Long-Term Care Updates

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New Drug Review: Pimavanserin for Parkinson's Disease Psychosis
By Lindsay Slowiczek, PharmD

Background & Epidemiology

Over 1 million people in the United States are diagnosed with Parkinson’s disease (PD), a number which is expected to almost double by the year 2030.¹,² Historically, research and treatment efforts have focused primarily on the motor symptoms of PD. Recently, however, the treatment of non-motor symptoms has become an important topic of research, as greater than 50% of patients with PD will develop Parkinson’s disease psychosis (PDP) within their lifetime.³ PDP is part of the spectrum of neuropsychiatric disorders associated with PD and is characterized by hallucinations, of which the most common are visual but may also take the form of auditory, olfactory, or gustatory. Patients may also experience delusions, which are often paranoid thoughts pertaining to spousal infidelity or intent of harm by unidentified people.⁴ The National Institute of Neurological Diseases and Stroke and the National Institute of Mental Health jointly unified the diagnostic criteria of PDP to include the presence of at least one psychotic symptom occurring after the onset and diagnosis of PD, which is either recurrent or lasting at least 1 month. The differential diagnosis must also exclude other causes of psychosis, such as dementia with Lewy bodies, delirium due to an alternative medical condition, and other ongoing psychiatric conditions.⁵ This article will discuss the hypothesized pathophysiology of PDP, summarize current treatment guidelines and recommendations, and provide prescribing information for pimavanserin, a newly approved drug for the treatment of PDP.

Pathophysiology

There are multiple risk factors that may be associated with the development of PDP, including pharmacological or genetic causes, comorbidities, and disease-related etiologies. Clinical and post-mortem research in the past decade has shown that visual hallucinations are associated with increased numbers of serotonin 5-HT2A receptors in visual processing centers in the neocortex. Studies have also found increased binding of 5-HT2A receptors in PD. The pathophysiology of delusions in PD patients is unknown, but they are less common and are often considered a deterioration of hallucinations.⁶ It is hypothesized that this serotonergic imbalance is partially responsible for the cognitive alterations and hallucinations experienced by patients with PDP.⁶,⁷

Current Guidelines & Therapy Options

In 2006, the American Academy of Neurology (AAN) issued clinical practice guidance related to depression, psychosis, and dementia in Parkinson disease, including treatment recommendations for non-motor symptoms experienced by PD patients. Based on the results of 4 small studies evaluating psychosis medications, AAN recommends that clozapine should be considered as a “likely effective” treatment option, and quetiapine may also be considered as “possibly effective”. Olanzapine should not be considered according to AAN guidelines based on trials demonstrating no significant benefit in psychotic symptoms but worsened motor function. The authors called for further research into treatment options for PDP due to clozapine’s potential for increased mortality and rare, but possible agranulocytosis, as well as a lack of evidence for efficacy of atypical antipsychotics without dopaminergic blocking effects.⁸

In 2010, the American Medical Directors Association (AMDA) published clinical practice guidelines on the management of Parkinson’s disease. These guidelines include clozapine 6.25-12.5 mg QHS to 25 mg BID or quetiapine 25 mg QHS to 200 mg daily as options for treatment of hallucinations and delusions in this population, although specific treatment recommendations are not made.⁹
In their Guide to the Management of Psychotic Disorders and Neuropsychiatric Symptoms of Dementia in Older Adults (2011), the American Geriatrics Society states that quetiapine 12.5-75 mg/day, olanzapine 2.5-5 mg/day, or clozapine 12.5-75 mg/day may be helpful in treating hallucinations associated with Parkinson’s disease. Patients receiving clozapine require regular CBC counts due to the risk of agranulocytosis.\(^\text{10}\)

The American Geriatrics Society 2015 Updated Beers Criteria for Potentially Inappropriate Medication Use in Older Adults provides a strong recommendation to avoid the use of first- and second-generation antipsychotics, except in the case of schizophrenia, bipolar disorder, or short-term use as an antiemetic during chemotherapy, citing an increased risk of cerebrovascular accident and greater rate of cognitive decline and mortality in dementia patients as the rationale. However, their use may be considered for behavioral problems of dementia or delirium after nonpharmacological options have failed or if they are not possible and if the patient is threatening harm to themselves or others. The Beers Criteria also includes a strong recommendation, based on moderate quality evidence, against the use of antipsychotics in patients with a history of falls. Antipsychotics should be used with caution in all geriatric patients as they have the potential to cause or exacerbate syndrome of inappropriate antidiuretic hormone secretion or hyponatremia. This is a strong recommendation based on moderate quality evidence. Finally, the Beers Criteria also strongly recommend against the use of all antipsychotics (except aripiprazole, clozapine, and quetiapine) for the treatment of Parkinson’s disease, due to their potential to worsen parkinsonian symptoms via dopamine-receptor antagonism.\(^\text{11}\)

**Pimavanserin Clinical Trials**

In a 6-week clinical trial of 199 patients, pimavanserin was found to be superior to placebo for improving hallucinations and delusions related to PD, as well as improving daytime wakefulness, nighttime sleep quality, and caregiver burden, without impairment of motor function.\(^\text{12}\) A smaller, 4 week placebo-controlled study was not powered to detect a statistically significant difference in psychosis symptoms, but did find an improvement in hallucinations and delusions compared to placebo.\(^\text{13}\) The adverse reactions most commonly leading to discontinuation in the trials were hallucinations, urinary tract infections, and fatigue. There was no treatment-related motor impairment reported in these studies.\(^\text{12,13}\) As a newly approved drug in 2016, pimavanserin was not addressed at the time of the aforementioned guidelines’ publications and its potential placement on the Beer’s List remains to be determined.

