

**PIMAVANSERIN: HITTING THE SPOT IN HALLUCINATION AND DELUSION OF PARKINSON'S DISEASE****Dick B. S. Brashier<sup>1</sup>, Prashant Mishra\*<sup>2</sup>, Htet Wai Moe<sup>3</sup>, Kedar G. Bandekar<sup>4</sup> and Neha Akhooon<sup>5</sup>**<sup>1</sup>Professor, Department of Pharmacology, Armed Forces Medical College, Pune- 411 040, Maharashtra, India.<sup>2</sup>Classified Specialist (Pharmacology), Armed Forces Medical Services, New Delhi - 110001.<sup>3,4,5</sup>Resident, Department of Pharmacology, Armed Forces Medical College, Pune- 411 040, Maharashtra, India.**\*Corresponding Author: Dr. Prashant Mishra**

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**ABSTRACT**

Parkinson's disease psychosis (PDP) is a vivid suffering with high morbidity and mortality rate in Parkinson's disease patients. After a long era of precautious atypical antipsychotic treatments, the first and safer drug Pimavanserin was recently approved by FDA. Pimavanserin is a highly selective 5-HT<sub>2A</sub> receptor inverse agonist. It showed high level of safety and tolerability with effective symptom control of Parkinson's disease psychosis. The most prominent benefit of Pimavanserin is avoidance of motoric and non-motoric side effects. Pimavanserin brings meaningful hopes to Parkinson's disease psychotic patients but further voluminous research needs to be engaged in the treatment of PDP.

**KEYWORDS:** Parkinson's disease psychosis, Pimavanserin, 5-HT<sub>2A</sub>**INTRODUCTION**

Parkinson's disease is a disorder of central nervous system degeneration affecting millions of people worldwide.<sup>[1]</sup> The risk of Parkinson's disease increases with increasing age. Patients suffer from motor symptoms like rigidity, bradykinesia, tremor, disturbed balance and posture. Cognitive decline and other non-motor symptoms including anxiety, depression, personality changes, sleep disorders, psychosis and dementia are also disturbing.<sup>[2]</sup> Though previously the focus of treatment used to emphasize motor symptoms, non-motor symptoms are receiving attention more as they are equally disturbing to patients.<sup>[3]</sup> Parkinson's disease psychosis is persistent and progressive. Psychotic symptoms particularly visual hallucinations and paranoid delusions are causing distress to patients and their caregivers.<sup>[1]</sup> These symptoms are associated with increased morbidity and mortality. Therefore antipsychotic drug treatment is often used to manage psychotic symptoms in PD patients.<sup>[2]</sup> Varieties of antipsychotic drugs are marketed but they are pharmacologically contraindicated for PD as they block the dopamine D<sub>2</sub> receptors which are the target for symptomatic DA replacement therapy in PD.<sup>[4]</sup> In the previous years, clozapine is the only atypical antipsychotic drug tolerated and effective in treating psychosis in PDP patients. Actually clozapine is used to treat schizophrenia and it is given at more than 10 fold lower doses to treat psychosis of PDP.<sup>[5]</sup> Clozapine at doses which are effective in PDP does not sufficiently block limbic DA D<sub>2</sub> receptor receptors to exert an

antipsychotic effect, and thus a more likely basis for its antipsychotic activity in PDP is serotonin (5-HT<sub>2A</sub>) receptor blockade.<sup>[6]</sup> This is consistent with evidence that hallucinations can result from the stimulation of cortical 5-HT<sub>2A</sub> receptors and can be blocked by 5-HT<sub>2A</sub> inverse agonists or antagonists. Therefore it has been postulated that drugs with specific blockade of (5-HT<sub>2A</sub>) receptor may have lesser side effects than atypical antipsychotics.<sup>[7]</sup> Clozapine has side effects mainly agranulocytosis and sedation. Another drug quetiapine is used to manage PDP but it has low efficacy and side effects like excessive sedation.<sup>[6]</sup> Both drugs have black box warning for use in elderly patients bringing inevitable risks of increased mortality and morbidity. The reports of increased mortality and morbidity in PDP patients treated with various antipsychotics raised concerns about the safety of those drugs and demand the development of safer treatments.<sup>[8]</sup>

In April 2016, the first drug to treat hallucinations and delusions associated with Parkinson's disease was approved by Food and Drug Administration (FDA). This drug Pimavanserin brings hopes to treat profoundly disturbing and disabling psychotic symptoms of Parkinson's disease and has lesser side effects than atypical antipsychotics.<sup>[9]</sup>

**MECHANISM OF ACTION**

Over five decades studying of serotonin(5-hydroxytryptamine) and classifying its receptors, it has been found that serotonin involved in regulation of

nearly every CNS function, including cognition, autonomic function, perception, aggression and mood etc.<sup>[10]</sup> Alterations in serotonergic neurotransmitters are implicated in nearly every neuropsychiatric disorder, including Parkinson's disease psychosis, major depression, schizophrenia and related psychotic disorders, and so on.<sup>7</sup> Side effects of many therapeutic drugs for neuropsychiatric disorders are due to nonspecific actions on 5-HT receptor subtypes.<sup>[11]</sup> Thus it has been proposed that drugs with selective action on distinct 5-HT receptors might provide novel and effective treatments with lesser side effects.<sup>[7]</sup> Pimavanserin is a novel selective 5-HT<sub>2A</sub> receptor inverse agonist and blockade of amphetamine- or the *N*-methyl-D-aspartate receptor is a prominent feature. In rodent studies, pimavanserin was found to readily cross the blood brain barrier and act as a CNS-active 5-HT<sub>2A</sub> inverse agonist. In human study, pimavanserin can strongly bind to 5-HT<sub>2A</sub> receptors in normal healthy volunteers. Pimavanserin has different structure with antipsychotic drugs, and compared to selective affinity for 5-HT<sub>2A</sub> receptor, pimavanserin has approximately 40-fold lower affinity for the 5-HT<sub>2C</sub> receptor and has no prominent activity at other G-protein-coupled receptors.<sup>[12]</sup>

