receptors for only a short time.

ANTIPSYCHOTICS USED FOR THE TREATMENT OF PARKINSON DISEASE PSYCHOSIS

A meta-analysis performed in 2015 by Jethwa and colleagues evaluated the effectiveness of clozapine, olanzapine, quetiapine (all used off label), and pimavanserin (US Food and Drug Administration approved) for treating PDP.[25] The analysis found clozapine and pimavanserin to be the only promising treatments for PDP, consistent with the recommendations made in the 2019 International Parkinson and Movement Disorder Society update on treatments for nonmotor symptoms of PD.[26] Neither quetiapine nor olanzapine was found to be effective for treating PDP.[25,26]

Clozapine

Clozapine has been shown to be effective for treating PDP without significantly affecting movement in 2 randomized controlled trials (RCTs).[27,28] The first trial conducted by Pollak and colleagues included 60 patients with drug-induced psychosis and PD.[27] Of the 32 patients who received clozapine, 25 had complete resolution of their delusions and hallucinations using a mean dose of 35.8 mg/d, although 19 patients had symptom relapse within 1 month of discontinuing treatment with clozapine. In the second trial conducted by the Parkinson Study Group, 60 patients with drug-induced psychosis and PD receiving a mean dose of 24.7 mg/d of clozapine experienced clinically significant improvements in all measures studied compared with placebo.[28] Overall, 3% of patients taking clozapine had to withdraw from clinical trials because of leukopenia/neutropenia. Therefore, patients taking this drug require close blood and physical monitoring.[25] Other reported AEs included somnolence, orthostatic hypotension, worsening of PD, and respiratory infections.[27,28]

Practical Tip: *Anticholinergic AEs associated with clozapine are less prominent at low doses (ie, < 50 mg/d) used to treat PDP. This allows clozapine to be safely used in geriatric patients, who are frequently the ones treated for PDP.*
– George T. Grossberg, MD

Pimavanserin

The novel selective 5-HT_{2A} inverse agonist pimavanserin has no meaningful dopaminergic affinity,[23] and was studied in 1 RCT included in the 2015 meta-analysis by Jethwa and colleagues.[25] This RCT reported a ≥ 20% improvement in the PD-adapted scale for assessment of positive symptoms in 63% of 95 patients receiving pimavanserin compared with 47% of 90 patients receiving placebo over a 6-week course.[29] Improvement in PDP symptoms occurred without a significant effect on movement. A follow-up review by Jethwa and colleagues in 2017 included trials of both pimavanserin and clozapine and confirmed the efficacy of pimavanserin for PDP according to individual study parameters.[30] A second RCT evaluating a 28-day treatment course of pimavanserin showed a trend toward improvement

in delusions and hallucinations.[31] The most common reason for pimavanserin study withdrawal was sedation and lack of efficacy.[30]

A recent retrospective real-world review of 17 patients with PDP, including 1 with Lewy body dementia, found pimavanserin was effective as both monotherapy and adjuvant therapy with dopamine receptor blockers for moderate-to-severe disease.[32] A total of 64.7% of participants reported improvement in their psychotic symptoms. Pimavanserin also facilitated a reduction or cessation of dopamine receptor blockers in this study. A second retrospective real-world review included 40 patients with visual hallucinations (44%), 49 patients with visual hallucinations and concomitant delusions (54%), and 2 patients with delusions only (2%).[33] Of the 91 patients treated with pimavanserin, 76% reported clinical improvement. An interesting finding of this study was that of the 18 patients who failed treatment, only 9 improved with subsequent antipsychotic treatment. Adverse events were reported in 20 patients, with worsening gait instability being the most common. Other known AEs associated with pimavanserin are peripheral edema and confusional state; most patients, however, tolerate the drug well.[25,33,34]

Quetiapine and Olanzapine

Jethwa and colleagues included data from 3 clinical trials studying quetiapine and did not find a significant improvement in psychosis symptoms.[25] However, significant levels of data heterogeneity were present among the studies and the overall effect size did not reach statistical significance. In the first study, Shotbolt and colleagues reported that quetiapine failed to significantly improve psychosis symptoms in 24 patients over a 12-week course.[35] In the second study, Fernandez and colleagues evaluated quetiapine in 8 of 16 patients with PDP and found improvements in visual hallucinations, without a significant effect on motor symptoms.[36] In the third study, conducted by Rabey and colleagues, patients were randomized to receive quetiapine (n = 30) or placebo (n = 28) and were followed for 3 months.[37] No significant treatment benefit was found for quetiapine. Withdrawal rates for all 3 studies were high, which could affect the reported results. The most common AE reported in these studies was drowsiness.[35-37] Other AEs were loss of balance/increase in parkinsonism, orthostatic hypotension, and headache.

