Update on the Management of Parkinson’s Disease: Focus on Psychosis

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Activity Description
Parkinson's disease psychosis (PDP) is a common neuropsychiatric manifestation of Parkinson's disease, presenting a significant burden on patients and care providers alike. Successful management of PDP necessitates awareness of its clinical presentation and risk factors as well as the pharmacology, safety, and efficacy data pertaining to treatment options. Management of patients with PDP in long-term care facilities can be particularly challenging, requiring familiarity with the current regulatory landscape of pharmacologic treatment for psychiatric symptoms. To help provide pharmacists with the knowledge necessary to deliver informed treatment recommendations for patients with PDP, a panel of experts was convened to develop a review encompassing the latest clinical data and expert opinion pertaining to treatment options. This review also explores the rationale supporting these different options, advancements in the understanding of the epidemiology and clinical presentation of PDP, and the current regulatory environment pertaining to antipsychotic use.

Learning Objectives
Upon completion of this educational activity, the learner should be able to:
• Compare the clinical features of PDP and the intrinsic and extrinsic risk factors for its development
• Review optimal management strategies for residents with PDP
• Evaluate the pharmacology, safety, and efficacy data of different pharmacologic treatment options for PDP

This CPE activity will include discussion of off-label use.

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Update on the Management of Parkinson's Disease: Focus on Psychosis

Introduction
More than half of patients with Parkinson's disease (PD) will experience psychotic symptoms during the course of their disease. The burden of Parkinson's disease psychosis (PDP) on patients and care providers can be quite profound, sometimes exceeding that imposed by the motor symptoms that are classically associated with PD. In fact, PDP has been established as a primary reason or predictor for hospitalization, admission to long-term residential care (LTC) facilities, and increased mortality. When patients with PDP are admitted to LTC facilities, their associated disruptive behaviors can have a significant effect on LTC personnel and other LTC residents. Balancing control of the motor and psychiatric symptoms of PD has been referred to as the "motion-emotion" conundrum, and historically has been challenging because of a paucity of evidence-based strategies.

However, there have been advancements in the understanding of the complex etiology of PDP, leading to new therapeutic approaches that may improve management of patients presenting in a variety of clinical settings.

Pharmacists are in a unique position along the continuum of care to provide support for patients with PDP by synthesizing information on PDP pathophysiology and clinical presentation and addressing pharmacologic challenges, such as drug-drug interactions and treatment side effects. Pharmacists are also able to make recommendations regarding appropriate antipsychotic use in a climate in which knowledge of safety and efficacy of different pharmacologic treatment options and regulatory considerations is of vital importance. The purpose of this article is to provide pharmacists with the knowledge necessary to deliver evidence-based treatment recommendations for patients with PDP. This review will encompass the latest clinical trial data pertaining to different treatment options, the "pharmacologic rationale" supporting these different options, advancements in the understanding of the epidemiology and clinical presentation of PDP, and the current regulatory landscape of antipsychotic use.

Epidemiology and Clinical Presentation
Prevalence estimates for PDP vary substantially, and as many as 60% of patients with PD will experience psychotic symptoms lasting at least one month during the course of their disease. The National Institute of Mental Health and the National Institute of Neurological Disorders and Stroke sponsored a workshop on PDP and published provisional diagnostic criteria in 2007. The standardized criteria include "presence" hallucinations and illusions, which are not part of the description of other psychotic disorders.

It is important for pharmacists to recognize the clinical spectrum of psychotic symptoms that may affect patients with PD, which range from illusions to hallucinations to delusional behavior (Table 1). Approximately one-third of patients who have received chronic dopaminergic therapy experience visual hallucinations. Hallucinations tend to be progressive in nature, with initial development typically occurring in the context of a clear sensorium and retained patient insight. However, this insight often dissipates as the disease progresses, with deteriorating thought disorder and potential emergence of delusions. Although hallucinations may not be upsetting to patients initially, psychotic symptoms should not be ignored or left unmanaged. In one study of patients with PD who were experiencing hallucinations, almost 96% of the patients progressed from benign hallucinations (thought disorder score of 2, with retained insight) to a state in which insight was lost (score of 3) or delusions occurred (score of 4), in a median time of < 2 years (range, 2 months to < 3 years). Approximately 5% to 10% of patients with PD may ultimately experience delusions during the course of their disease.

PDP exhibits characteristic features that may help to distinguish it from psychotic symptoms associated with other conditions, such as delirium, schizophrenia, bipolar disorder, and psychotic depression (Table 2). Early identification of PDP may help facilitate its timely management.

