

## Role of Pimavanserin in Psychosis Associated with Parkinson's Disease

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### Abstract

Pimavanserin was approved by the FDA for treating Parkinson's disease (PD) psychosis. Based upon 21 completed studies. This review article is to understand PD psychosis and assess the efficacy and safety of pimavanserin. A literature searches (PubMed and Google Scholar) were carried out using the keyword "pimavanserin" and cross-referencing it with PD, psychosis, efficacy, safety and clinical trial. Pimavanserin was associated with a 5.79-point decrease in SAPS-PD scale compared to the 2.73-point decrease in participants receiving placebo ( $P < .001$ ). There were statistically significant improvements in pimavanserin treated patients in the persecutory delusions, ideas and delusions of reference and global ratings of delusions. Pimavanserin was well tolerated with no significant safety concerns or worsening of motor function. A dose that was shown to be effective in clinical trials was 34 mg daily.

**Keywords:** Pimavanserin; Parkinson's Disease; Psychosis; Efficacy; Safety

### Abbreviations

PD: Parkinson's Disease; FP: Feeling of Presence; SAPS-PD: Parkinson's Disease-Adapted Scale for Assessment of Positive Symptoms; CYP450: Cytochrome P450

### Introduction

Parkinson disease (PD) is one of the most common neurologic disorders, affecting approximately 1% of individuals older than 60 years and causing progressive disability that can be slowed but not halted, by treatment [1]. In accordance with the National Institute of Neurological Disorders and Stroke – National Institute of Mental health consensus workgroup [2], symptoms of the psychosis spectrum in early stages of PD include minor experiences, such as passage and presence hallucinations, illusions, and formed hallucinations- most commonly, recurring visual hallucinations of people, animals or inanimate objects with preserved insight. In later PD stages, delusions and hallucinations occur in other modalities, for example, auditory hallucinations consisting of a voice that may not be comprehensible, or non-verbal sounds, such as steps or music. The hallucinations tend to occur in conditions of low ambient stimulation, typically when the individual is alone in a quiet environment, are experienced several times a day, and last for seconds to minutes in the initial stages [2].

To determine the characteristics of cerebral glucose metabolism in Parkinson's disease patients with visual hallucinations, group comparison studies using fluorodeoxyglucose positron emission tomography were performed [3]. Non-demented PD patients in advanced stages were classified into two groups: patients with and without visual hallucinations. In patients with hallucinations, the relative regional cerebral glucose metabolic rate was greater in the frontal areas, especially in the left superior frontal gyrus. It was shown that rela-

tive frontal hyper-metabolism may be a feature of Parkinson's disease patients with visual hallucinations. Non-hallucinating PD subjects showed greater activation in the parietal lobe and cingulate gyrus compared to hallucinating PD subjects [4]. In contrast, the hallucinating subjects showed significantly greater activation in the inferior frontal gyrus and the caudate nucleus.

Pimavanserin is a viable treatment option approved by the FDA in April 2016 for treating hallucinations and delusions associated with PD. It became the first drug registered for use against psychotic symptoms in any movement disorder. The objective of this review is to understand the clinical stages of PD psychosis and assess the efficacy and safety of pimavanserin based upon the latest studies.

### Materials and Methods

Literature searches (PubMed and Google Scholar) were carried out (1 January 2008 to 30 April 2018) using the keyword "Pimavanserin" and cross-referencing it with Parkinson's disease, psychosis, efficacy, safety and clinical trial. Publications found through this indexed search were reviewed and manually screened to identify relevant studies.

### Discussion

#### Early PD psychosis symptoms

According to a study report on the largest series of PD patients [5], 52 non-demented PD patients reporting a feeling of presence (FP) i.e. the vivid sensation that somebody other than oneself is present nearby. FP characteristics for the preceding month were recorded in a questionnaire survey. This group was compared with 78 PD patients without FP. Around half the patients said that they recognized the 'identity' of the presence. About 75% of patients said the FP was short lasting, non-distressing and occurred while indoors [5]. Most patients checked for a real presence but their insight was preserved. In 31% of cases, the patients had unformed visual hallucinations with the FP [5].