One important finding from the olanzapine studies included in the meta-analysis was its association with an increased risk of parkinsonism and cerebrovascular accidents, prompting Jethwa and colleagues to recommend its use with caution.[25] Bear in mind, though, that cerebrovascular accidents are not associated solely with olanzapine because all atypical antipsychotics have an US Food and Drug Administration black box warning that highlights the risk of stroke and mortality in elderly patients with comorbid dementia.[30]

Table 3. Movement Disorder Society 2019 Updated Evidence-Based Medicine Review Designations for Antipsychotics for Parkinson Disease Psychosis[26]

Drug	Efficacy	Safety	Practice Implications
Clozapine*	Efficacious	Acceptable risk with specialized monitoring	Clinically useful
Olanzapine*	Not efficacious	Unacceptable risk	Not useful
Quetiapine*	Insufficient evidence	Acceptable risk without specialized monitoring	Possibly useful
Pimavanserin	Efficacious	Acceptable risk without specialized monitoring	Clinically useful

* Used off label for Parkinson disease psychosis

Reprinted from *Movement Disorders,* Seppi K, Ray Chadhuri K, Coelho M, et al, Update on treatments for nonmotor symptoms of Parkinson's disease—an evidence-based medicine review, 180-198, Copyright 2019, with permission from John Wiley and Sons.

Similar to the findings of Jethwa and colleagues, the 2019 Movement Disorder Society update on treatments for nonmotor symptoms of PD identified both clozapine and pimavanserin as being efficacious for treating PDP **(Table 3)**.[26] Quetiapine was found to have insufficient high-quality evidence to evaluate its role in treating PDP, and was therefore deemed "possibly useful" in clinical practice. Olanzapine was deemed "not useful".

Practical Tip: *There is no single antipsychotic treatment that universally works for PDP. Each drug has some percentage of patients who discontinue the drug because of a lack of efficacy. Selecting an antipsychotic for PDP sometimes involves a trial-and-error approach.* ***– Marc E. Agronin, MD***

Because no single antipsychotic drug works in every person experiencing PDP, choosing a drug can be challenging. The AE profile for each drug might help in selecting an agent, depending on the comorbidities or PD symptoms a particular patient experiences. For example, drugs associated with heavy sedation should be avoided in patients complaining of somnolence. The opposite would be true if a patient was complaining of insomnia.

Another useful tool to use when selecting a drug for the elderly population is the American Geriatrics Society (AGS) Beers Criteria, which offer valuable guidelines that identify medications that should be avoided in older adults.[38] In general, the Beers Criteria recommend avoiding all antipsychotic drugs in people with PD. However, an exception to this recommendation is made for clozapine, quetiapine, and pimavanserin, all 3 of which can be used safely to treat PDP in the elderly. Both pimavanserin and clozapine appear to be the least likely

antipsychotic drugs to precipitate worsening of PD. As for quetiapine, AGS indicates it has been studied only in low-quality clinical trials, with limited efficacy in most of the trials.

Both pimavanserin and clozapine appear to be the least likely antipsychotic drugs to precipitate worsening of PD. As for quetiapine, AGS indicates it has been studied only in low-quality clinical trials, with limited efficacy in most of the trials. ***– Dana Saffel, PharmD***

CASE 2: PATIENT WITH SEVERE PARKINSON DISEASE PSYCHOSIS

From the Files of Pratap Chand, MD, FRCP

A 73-year-old man with PD diagnosed in 2007 had been taking multiple PD medications to control his symptoms. He experienced motor fluctuations and shortness of breath between doses when the medication effects began to wear off, and severe, disabling dyskinesia when his medications were effective. He had occasional vivid hallucinations that began in 2009 and rapid eye movement sleep behavior disorder with dream reenactments. In 2015, he successfully underwent bilateral staged subthalamic nucleus deep brain stimulation and underwent sequential programming of the deep brain stimulator over several months.