PDP is generally a manifestation of well-established PD; however, recent research suggests that psychosis may appear much earlier in the course of PD, with minor hallucinations possibly occurring prior to the onset of motor symptoms.

Risk Factors or Correlates
Multiple risk factors or correlates for PDP have been identified, including patient age, severity and duration of underlying PD, cognitive impairment, and dementia. Comorbid psychiatric problems, such as depression or anxiety; sleep disorders, such as rapid eye movement sleep behavior disorder; and visual impairment have also been linked to the emergence of PDP.

A family history of dementia and the presence of axial parkinsonism have been associated with the development of psychotic behaviors. With respect to pharmacologic interventions, medications used to treat underlying PD (dopaminergic and nondopaminergic) and polypharmacy with psychoactive drugs, including antidepressants, anxiolytics, and/or hypnotics, have also been associated with the emergence of PDP.

Etiology
The exact etiology of PDP has not been identified. Different models for the etiology of PDP involve neurotransmitter, structural, functional, or metabolic brain abnormalities, as well as changes in visual processing pathways and sleep disorders. The complexity of PDP etiology is apparent from a number of recent studies.

Multiple drug classes, such as catechol-O-methyltransferase inhibitors, dopamine agonists, levodopa, and monoamine oxidase inhibitors, have been associated with psychotic behavior. Although the emergence of PDP is often associated with the use of chronic dopaminergic therapy, several studies indicate that dopaminergic therapy is not the sole cause for the emergence of PDP.

Processes involving different neurotransmitters (dopamine, serotonin, and acetylcholine) have all been implicated in the development of PDP. Hypersensitivity of mesocortical and mesolimbic dopamine receptors may kindle psychotic behavior.
Table 1. Proposed Diagnostic Criteria for Parkinson’s Disease Psychosis

<table>
<thead>
<tr>
<th>Criteria (Presence of One or More of the Following)</th>
<th>Description and Detail</th>
<th>Examples</th>
</tr>
</thead>
<tbody>
<tr>
<td>Illusions</td>
<td>Misperception of actual objects</td>
<td>Seeing inanimate objects as living beings – a chair mistaken for a dog, a bedpost mistaken for a tree</td>
</tr>
<tr>
<td>False sense of presence</td>
<td>Perception of person or other entity close by</td>
<td>Feeling like there is someone standing by one’s side – a patient’s report of a “guardian angel” standing nearby</td>
</tr>
<tr>
<td>Hallucinations</td>
<td>Simple or complex; may occur in different domains</td>
<td>Simple: Passage hallucinations: catching a glimpse or sensing that a dog, cat, or person is passing sideways Complex: Seeing children playing; small, furry animals scurrying; or distorted, bizarre figures Hearing indistinguishable sounds or music of various types Feeling of being touched by someone Smelling pleasant or unpleasant odors</td>
</tr>
<tr>
<td>Delusions</td>
<td>Fixed, false beliefs</td>
<td>Common delusions: Jealousy or spousal infidelity Paranoia Stealing Abandonment Misidentification syndromes: specific type of delusion; occurs frequently in patients who also have dementia Capgras syndrome: patient thinks that his/her recognizable spouse is an imposter Fregoli syndrome: patient believes that familiar people are, often malevolently, disguised as strangers</td>
</tr>
<tr>
<td>Duration</td>
<td>Symptoms are recurrent or continuous for ≥ 1 month</td>
<td></td>
</tr>
<tr>
<td>Exclusion of other sources of symptoms</td>
<td>Symptoms should not be better accounted for by other sources, such as dementia with Lewy bodies, schizophrenia, schizoaffective disorder, mood disorder with psychotic features, delusional disorder, or delirium</td>
<td></td>
</tr>
<tr>
<td>Associated features</td>
<td>• With/without dementia • With/without insight • With/without specific treatment for Parkinson’s disease</td>
<td></td>
</tr>
</tbody>
</table>


Source: References 5, 8.