**Indication, Pharmacology, & Dosing**

Based on the results of these clinical trials, pimavanserin was granted breakthrough therapy designation for the treatment of hallucinations and delusions associated with PDP and is the first drug approved for this indication.\(^\text{14,15}\) Pimavanserin’s antipsychotic effects are mediated through both inverse agonist and antagonist activity at 5-HT2A receptors, with additional, lesser activity at 5-HT2C receptors. It has no appreciable affinity to 5-HT2B, dopaminergic, histaminic, muscarinic, or adrenergic receptors and no affinity for calcium channels.\(^\text{16}\) While classified as an atypical antipsychotic, it does not antagonize dopamine receptors and has not shown to worsen parkinsonian symptoms in clinical trials, due to its unique mechanism of action.\(^\text{12}\)

Pimavanserin is administered as two 17 mg tablets for a dose of 34 mg orally once daily, with or without food. The drug is 95% plasma protein bound and metabolism occurs primarily via CYP3A4, CYP3A5, and to a lesser extent CYP2J2 and CYP2D6. The median half-life of the parent drug is 57 hours and the major active metabolite’s half-life is approximately 200 hours. There is no dosage adjustment necessary for mild to moderate renal impairment (CrCl ≥30mL/min). However, the drug was not studied in patients with CrCl <30mL/min so use is not recommended in this population. Pimavanserin is also not recommended for use in patients with any degree of hepatic impairment, as it was not studied in this population. Dosage decrease to 17 mg once daily is recommended if taken concomitantly with a strong CYP3A4 inhibitor and careful monitoring for reduced efficacy is required for patients taking a strong CYP3A4 inducer with pimavanserin (see Table 1).\(^\text{14,16}\)
Table 1. Potential Drug Interactions with Pimavanserin

<table>
<thead>
<tr>
<th>Interacting Drug</th>
<th>Effect of Interaction</th>
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<tbody>
<tr>
<td><strong>QT Interval Prolonging Drugs</strong> (e.g. antipsychotics, certain antibiotics, certain antidepressants, Class IA and Class 3 antiarrhythmic agents)</td>
<td>Administration of pimavanserin with other agents that are known to prolong the QT interval can have an additive effect on the QT interval and increase the risk for fatal arrhythmias. Concomitant use should be avoided.</td>
</tr>
<tr>
<td><strong>Strong CYP3A4 Inhibitors</strong> (e.g. clarithromycin, indinavir, ketoconazole)</td>
<td>Concomitant use of pimavanserin with a strong CYP3A4 inhibitor increases pimavanserin exposure. The manufacturer recommends decreasing the dose of pimavanserin to 17 mg orally once daily if co-administered with a strong CYP3A4 inhibitor.</td>
</tr>
<tr>
<td><strong>Strong CYP3A4 Inducers</strong> (e.g. carbamazepine, phenytoin, rifampin, St. John’s wort)</td>
<td>Concomitant use of pimavanserin with a strong CYP3A4 inducer may reduce pimavanserin exposure and potentially decrease efficacy. Monitor for reduced efficacy. A possible dosage increase may be necessary.</td>
</tr>
</tbody>
</table>

**Black Box Warning, Warnings/Precautions & Adverse Effects**

A black box warning for pimavanserin states that there is increased mortality in elderly patients with dementia-related psychosis who are treated with antipsychotic drugs. Antipsychotic drugs as a class have been shown to increase the all-cause risk of death in this patient population, with a risk of death in drug-treated patients of 1.6- to 1.7-times that in placebo-treated patients. Causes of death vary, but many are cardiovascular or infectious in nature.

Pimavanserin has also been shown to increase the QT interval and should be avoided in combination with other drugs known to prolong the QT interval, such as Class IA or Class 3 antiarrhythmic agents, certain antipsychotics (e.g. ziprasidone, chlorpromazine, thioridazine), and certain antibiotics (e.g. gatifloxacin, moxifloxacin), and patients with known QT prolongation (see Table 1). Pimavanserin should be avoided in patients with a history of cardiac arrhythmias or in other circumstances that may increase the risk of the occurrence of torsades de pointes and/or sudden death, including symptomatic bradycardia, hypokalemia or hypomagnesemia, and the presence of congenital prolongation of the QT interval.

In 6-week clinical trials for pimavanserin, the adverse reactions most commonly leading to discontinuation were hallucinations, urinary tract infection, and fatigue. Other commonly reported adverse reactions include confusional state, constipation, falls, gait disturbance, nausea, and peripheral edema.

**Summary & Place in Therapy**

Pimavanserin is the first atypical antipsychotic to receive FDA approval for the treatment of Parkinson’s disease psychosis. Its unique mechanism of action as a 5HT2A receptor antagonist and inverse agonist may be advantageous in treating Parkinson’s disease hallucinations and delusions without worsening motor symptoms, due to a lack of dopaminergic activity. Pimavanserin prolongs the QT interval and should be avoided in patients receiving other medications that prolong the QTc. Additionally, as an atypical antipsychotic, this drug carries the class-wide black box warning for increased mortality in elderly patients. Due to its recent FDA approval, pimavanserin is not recognized in current treatment guidelines, though it may be beneficial in patients who require management of Parkinson’s disease psychosis.
References


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