His pretreatment medications included the following:

- Carbidopa/Levodopa 25/100 mg 2 tabs 4 times per day
- Entacapone 200 mg 4 times per day
- Ropinirole sustained release 4 mg per day
- Amantadine 100 mg twice a day
- Rasagiline 1 mg per day

Following deep brain stimulation treatment, the patient's dopaminergic medication dosages were reduced considerably and he was eventually treated with only carbidopa/levodopa. His PD symptoms stabilized and he no longer experienced wearing-off symptoms or dyskinesia. His visual hallucinations worsened, however, and he was convinced his wife was conniving with strangers to harm him. He also believed his wife was trying to poison him, and he refused to eat any food or take any medications she gave him. As his symptoms worsened, he began to wander off and was unable to find his way home.

The severity of the patient's hallucinations slowly increased, and in 2016 he was hospitalized for treatment. On admission, his physical examination and laboratory evaluation were normal, and a review of his medications found none that could be contributing to his hallucinations. He was diagnosed with PDP and prescribed pimavanserin, but the drug was unavailable at the facility. Instead, he was started on quetiapine 25 mg twice a day. The patient's symptoms improved with quetiapine, and he was discharged home with a prescription for that drug, although the plan was to switch him to pimavanserin 34 mg/d once he filled the prescription through his mail-in pharmacy. When the pimavanserin arrived, the patient began taking it in conjunction with quetiapine, which was cross-tapered for 2 weeks. After 2 weeks, quetiapine was reduced to once per day and then discontinued a week later. After 3 months, his hallucinations and delusions completely resolved with pimavanserin alone.

Practical Tip: *When switching a patient from 1 antipsychotic drug to another, it is important to cross-taper the 2 drugs for a short period and then to gradually reduce the dose of the drug that is being discontinued.* ***– Pratap Chand, MD, FRCP***

Practical Tip: *Pimavanserin has a long half-life and autotapers to a therapeutic level, so it is appropriate to start at the therapeutic dose of 34 mg. Similarly, if pimavanserin needs to be discontinued, it is appropriate to stop the drug without tapering.* ***– Dana Saffel, PharmD***

SUMMARY

PDP affects up to 60% of patients with PD and is a leading cause of morbidity and mortality in this patient population.[1] Originally, the cause of PDP was thought to be secondary to use of dopaminergic agents,[1] but new evidence shows that drug-naïve patients can present with PDP prior to onset of PD motor symptoms, indicating a more complex pathophysiology for this disease.[8] Although early detection and treatment of PDP is key to lessening the burden for both patients and caregivers, treating PDP is often challenging and frequently a balancing act of optimizing treatment of motor symptoms vs that of psychosis symptoms. Using both nonpharmacologic and pharmacologic treatments can help effectively treat psychosis symptoms. When antipsychotic agents are needed, an understanding of their safety and efficacy in relation to their individual receptor-binding characteristics can aid in management decisions and in minimizing AEs. The Beers Criteria also provide guidance for reducing the likelihood of AEs associated with medication use in elderly patients.[38]

Progress in treating PDP is under way, and the addition of pimavanserin to clinicians' armamentarium can help minimize the AEs associated with treating PDP while simultaneously allowing patients to maintain their motor function. As a better understanding of PDP develops and as new treatments become available, quality of life for patients with PDP and their caregivers will continue to improve.

