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Pimavanserin for Parkinson Disease Psychosis

To the Editor: Parkinson disease affects approximately 1 million Americans with approximately 60,000 people diagnosed annually.[1] Nearly $25 billion is spent each year to combat Parkinson disease.[1] This disorder is characterized by degeneration of dopaminergic neurons in the substantia nigra and manifests with motor and nonmotor symptoms.

Psychosis is a disabling component of the nonmotor manifestations, presenting in 50% of cases.[2] Associated with poor outcomes, psychosis worsens the prognosis in patients with Parkinson disease and often results in nursing home placement.[2]

Clinical Features. Parkinson disease psychosis (PDP) commonly manifests in people with advanced neuropathology.[3] Diagnosis of PDP mandates preexisting Parkinson disease and over 1 month of psychotic symptoms.[3] The commonly utilized National Institute of Neurologic Disorders and National Institute of Mental Health Work Group criteria[4] for diagnosing PDP evidences more than 90% specificity and sensitivity.

Psychotic symptoms include hallucinations that are predominantly visual and more common than delusions.[3] Hallucinations and illusions are often associated with sensations of a presence nearby. The delusions are paranoid in nature and signal severe disease.[2–4]

Intact sensorium, intellect, and insight are initially retained but gradually deteriorate with disease progression. When present, psychoses are often accompanied by impaired cognition and depression. Delirium, dementia, and other ailments should be ruled out prior to establishing PDP as a diagnosis.

Pathophysiology. The pathology of PDP is multifactorial and may arise from neurodegeneration and receptor-level mechanisms.[1–4] Monoaminergic system dysfunction, Lewy body pathology, and defective visuospatial cognition are implicated.[4] PDP is more common in elderly men, less educated individuals, and those with chronic or comorbid illnesses.[5]

Treatment. With no disease-modifying pharmacotherapy for treatment of Parkinson disease, symptomatic therapies are the primary management. When treating PDP, it is recommended to first reduce the dosage of anti-Parkinson drugs, such as dopamine (D_2) agonists and anticholinergic medications.

While most antipsychotic pharmaceuticals attenuate psychotic manifestations, they may worsen parkinsonian motor features by D_2 receptor blockade. These medications enhance the risk for neuroleptic sensitivity reactions and are cited with "black-box" warnings of heightened mortality when prescribed to elderly demented patients.[3]

Quetiapine and clozapine are the preferred medications for treatment of PDP. They possess relatively less D_2 dopamine receptor blockade, with few extrapyramidal features.[6] Quetiapine is more frequently prescribed for PDP; however, symptom remission may be less robust.[7] Clozapine has significant efficacy but warrants caution due to rare but potentially fatal bone marrow suppression, mandating hematologic monitoring.[3]

Pimavanserin. Pimavanserin was approved for use in 2016 and has been marketed under the brand name Nuplazid. Indicated to treat patients with PDP, pimavanserin acts by selective inverse agonism at 5-HT_{2A} receptors in the mesolimbic system.[3,5–8] Owing to high serotonin receptor selectivity and low cross-reactivity, pimavanserin is reportedly effective without worsening antidopaminergic motor symptoms.

Pimavanserin is excreted through urine after cytochrome P450 3A4 hepatic enzyme metabolism. With a half-life of nearly 200 hours, pimavanserin is well suited for once-daily dosing.[8]

As of May 2018, the drug's safety is currently being reevaluated following reports[9] of serious adverse events, including worsening of psychoses and fatal reactions. These findings deserve close observation as research progresses.

Advantages. Although the efficacy of pimavanserin is not fully established, it is documented to be well tolerated with no significant safety concerns.[3] Pimavanserin does not worsen motor symptoms or compromise cognition.

Disadvantages. Pimavanserin can induce electrocardiographic QT-interval prolongation, with or without adverse cardiac outcomes.[9] Pimavanserin is not recommended for patients with preexisting QT prolongation or a history of arrhythmias. It is also contraindicated with medications that might prolong the QT interval or with pharmaceuticals that interfere with hepatic metabolism. Other pimavanserin-induced problems include gait instability, falls, confusion, edema, and constipation.[9] Safety of pimavanserin during pregnancy and lactation is unknown.

Conclusion. Psychosis in people with Parkinson disease causes functional decline, adversely impacts quality of life, and increases the likelihood of institutionalization. Pimavanserin is approved for its efficacy in the treatment of psychosis in patients with Parkinson disease.[10] Despite being a promising treatment, prescription of pimavanserin mandates a balance between clinical indications and safety concerns. A better understanding of cardiac precautions is a current focus.

References

1. Statistics. Parkinson's Foundation. Parkinson's Foundation website. http://parkinson.org/Understanding-Parkinsons/Causes-and-Statistics/Statistics Accessed October 1, 2018.
2. Starkstein SE, Brockman S, Hayhow BD. Psychiatric syndromes in Parkinson's disease. *Curr Opin Psychiatry*. 2012;25(6):468–472.
3. 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.
4. 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.
5. Yuan M, Sperry L, Malhado-Chang N, et al. Atypical antipsychotic therapy in Parkinson's disease psychosis: a retrospective study. *Brain Behav*. 2017;7(6):e00639.
6. Combs BL, Cox AG. Update on the treatment of Parkinson's disease psychosis: role of pimavanserin. *Neuropsychiatr Dis Treat*. 2017;13:737–744.
7. Hawkins T, Berman BD. Pimavanserin: a novel therapeutic option for Parkinson disease psychosis. *Neurol Clin Pract*. 2017;7(2):157–162.
8. Bozymski KM, Lowe DK, Pasternak KM, et al. Pimavanserin: a novel antipsychotic for Parkinson's disease psychosis. *Ann Pharmacother*. 2017;51(6):479–487.
9. Webster P. Pimavanserin evaluated by the FDA. *Lancet*. 2018;391(10132):1762.
10. Kitten AK, Hallowell SA, Saklad SR, et al. Pimavanserin: a novel drug approved to treat Parkinson's disease psychosis. *Innov Clin Neurosci*. 2018;15(1–2):16–22.

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