#### PHARMACOKINETICS

Pimavanserin is readily absorbed in gastrointestinal tract and is generally unaffected by high-fat meal.<sup>[10]</sup> The median  $T_{max}$  is 6 (range 4-24) hours. The mean plasma half-life is approximately 55-60 hours and steady state is achieved in 12 days (5 half-lives) of once-daily dosing. *Bioavailability of oral tablet form and solution form was essentially the same.* Pimavanserin is highly protein bound (~95%) and *protein binding is dose-dependent.* predominantly metabolized by CYP3A4 and CYP3A5. CYP3A4 is the major enzyme responsible for the formation of its major active metabolite (AC-279). Approximately 0.55% was eliminated unchanged in urine and 1.53% was eliminated in feces after 10 days. *The pharmacokinetic variation of pimavanserin was not seen in patients with mild to moderate renal impaired patients compared to normal renal functioning patients. There is no clinically relevant effect of age, sex, weight and ethnicity of patients affecting pharmacokinetic of pimavanserin.*

#### DRUG INTERACTION

Pimavanserin prolongs the QT interval and so it should not be given with drugs which prolong QT interval.<sup>[2]</sup> Antiarrhythmic like quinidine, procainamide, amiodarone, sotalol; antipsychotics like chlorpromazine, thioridazine and antibiotics like gatifloxacin, moxifloxacin results in prolongation of QT interval and increases the risk of cardiac arrhythmia.<sup>[13]</sup> Strong CYP3A4 enzyme inducers like rifampicin, carbamazepine, phenytoin and inhibitors like itraconazole, ketoconazole, clarithromycin may alter the level of Pimavanserin.<sup>[2]</sup>

#### CLINICAL TRIALS

The efficacy of pimavanserin was demonstrated in a 6-week, randomized, placebo-controlled, parallel-group study.<sup>[14]</sup> This trial is an outpatient study, randomizing 199 patients in a 1:1 ratio to pimavanserin 34 mg or placebo once daily. Study patients are male or female aged 40 years or older, had a diagnosis of Parkinson's disease established at least one year prior to study entry. They had psychotic symptoms (hallucinations and/or delusions) that started after PD diagnosis and symptoms were severe and frequent enough to take treatment with antipsychotic.<sup>[14]</sup> Patients having Mini-Mental State Examination (MMSE) score  $\geq 21$  and being able to self-report symptoms were included in study. The antipsychotic medications had been given for at least 30 days before starting and throughout the study period. To evaluate the efficacy of pimavanserin, the PD adapted Scale for the Assessment of Positive Symptoms (SAPS-PD) was used. SAPS-PD is a 9-item scale and higher scores reflect greater severity of illness and a negative change in score indicates improvement.<sup>[14]</sup> Pimavanserin was statistically significant superior to placebo in decreasing frequency and or severity of hallucinations and delusions associated with PDP in assessing by central, independent and blinded raters using SAPS-PD scale. Compared to placebo, pimavanserin did not show an effect on motor function when assessed using Unified Parkinson's Disease Rating Scale.<sup>[14]</sup>

#### ADVERSE EFFECTS, CONTRAINDICATIONS AND SPECIAL POPULATION

The most probable side effects were peripheral edema, fall, urinary tract infection, confusional state, nausea, dizziness and constipation. There are no contraindications for taking pimavanserin.<sup>[11]</sup> Precautions should be taken in elderly patients with dementia-related psychosis as antipsychotic drugs increase the all-cause risk of death in this type of patients. Pimavanserin is not approved for treatment of patients with dementia-related psychosis not associated with PDP.<sup>[16]</sup> Patients with history of cardiac arrhythmias, symptomatic bradycardia or congenital prolongation of QT interval should not be given pimavanserin. Hypokalemia and hypomagnesemia are alarming factors to avoid use of pimavanserin.<sup>[17]</sup> The estimated background risk of major birth defects and miscarriage is 2-4% and 15-20% respectively. The risks and benefits of drug should be considered in lactating mother. No dose adjustment is needed in elderly patients.<sup>[18]</sup> Dosage adjustment is not needed in mild to moderate renal impairment but pimavanserin is not recommended in patients with severe renal impairment. Use of pimavanserin is not recommended in patients with hepatic impairment.<sup>[19]</sup>

#### DRUG ABUSE AND DEPENDENCE

Pimavanserin is not a controlled drug and there is no increase in drug-seeking behavior, misuse and abuse once marketed.<sup>[18]</sup>

**PRESENT STATUS**

Pimavanserin is available as 17 mg coated tablet. The recommended dose is 34 mg taken as two 17 mg tablets together. It can be taken with or without food. Dose should be reduced (50%) when taken together with a potent CYP3A4 inhibitor.<sup>[20]</sup>

**CONCLUSION**

Being the first effective and well tolerated treatment of Parkinson's disease induced psychosis pimavanserin brings hope to the patients suffering from this distressful condition, although long term safety can not be commented upon right now as the clinical experience with this drug is in infancy stage. It is particularly beneficial as it does not block dopamine or worsen motor symptoms of Parkinson's disease.<sup>[20]</sup> Pimavanserin has been granted breakthrough designation and priority review by the Food and Drug Administration (FDA).<sup>[19]</sup> As Pimavanserin is the first drug approved recently, further research needs to be addressed expansively in the treatment of PDP.

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