Table 2. Clinical Features of Psychosis in Parkinson’s Disease Psychosis and Other Conditions

<table>
<thead>
<tr>
<th>Clinical Feature</th>
<th>Parkinson’s Disease Psychosis</th>
<th>Psychotic Symptoms Secondary to Other Conditions</th>
</tr>
</thead>
<tbody>
<tr>
<td>Hallucinations</td>
<td>• Primarily visual in nature</td>
<td>• Patients with delirium typically do not possess a clear sensorium</td>
</tr>
<tr>
<td></td>
<td>• May occur in multiple modalities (i.e., visual, auditory, tactile, olfactory, and gustatory)</td>
<td>• More likely to be auditory for patients with schizophrenia or schizoaffective disorder as well as more threatening and specific in nature</td>
</tr>
<tr>
<td></td>
<td>• May initially present in patients with a clear sensorium</td>
<td></td>
</tr>
<tr>
<td></td>
<td>• Auditory hallucinations are typically vague and nonthreatening (e.g., hearing music or whispering)</td>
<td></td>
</tr>
<tr>
<td>Delusions</td>
<td>• Commonly paranoid in nature (spousal infidelity, stealing, abandonment)</td>
<td>Delusions of grandiosity are more common in patients with bipolar disorder than in patients with PDP</td>
</tr>
<tr>
<td></td>
<td>• Commonly focused and systematized</td>
<td></td>
</tr>
<tr>
<td>Nihilism/self-deprecation</td>
<td>Lower incidence</td>
<td>Higher incidence for patients with psychotic depression</td>
</tr>
<tr>
<td>Time course</td>
<td>Chronic</td>
<td>More acute onset than PDP</td>
</tr>
</tbody>
</table>

Source: References 8, 12-15.
and several studies have implicated the role of the serotoninergic system in the development of PDP. One such study, conducted by Ballanger and colleagues, involved the use of positron emission tomography brain imaging. This study demonstrated that serotonin (5-hydroxytryptamine [5-HT]) receptors may govern the emergence of visual hallucinations through increased binding (i.e., increased serotoninergic activity) in the ventral visual pathway. An autopsy study using autoradiographic binding to define 5-HT1A receptors found increased binding in the inferolateral temporal cortex of patients with PD and hallucinations compared with patients with PD who had no hallucinations.

**Medical Management of Parkinson’s Disease Psychosis**

Published approaches to the management of patients with PDP suggest beginning by establishing the diagnosis of PDP and ruling out non–PD-related sources of psychotic behavior. Pharmacologic management should include a review of current medications and consider a reduction of the medications that may be contributing to the psychotic symptoms. If additional measures are needed, the use of medications to control psychotic symptoms may be considered (Figure 1).

**Initial Management Approaches**

As an initial step in the management of patients with PD who have psychotic symptoms, Olanow and colleagues have recommended ruling out non–PD-related sources of psychotic behavior. These include comorbid illnesses, metabolic abnormalities, medication toxicity, sensory deprivation, infection, and the presence of structural lesions. Indeed, infection and electrolyte imbalance may create a state of delirium, which may present with hallucinations or delusions.

The differential for PDP also includes various forms of dementia (including dementia with Lewy bodies and PD dementia; please see Similarities Between Dementia With Lewy Bodies and Parkinson's Disease Dementia), as well as primary psychiatric conditions, such as psychotic depression, schizophrenia, and schizoaffective disorder.

**Nonpharmacologic Measures**

Nonpharmacologic approaches may be helpful in the management of patients with PDP, particularly if the symptoms are mild. Use of illumination (nightlight) to help patients establish boundaries of a room may help with the management of hallucinations that occur in dim light or during evening hours. Coaching patients to use visual techniques, such as focusing more intently on objects or looking in a direction away from the hallucination, may be helpful. Cognitive techniques, such as discussing hallucinations with family members and care providers, have also been employed.

Brief psychosocial therapy (BPST) may also be appropriate for patients with mild-to-moderate psychotic behavioral symptoms. It is meant to be used with the family and should be individually tailored to the needs of the patient (e.g., BPST may consist of short daily sessions focused on social interaction, personalized music, or removal of environmental triggers). The viability of this strategy was initially validated in CALM-AD (Trial of a Cholinesterase Inhibitor and Atypical Neuroleptic in the Management of Agitation in Alzheimer’s Disease), in which patients with Alzheimer’s disease and clinically significant agitation received four weeks of BPST prior to pharmacotherapy randomization. In this study, 43% of patients achieved a 30% improvement in their level of agitation.
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Figure 1. Authors’ Suggested Management Approach for Symptoms of Psychosis in a Patient With Parkinson’s Disease