FOR INSTANT PROCESSING, COMPLETE THE CME/CE POST TEST ONLINE AT https://tinyurl.com/QoLinPDP

REFERENCES

1. Goldman JG, Vaughan CL, Goetz CG. An update expert opinion on management and research strategies in Parkinson's disease psychosis. *Expert Opin Pharmacother.* 2011;12(13):2009-2024.
2. Stahl SM. Antipsychotic agents. In: *Stahl's Essential Psychopharmacology: Neuroscientific Basis and Practical Applications.* 4th ed. Cambridge, UK: Cambridge University Press; 2013.
3. Goetz CG, Fan W, Leurgans S, Bernard B, Stebbins GT. The malignant course of "benign hallucinations" in Parkinson disease. *Arch Neurol.* 2006;63(5):713-716.
4. Fénelon G. Psychosis in Parkinson's disease: phenomenology, frequency, risk factors, and current understanding of pathophysiologic mechanisms. *CNS Spectr.* 2008;13(3)(suppl 4):18-25.
5. Diederich NJ, Pieri V, Goetz CG. Coping strategies for visual hallucinations in Parkinson's disease. *Mov Disord.* 2003;18(7):831-832.
6. Chaudhuri KR, Prieto-Jurcynska C, Naidu Y, et al. The nondeclaration of nonmotor symptoms of Parkinson's disease to health care professionals: an international study using the nonmotor symptoms questionnaire. *Mov Disord.* 2010;25(6):704-709.
7. Zahodne LB, Fernandez HH. Pathophysiology and treatment of psychosis in Parkinson's disease: a review. *Drugs Aging.* 2008;25(8):665-682.
8. Pagonabarraga J, Martinez-Horta S, Fernández de Bobadilla R, et al. Minor hallucinations occur in drug-naive Parkinson's disease patients, even from the premotor phase. *Mov Disord.* 2016;31(1):45-52.
9. Ravina B, Marder K, Fernandez HH, et al. Diagnostic criteria for psychosis in Parkinson's disease: report of an NINDS, NIMH work group. *Mov Disord.* 2007;22(8):1061-1068.
10. Schrag A, Hovris A, Morley D, Quinn N, Jahanshahi M. Caregiver-burden in Parkinson's disease is closely associated with psychiatric symptoms, falls, and disability. *Parkinsonism Relat Disord.* 2006;12(1):35-41.
11. Klein C, Prokhorov T, Miniovitz A, Dobronevsky E, Rabey JM. Admission of Parkinsonian patients to a neurological ward in a community hospital. *J Neural Transm (Vienna).* 2009;116(11):1509-1512.
12. Chang A, Fox SH. Psychosis in Parkinson's disease: epidemiology, pathophysiology, and management. *Drugs.* 2016;76(11):1093-1118.
13. Lee AH, Weintraub D. Psychosis in Parkinson's disease without dementia: common and comorbid with other non-motor symptoms. *Mov Disord.* 2012;27(7):858-863.
14. de la Riva P, Smith K, Xie SX, Weintraub D. Course of psychiatric symptoms and global cognition in early Parkinson disease. *Neurology.* 2014;83(12):1096-1103.
15. Stahl SM. Parkinson's disease psychosis as a serotonin-dopamine imbalance syndrome. *CNS Spectr.* 2016;21(5):355-359.
16. Fénelon G, Soulas T, Zenasni F, Cleret de Langavant L. The changing face of Parkinson's disease-associated psychosis: a cross-sectional study based on the new NINDS-NIMH criteria. *Mov Disord.* 2010;25(6):763-766.
17. Vaughan CL, Goldman JG. Psychosis and Parkinson's disease. In: Frucht SJ, ed. *Movement Disorder Emergencies: Diagnosis and Treatment.* 2nd ed. New York, NY: Humana Press; 2013:75-92.
18. Merims D, Shabtai H, Korczyn AD, Peretz C, Weizman N, Giladi N. Antiparkinsonian medication is not a risk factor for the development of hallucinations in Parkinson's disease. *J Neural Transm (Vienna).* 2004;111(10-11):1447-1453.
19. Zahodne LB, Fernandez HH. Parkinson's psychosis. *Curr Treat Options Neurol.* 2010;12(3):200-211.