<table>
<thead>
<tr>
<th>Management Approach</th>
<th>Examples</th>
</tr>
</thead>
<tbody>
<tr>
<td>Identify and characterize the symptoms of psychosis in patients with PD</td>
<td>Content, duration, frequency, recurrence, severity, and type of delusions and/or hallucinations</td>
</tr>
<tr>
<td>Rule out and treat delirium and other medical or sensory causes of psychosis</td>
<td>Address dehydration, dementia, dim lighting, electrolyte abnormalities, medication toxidrome, pain, sundowning, and sensory deficits</td>
</tr>
<tr>
<td>When possible, discontinue or reduce possible offending non-PD agents</td>
<td></td>
</tr>
<tr>
<td>No</td>
<td>Yes</td>
</tr>
<tr>
<td>Continue current management and reassess</td>
<td>Discontinue or reduce dose of PD drugs</td>
</tr>
<tr>
<td>No</td>
<td>Yes</td>
</tr>
<tr>
<td>Continue current management and reassess</td>
<td>Determine diagnosis of PDP*</td>
</tr>
<tr>
<td>No</td>
<td>Yes</td>
</tr>
<tr>
<td>Implement nonpharmacologic brief psychosocial therapy adapted for PD</td>
<td></td>
</tr>
<tr>
<td>No</td>
<td>Yes</td>
</tr>
<tr>
<td>Consider initiation of clozapine†, pimavanserin‡, or quetiapine§</td>
<td></td>
</tr>
</tbody>
</table>

Abbreviations: COMT = Catechol-O-methyltransferase, PD = Parkinson’s disease, PDP = Parkinson’s disease psychosis.
* Based on provisional National Institute of Mental Health and National Institute of Neurological Disorders and Stroke diagnostic criteria.
† Clozapine is indicated for treatment-resistant schizophrenia and reducing suicidal behavior in patients with schizophrenia or schizoaffective disorder. It is not indicated for PDP. There is a need for specialized monitoring with the use of clozapine. Please see the package insert for further information regarding safety risks.
‡ Pimavanserin is indicated by the FDA for the treatment of hallucinations and delusions associated with PDP. Pimavanserin should be avoided in patients who use drugs that increase the QT interval and in patients with risk factors for prolonged QT interval. Please see the package insert for further information regarding safety risks.
§ Quetiapine is indicated for the treatment of schizophrenia, manic episodes associated with bipolar I disorder, and depressive episodes associated with bipolar disorder. It is not indicated for PDP. Please see the package insert for further information regarding safety risks.

Pharmacologic Management

If the aforementioned measures are insufficient to provide adequate control of psychotic symptoms, then use of antipsychotic therapy should be considered (Figure 1). In LTC facilities, residents with PDP often have comorbid dementia, and black box warnings exist for the use of either typical or atypical antipsychotics in elderly patients with dementia.33 The risk of mortality specifically for patients with PD has been further reinforced by a retrospective matched-cohort study conducted by Weintraub and colleagues.34 This study showed that the use of an antipsychotic by patients with PD was associated with a risk of death that was more than twice that of patients who did not use antipsychotics (intent-to-treat hazard ratio, 2.35; 95% confidence interval, 2.08-2.66; P < .001).35 The risk associated with typical antipsychotic use was greater than the risk associated with atypical antipsychotics (intent-to-treat hazard ratio, 1.54; 95% confidence interval, 1.24-1.91; P < .001).35 Other antipsychotic risks include (but are not limited to) orthostatic hypotension, somnolence, and an increased risk of falls.35 Awareness of these treatment risks, along with treatment acquisition costs, the risks of untreated psychosis, and the evidence supporting different treatment options, should be incorporated into treatment decisions.34,35

Clozapine. Clozapine is an atypical antipsychotic used off-label for the treatment of PDP. Clozapine is an antagonist for multiple receptor types, including 5-HT2A, and, to a lesser extent, dopamine D2.6 In the 2006 American Academy of Neurology practice parameter, clozapine was given level B evidence (requiring at least one class I study or two consistent class II studies) of efficacy for the management of PDP.37 The Movement Disorder Society Evidence-Based Medicine Review in 2011 further supported the designation of clozapine as effective in the treatment of PDP.31 Clozapine is associated with a relatively low risk of exacerbation of motor symptoms.35 This is a result of the preferential binding of clozapine to 5-HT2A, to 5-HT2C, receptors, with less affinity for D2 receptors than many other antipsychotic drugs historically used in the treatment of PDP (Table 3).13,36
**Table 3. Receptor Selectivity of Antipsychotic Drugs Used in the Treatment of Parkinson’s Disease Psychosis**

<table>
<thead>
<tr>
<th>Receptor Class</th>
<th>Clozapine</th>
<th>Haloperidol</th>
<th>Olanzapine</th>
<th>Pimavanserin</th>
<th>Quetiapine</th>
<th>Risperidone</th>
</tr>
</thead>
<tbody>
<tr>
<td>Serotonin</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>5-HT\textsubscript{2A}</td>
<td>7</td>
<td>50</td>
<td>2.5</td>
<td>0.4</td>
<td>250</td>
<td>0.2</td>
</tr>
<tr>
<td>5-HT\textsubscript{2B}</td>
<td>40</td>
<td>NR</td>
<td>80</td>
<td>NR</td>
<td>1100</td>
<td>12</td>
</tr>
<tr>
<td>5-HT\textsubscript{2C}</td>
<td>40</td>
<td>NR</td>
<td>80</td>
<td>16</td>
<td>NR</td>
<td>100</td>
</tr>
<tr>
<td>5-HT\textsubscript{1A}</td>
<td>NR</td>
<td>NR</td>
<td>NR</td>
<td>NR</td>
<td>NR</td>
<td>NR</td>
</tr>
<tr>
<td>Dopamine</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>D1</td>
<td>NR</td>
<td>100</td>
<td>100</td>
<td>NR</td>
<td>NP</td>
<td>60</td>
</tr>
<tr>
<td>D2</td>
<td>50</td>
<td>0.1</td>
<td>4</td>
<td>NR</td>
<td>30</td>
<td>0.5</td>
</tr>
<tr>
<td>D3</td>
<td>NR</td>
<td>0.2</td>
<td>25</td>
<td>NR</td>
<td>9</td>
<td>13</td>
</tr>
</tbody>
</table>

**Abbreviations:** HT = Hydroxytryptamine, NP = Not performed, NR = No response.

Data are dissociation equilibrium constant values in nanomoles. Smaller dissociation equilibrium constant values correspond with greater receptor-binding affinity.

**Source:** Reference 36.

Doses of clozapine used for PDP range from 6.25 to 50 mg orally per day, which are far lower than those used in the treatment of schizophrenia (300-900 mg daily).\textsuperscript{13,36} A notable adverse event associated with clozapine is a small (0.38%) but serious risk of development of agranulocytosis, necessitating regular monitoring of the absolute neutrophil count.\textsuperscript{38,39} Other potential side effects include orthostatic hypotension and sedation. Patients need to have their blood drawn on a weekly basis for the first six months of therapy, with the interval extending to every two weeks for the following six months, and extending to every month thereafter.\textsuperscript{40} This need for serial monitoring and safety concerns have been identified as barriers to clozapine use in nursing homes, despite the demonstrated clinical efficacy of clozapine.\textsuperscript{41} All prescribers and dispensers of clozapine must enroll in the Clozapine Risk Evaluation and Mitigation Strategy program.\textsuperscript{39} The initial Pre-Dispense Authorization was launched on May 20, 2016, and a full Pre-Dispense Authorization is scheduled to be launched later in 2016.

**Pimavanserin.** Pimavanserin is a novel 5-HT\textsubscript{2A} inverse agonist, and the first drug approved by the FDA for the treatment of PDP.\textsuperscript{42} It binds preferentially to the 5-HT\textsubscript{2A} receptor, and has low binding affinity to the 5-HT\textsubscript{2C} subtype (Table 3).\textsuperscript{36} Pimavanserin has no clinically relevant affinity for other receptors, including dopaminergic, adrenergic, muscarinic, or histaminergic receptors. Blockade of dopaminergic receptors, in particular, accounts for the parkinsonism side effects seen with many other antipsychotic therapies.\textsuperscript{36} As an inverse agonist, pimavanserin downregulates intrinsic activity at the 5-HT\textsubscript{2A} receptor (i.e., reduces serotoninergic activity) (Figure 2).

The approval of pimavanserin was largely based on the results of a six-week randomized, double-blind, placebo-controlled, phase 3 study by Cummings and colleagues in patients with PDP.\textsuperscript{26} The study included 199 patients randomized to either 40 mg of pimavanserin tartrate (equivalent to 34 mg of pimavanserin-free base) or placebo after a two-week period of BPST. Those patients who had a significant response to BPST were not included in the randomized medication phase of the study. In the placebo group, 36% of the patients used a cholinesterase inhibitor at baseline and throughout the course of the study, whereas 33% of the patients in the pimavanserin group used a cholinesterase inhibitor; 99% of both groups used dopaminergic drugs at baseline and throughout the course of the study.\textsuperscript{26} Patients who received pimavanserin had statistically significant improvements in PD-adapted Scale for the Assessment of Positive Symptoms (SAPS-PD) scores relative to placebo (−5.79 vs −2.73; \(P = .001\)), the primary end point for this study.\textsuperscript{26} An earlier study conducted by Voss and colleagues established 2.33 points as a clinically meaningful change for the SAPS-PD.\textsuperscript{43} Pimavanserin also demonstrated greater improvements in clinical global impression improvement (2.78 vs 3.45; \(P = .0011\)) and clinical global impression severity (−1.02 vs -0.44; \(P = .0007\)) scores relative to placebo.\textsuperscript{26} In addition, patients who received pimavanserin had statistically significant improvements in caregiver burden scores (\(P = .002\)) and sleep measures (nighttime sleep [\(P = .045\)] and daytime wakefulness [\(P = .012\)]).\textsuperscript{26} An FDA analysis of pimavanserin investigations found that the number needed to treat to achieve a greater than 50% reduction in...
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SAPS-PD scores was 11 for the Cummings study, whereas the number needed to harm was 100. A recent meta-analysis of randomized placebo-controlled trials has further supported the efficacy and tolerability of pimavanserin in the treatment of patients with PD.