20. Ballard C, Brown R, Fossey J, et al. Brief psychosocial therapy for the treatment of agitation in Alzheimer disease (the CALM-AD trial). *Am J Geriatr Psychiatry.* 2009;17(9):726-733.
21. Friedman JH. Parkinson disease psychosis: update. *Behav Neurol.* 2013;27(4):469-477.
22. Goldman JG, Holden S. Treatment of psychosis and dementia in Parkinson's disease. *Curr Treat Options Neurol.* 2014;16(3):281.
23. Hacksell U, Burstein ES, McFarland K, Mills RG, Williams H. On the discovery and development of pimavanserin: a novel drug candidate for Parkinson's psychosis. *Neurochem Res.* 2014;39(10):2008-2017.
24. Moller MD. Side effects of antipsychotic medications: understanding the variables. Medscape Web site. https://www.medscape.org/viewarticle/703934. Accessed June 5, 2019.
25. Jethwa KD, Onalaja OA. Antipsychotics for the management of psychosis in Parkinson's disease: systematic review and meta-analysis. *BJPsych Open.* 2015;1(1):27-33.
26. Seppi K, Ray Chaudhuri K, Coelho M, et al; and the collaborators of the Parkinson's Disease Update on Non-Motor Symptoms Study Group on behalf of the Movement Disorders Society Evidence-Based Medicine Committee. Update on treatments for nonmotor symptoms of Parkinson's disease—an evidence-based medicine review. *Mov Disord.* 2019;34(2):180-198.
27. Pollak P, Tison F, Rascol O, et al. Clozapine in drug induced psychosis in Parkinson's disease: a randomised, placebo controlled study with open follow up. *J Neurol Neurosurg Psychiatry.* 2004;75(5):689-695.
28. Parkinson Study Group. Low-dose clozapine for the treatment of drug-induced psychosis in Parkinson's disease. *N Engl J Med.* 1999;340(10):757-763.
29. Cummings J, Isaacson S, Mills R, et al. Pimavanserin for patients with Parkinson's disease psychosis: a randomised, placebo-controlled phase 3 trial. *Lancet.* 2014;383(9916):533-540.
30. Jethwa KD. Antipsychotics for the management of Parkinson's disease psychosis. *Int J Geriatr Psychiatry.* 2017;32(4):464-465.
31. Meltzer HY, Mills R, Revell S, et al. Pimavanserin, a serotonin(2A) receptor inverse agonist, for the treatment of Parkinson's disease psychosis. *Neuropsychopharmacology.* 2010;35(4):881-892.
32. Mahajan A, Bulica B, Ahmad A, et al. Pimavanserin use in a movement disorders clinic: a single-center experience. *Neurol Sci.* 2018;39(10):1767-1771.
33. Sellers J, Darby RR, Farooque A, Claassen DO. Pimavanserin for psychosis in Parkinson's disease-related disorders: a retrospective chart review. *Drugs Aging.* 2019; 36(7):647-653.
34. NUPLAZID [package insert]. San Diego, CA: ACADIA Pharmaceuticals Inc; 2018.
35. Shotbolt P, Samuel M, Fox C, David AS. A randomized controlled trial of quetiapine for psychosis in Parkinson's disease. *Neuropsychiatr Dis Treat.* 2009;5:327-332.
36. Fernandez HH, Okun MS, Rodriguez RL, et al. Quetiapine improves visual hallucinations in Parkinson disease but not through normalization of sleep architecture: results from a double-blind clinical-polysomnography study. *Int J Neurosci.* 2009;119(12):2196-2205.
37. Rabey JM, Prokhorov T, Miniovitz A, Dobronevsky E, Klein C. Effect of quetiapine in psychotic Parkinson's disease patients: a double-blind labeled study of 3 months' duration. *Mov Disord.* 2007;22(3):313-318.
38. 2019 American Geriatrics Society Beers Criteria® Update Expert Panel. American Geriatrics Society 2019 updated AGS Beers Critera® for potentially inappropriate medication use in older adults. *J Am Geriatr Soc.* 2019;67(4):674-694.