Pimavanserin is categorized as an antipsychotic and thus has a black box warning similar to those issued for other antipsychotics regarding the elevated risk of mortality in elderly patients with dementia. Pimavanserin is usually initiated at 34 mg orally once daily, without the need for drug titration or adjustment of concomitant carbidopa/levodopa. Patients who take strong cytochrome P450 3A4 inhibitors, such as itraconazole, ketoconazole, clarithromycin, or indinavir, should take 17 mg instead of 34 mg. Pimavanserin should also be avoided in patients who have risk factors for prolonged QT interval or take medications that increase the QT interval.

Quetiapine. Another agent commonly used in clinical practice as an off-label treatment for PDP is quetiapine. Nearly two-thirds of patients with PD and psychosis who received antipsychotic treatment were treated with quetiapine in a large Veterans Affairs study published by Weintraub and colleagues in 2011. It is similar in structure to clozapine, and, as with clozapine, there is less potential to exacerbate parkinsonism relative to the potential of typical antipsychotics. Quetiapine functions as an antagonist at multiple neurotransmitter receptors, including 5-HT2A, as well as a partial agonist at 5-HT1A. Although quetiapine has demonstrated comparable efficacy to clozapine in comparator studies, placebo-controlled studies assessing its efficacy in the treatment of PDP have yielded inconsistent results, and the American Academy of Neurology practice parameter has deemed quetiapine as having level C evidence: “insufficient evidence, acceptable safety risk without need for specialized monitoring, but investigational practice implications.” Quetiapine dosing for patients with PDP typically begins with 12.5 mg orally every night, and is gradually increased to a range of 50 to 150 mg at night.

Other Antipsychotic Therapies. Most other antipsychotics should not be used in the treatment of PDP. Many typical and atypical antipsychotics block dopamine D2 receptors, which are the targets of dopamine replacement therapy, resulting in worsening parkinsonism. Olanzapine carries a substantial risk of exacerbating parkinsonism, and is considered unlikely to be efficacious in the treatment of PDP. Aripiprazole and risperidone have also been studied as a means of treating PD, but these medications have been linked to worsening parkinsonism.

Cholinesterase Inhibitors. Previous clinical investigations have assessed the role of cholinesterase inhibitors, such as rivastigmine and donepezil, in the treatment of PDP although these have been smaller studies and open-label trials. No large, randomized, placebo-controlled trials assessing the role of cholinesterase inhibitors in the treatment of PDP have been conducted.

A planned subanalysis from the EXPRESS (Exelon in Parkinson’s Disease Dementia Study) group evaluated the role of rivastigmine in the treatment of dementia associated with PD for both hallucinating and nonhallucinating patients. Patients with hallucinations had a greater improvement in cognitive scores compared with placebo (change in Alzheimer’s Disease Assessment Scale–Cognitive Subscale: 4.27; P = .002) than nonhallucinating patients (change in Alzheimer’s Disease Assessment Scale cognitive subscale: 2.09; P = .015). Neuropsychiatric Inventory-10 scores also showed greater improvements (rivastigmine vs placebo) in hallucinating patients than in nonhallucinating patients. For other neuropsychiatric symptoms, rivastigmine appeared to provide the greatest benefits on agitation/aggression (P < .05), delusions, hallucinations, depression/dysphoria, anxiety, and apathy/indifference in the visual hallucinating subgroup.

Regulatory Environment and Clinical Implications for Antipsychotic Use in Long-Term Care

Pharmacists involved in the care of patients with PDP need to be cognizant of the current regulatory environment governing the use of antipsychotics. In 2012, the Centers for Medicare & Medicaid Services launched the National Initiative to Improve Dementia Care, focusing on “appropriate care and use of antipsychotic medications for nursing home patients.” This initiative takes a multifaceted approach to improve the care of persons with dementia through actions, such as increased enforcement of existing regulations (namely, F329 and F309), education, and public reporting of quality measures.


✓ “Within the first year in which a resident is admitted on an antipsychotic medication or after the facility has initiated an antipsychotic medication, the facility must attempt a GDR in two separate quarters (with at least one month between the attempts), unless clinically contraindicated. After the first year, a GDR must be attempted annually, unless clinically contraindicated.

✓ For any individual who is receiving an antipsychotic medication to treat behavioral symptoms related to dementia, the GDR may be considered clinically contraindicated if:
  • The resident’s target symptoms returned or worsened after the most recent attempt at a GDR within the facility; and
  • The physician has documented the clinical rationale for why any additional attempted dose reduction at that time would be likely to impair the resident’s function or increase distressed behavior.

Pharmacists will need to ensure ongoing monitoring of all antipsychotics, including pimavanserin. Special considerations
need to be given to the dosing as well as duration of therapy in light of the underlying etiology.

**Multidisciplinary Communication**

It is important for pharmacists to communicate regularly with other members of the care team when developing treatment plans for patients with PDP. Patients who need to make the transition from independent living to placement in LTC facilities may face additional scrutiny and possible discontinuation of pharmacologic therapies that have been effective in controlling PDP. Hallucinations may recur when patients are subject to discontinuation of atypical antipsychotic therapy, and psychotic symptoms may “rebound” to levels that are worse than pretreatment levels. Educating nursing facility clinicians and staff on the safety and efficacy of different pharmacologic options for patients with PDP is important to optimize outcomes.

**Conclusions**

Given the complex nature of PDP, pharmacists need to possess an understanding of the iatrogenic and disease-related factors that can lead to its emergence. Awareness of the clinical features of PDP may help facilitate timely evaluation and treatment. Multiple neurotransmitters, such as dopamine, serotonin, and acetylcholine, may be involved in the development of PDP, and clinicians face a difficult challenge controlling psychotic manifestations while preserving management of motor symptoms. Conventional treatment has relied on a reduction of medications used to treat the motor symptoms of PD or off-label use of antipsychotic agents indicated for other psychiatric disorders. PDP is clinically different from these disorders, with a complex etiology that may involve both iatrogenic and disease-related components. Clinical evidence supports the idea that treatments that have a less pronounced effect on dopamine receptors and target primarily serotonin receptors, including some atypical antipsychotics, may help clinicians preserve the balance between motor and nonmotor symptoms. The approval of pimavanserin, the first drug labeled for use in PDP, provides a new treatment option, with a mechanism of action that is relevant to the complex etiology of PDP. Pharmacologic acquisition costs, the need for monitoring, and individual patient characteristics and histories are all elements that need to be assessed prior to the selection of therapy. Pharmacists, particularly those practicing in the LTC setting, can help tailor treatments to individual patients, reducing polypharmacy when appropriate.
Clinical Note

References


CME Post-Test Questions Worksheet

1. Which test needs to be performed regularly as part of the Risk Evaluation and Mitigation Strategy program for prescription of clozapine?
   A. Absolute neutrophil count
   B. Complete blood count
   C. Blood urea nitrogen and creatinine
   D. Aspartate transaminase/alanine transaminase

2. Pimavanserin is an inverse agonist with a high affinity for ___________ receptors.
   A. D1
   B. D2
   C. H1
   D. 5-HT2A

3. Which of the following statements regarding hallucinations in PDP is true?
   A. They are primarily auditory in nature at the onset of PDP
   B. They are frequently specific and threatening in nature
   C. They may present in the context of a clear sensorium
   D. They occur in only 1 sensory modality

4. When considering a reduction of medications used in the treatment of PD as a means of addressing psychotic behavior, which medication has been recommended to be reduced LAST?
   A. Catechol-O-methyltransferase inhibitors
   B. Levodopa
   C. Amantadine
   D. Trihexyphenidyl

5. Which of the following is NOT a risk factor or correlate for PDP?
   A. Use of dopaminergic therapy
   B. Duration of underlying PD
   C. Severity of underlying PD
   D. These are all risk factors or correlates for the emergence of PDP

6. According to the American Academy of Neurology practice parameter, the grade of evidence supporting the consideration of quetiapine in the treatment of PDP is level _____.
   A. A
   B. B
   C. C
   D. U

7. The use of typical antipsychotics is usually associated with worsening of motor symptoms because of their antagonist activity at _______ receptors.
   A. D2
   B. H1
   C. 5-HT2A
   D. 5-HT2C