INSTANT CME/CE CERTIFICATE AVAILABLE WITH ONLINE TESTING AND COURSE EVALUATION AT https://tinyurl.com/QoLinPDP

CME/CE POST TEST QUESTIONS

To obtain CME/CE credit for this activity, complete the CME/CE Post Test and course evaluation online at **https://tinyurl.com/QoLinPDP.** Upon successful completion of the post test and evaluation, you will be able to generate an instant certificate of credit.

See detailed instructions under **To Obtain CME/CE Credit** on page 2.

1. Which of the following is true regarding the pathophysiology of PDP?
   a. PDP is dependent on duration of exposure to dopaminergic drugs and is generally seen in patients who have had the disease for at least 10 years
   b. PDP is a serotonin/dopamine imbalance that develops through exposure to dopaminergic agents
   c. PDP can develop independently from dopaminergic drug exposure and can therefore develop earlier in the disease course than previously thought
   d. PDP occurs through decreased dopamine activity in the cerebral cortex caused by downregulation of 5-HT_{2A} receptors

2. A 76-year-old woman with PD reports seeing frightening people several times a day who, she believes, are trying to attack her. She is currently taking levodopa/carbidopa to treat her PD. After taking a thorough history, which is the best first step in treating this patient?
   a. Assess for potential secondary causes of her hallucinations
   b. Recommend coping strategies to help reduce her fear when she "sees" the frightening people
   c. Evaluate her environment to identify potential changes that could reduce her hallucinations
   d. Reduce her dose of levodopa/carbidopa

3. An 81-year-old man with a history of PDP requires treatment with an antipsychotic. He has a history of falls and was treated for a wrist fracture last year after a particularly bad fall. When considering the neurotransmitter receptor interactions of each of the antipsychotics, which class of drugs should be avoided in this patient to reduce his fall risk?
   a. Pines (clozapine, quetiapine, olanzapine)
   b. Dones (risperidone, paliperidone, lurasidone)
   c. Pips and rips (aripiprazole, brexpiprazole, cariprazine)
   d. None of the antipsychotics will increase his fall risk

4. A 74-year-old man with a history of PDP requires treatment with an antipsychotic. His wife is concerned that adding a new medication might worsen his excessive daytime sleepiness, and she is requesting a medication that will not make him tired. When considering the side-effect profile of each of the antipsychotics used to treat PDP, which is the LEAST likely to worsen this symptom?
   a. Clozapine
   b. Quetiapine
   c. Pimavanserin
   d. Risperidone

5. Which of the following clinical features of PD have been associated with the most significant effect on caregiver quality of life?
   a. Motor fluctuations and involuntary movements
   b. Confusion, hallucinations, and falls
   c. Depression and forgetfulness
   d. Bladder problems and depression

6. A 76-year-old man with a 10-year history of PD and a 2-year history of visual hallucinations and paranoid ideation has recently been admitted to a long-term care facility. He reports seeing "suspicious-looking" men sneaking past his window a few times a week and worries that they are going to rob him. He is taking the lowest effective dose of levodopa/carbidopa. What is the best next step for managing this patient's symptoms?
   a. Observation only
   b. Prescribe an antipsychotic
   c. Reduce his carbidopa/levodopa dose
   d. Order a urinalysis

7. According to recent real-world studies, patients with PDP treated with pimavanserin have an approximate ____ chance of improvement in their symptoms.
   a. 20% to 30%
   b. 40% to 50%
   c. 60% to 70%
   d. 80% to 90%

8. Which of the following antipsychotics is the most likely to cause sedation and orthostatic hypotension owing to action on the histaminic and adrenergic receptors?
   a. Quetiapine
   b. Pimavanserin
   c. Aripiprazole
   d. Risperidone

9. Increased _____ signaling in the _____ and _____ is theorized to cause visual hallucinations and other symptoms of psychosis in PDP, respectively.
   a. Serotonin, prefrontal cortex, ventral striatum
   b. Dopamine, prefrontal cortex, ventral striatum
   c. Serotonin, ventral striatum, ventral tegmental area
   d. Dopamine, ventral striatum, ventral tegmental area

10. A 78-year-old woman with PD reported seeing terrifying dogs several times a day that she believes are trying to attack her. After ruling out secondary causes, including non-PD medications, her carbidopa/levodopa dose was reduced. She suffered a subsequent fall, with injury, as a result of worsening gait instability. Which of the following is the LEAST appropriate treatment for this patient's PDP, given the risk of orthostatic hypotension?
    a. Clozapine
    b. Risperidone
    c. Pimavanserin
    d. Aripiprazole