8. Which of the following is necessary to forego a gradual dose reduction of antipsychotic therapy for patients in nursing homes?
   A. Physician documentation of clinical rationale for avoiding additional attempts in reduction
   B. Return or worsening of target symptoms following a discontinuation attempt
   C. A and B
   D. Use of atypical antipsychotic therapy

9. Which of the following nonpharmacologic therapy choices has been used in the treatment of visual hallucinations associated with PDP?
   A. Turning on the lights in dimly lit environments
   B. Discussing hallucinations with family members and care providers
   C. Looking away from the hallucination
   D. All the above

10. Which group of antipsychotics has been associated with a low risk of exacerbating motor symptoms in patients with PD?
    A. Aripiprazole, clozapine, haloperidol
    B. Clozapine, pimavanserin, quetiapine
    C. Pimavanserin, quetiapine, olanzapine
    D. Aripiprazole, haloperidol, quetiapine

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### Evaluation Worksheet

**Please rate the overall activity:**

1. The topic met my needs (relevant to practice, right level of content, timely).  
   - Strongly agree  
   - Agree  
   - Disagree  
   - Strongly disagree

2. The authors were knowledgeable of the subject matter.  
   - Strongly agree  
   - Agree  
   - Disagree  
   - Strongly disagree

3. The teaching/learning methods were effective.  
   - Strongly agree  
   - Agree  
   - Disagree  
   - Strongly disagree

4. The quality of educational materials met expectations.  
   - Strongly agree  
   - Agree  
   - Disagree  
   - Strongly disagree

5. The activity was objective, balanced, and free of commercial bias.  
   - Strongly agree  
   - Agree  
   - Disagree  
   - Strongly disagree

If not, please describe ____________________________________________________________

6. Please rate the extent to which you agree/disagree that the activity supported the achievement of each learning objective.

<table>
<thead>
<tr>
<th>Learning Objective</th>
<th>Strongly agree</th>
<th>Agree</th>
<th>Disagree</th>
<th>Strongly disagree</th>
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</thead>
<tbody>
<tr>
<td>Compare the clinical features of PDP and the intrinsic and extrinsic risk factors for its development</td>
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<td>○</td>
<td>○</td>
<td>○</td>
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<tr>
<td>Review optimal management strategies for residents with PDP</td>
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<td>○</td>
<td>○</td>
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<tr>
<td>Evaluate the pharmacology, safety, and efficacy data of different pharmacologic treatment options for PDP</td>
<td>○</td>
<td>○</td>
<td>○</td>
<td>○</td>
</tr>
</tbody>
</table>

7. Were the post-test questions relevant to this CPE activity?  
   - Strongly agree  
   - Agree  
   - Disagree  
   - Strongly disagree

**About you:**

8. How many patients with PD do you see in a typical week?  
   - Less than 5  
   - 5 to 15  
   - 16 to 25  
   - 26 to 35  
   - 36 to 45  
   - More than 45

9. How many patients with PDP do you see in a typical week?  
   - 1 or less  
   - 2 to 5  
   - 6 to 10  
   - 11 to 15  
   - 16 to 20  
   - More than 20
Evaluation Worksheet (continued)

For each of the following, please consider your knowledge of the topics covered before participating in the activity and then rate your current knowledge:

<table>
<thead>
<tr>
<th></th>
<th>Improved</th>
<th>Somewhat improved</th>
<th>About the same</th>
<th>Somewhat worse</th>
<th>Worse</th>
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<tr>
<td>10. The safety and efficacy of pharmacologic treatment options for PDP</td>
<td>O</td>
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<td>11. The mechanisms of action of each of the therapies used for PDP</td>
<td>O</td>
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<th></th>
<th>More often</th>
<th>Somewhat more often</th>
<th>About the same</th>
<th>Less than before</th>
<th>I need more information to make a change</th>
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<tr>
<td>12. Compared to before, I would now consider recommending pharmacologic treatment changes for residents with PDP:</td>
<td>O</td>
<td>O</td>
<td>O</td>
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</tr>
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</table>

13. Do you intend to make any other changes to your practice based on what was learned?

If yes, what would those changes be? ____________________________________________________________

14. Are there any other comments about the learning methods you would like to share with the faculty (pre-tests, post-tests, interactive learning activities and quizzes within the course, cases, etc)? ____________________________________________________________

15. Any other comments? (suggestions for speakers, future activity topics, etc) ____________________________________________________________

16. How long did it take for you to complete this activity?
   Round up to the nearest half hour.

<table>
<thead>
<tr>
<th></th>
<th>Less than 30 minutes</th>
<th>Less than 1 hour</th>
<th>Less than 1.5 hours</th>
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