There have been studies on formed hallucinations in PD which found an association between the cognitive profile and the type of hallucination experienced. Patients with PD whose hallucinations were of unfamiliar content have more profound deficits of inhibitory executive function than do the patients with hallucinations that are recognized [6]. Additional visual symptoms that may be observed include isolated diplopia, freezing (walking cessation when passing through narrow spaces) and spatial misjudgment [7,8].

#### Late PD psychosis symptoms

As PD progresses, hallucinations in non-visual (auditory, tactile and olfactory) modalities occur alongside visual hallucinations. These non-visual hallucinations are not confined to end-stage PD dementia but are also found in patients whose cognition is relatively intact with a Mini-Mental State Examination score of 24 or 25 [9,10].

One study has estimated the prevalence of delusions in a PD clinical setting was 16% [11]. Unique delusions include the Capgras delusion (the belief that someone familiar has been replaced by an imposter), reduplicative paramnesia (the belief that a room or place has been duplicated and is present at two locations simultaneously) and the mirror sign (failure to recognize oneself in the mirror). In patients who have Dementia with Lewy bodies, the prevalence of delusion syndromes was found to increase with greater cognitive decline [12]. A similar trend was observed in individuals with Alzheimer's disease, although the prevalence was lower overall. A smaller-scale study of patients with PD dementia found a 16.7% prevalence of delusional symptoms [13].

#### Mechanism of action of Pimavanserin

Pimavanserin is a partial inverse agonist and antagonist at 5-HT<sub>2a</sub> receptors. The selectivity for 5-HT<sub>2a</sub> receptors by sparing the dopamine postsynaptic receptors differentiates it from other antipsychotics used for PD psychosis [14]. Pimavanserin binds with extremely high affinity to 5-HT<sub>2a</sub> and much lower affinity to 5-HT<sub>2b</sub>, 5-HT<sub>2c</sub>, and dopaminergic (D<sub>3</sub>), muscarinic (M<sub>5</sub>) and opioid receptors [15]. The active metabolite of pimavanserin, AC-279 has a half-life of 200 hours. Studies on animals have shown that there are reactive adap-

tations in serotonergic signaling which includes upregulation of 5-HT<sub>2a</sub> mRNA in the striatum [16]. Hence, pimavanserin specifically targets the 5-HT<sub>2a</sub> receptor and is highly effective.

### Efficacy of Pimavanserin

In a six week, randomized, double-blinded, placebo-controlled study, adults aged  $\geq 40$  years with PD psychosis were enrolled [17]. Participants were randomly allocated (1:1) to receive pimavanserin 40 mg daily or matched placebo. The primary outcome measure was an antipsychotic benefit as assessed by independent raters with the Parkinson's disease-adapted scale for assessment of positive symptoms (SAPS-PD) scale. All patients received at least one dose of pimavanserin and had a SAPS-PD assessment at baseline and at least one follow-up. Pimavanserin was associated with a 5.79-point decrease in SAPS-PD scale compared to the 2.73-point decrease in participants receiving placebo (difference - 3.06,  $P < .001$ ). Pimavanserin was well tolerated with no significant safety concerns or worsening of motor function. This trial concluded that pimavanserin may benefit patients with PD psychosis [17].

In another study, a randomized, placebo-controlled, double-blind trial of eight weeks duration [18], patients were randomly assigned to receive pimavanserin or placebo at a ratio of 1:1. Pimavanserin was started at 20 mg on day 1, with increases to 40 or 60 mg daily dose on days 8 and 15 respectively; depending on individual clinical response. PD psychosis was assessed by the SAPS-PD, the Parkinson's Psychosis Rating Scale, and the Clinical Global Impression-Severity. It was more effective than placebo, in improving both hallucinations and delusions, as measured by the SAPS-PD global hallucinations and delusions items, and the unified PD rating scale thought disorder measure. It was seen that there was a statistically significant improvement in the global rating of hallucinations in the Pimavanserin-treated patients ( $P = .02$ , effect size = .58). There were considerable improvements in pimavanserin treated patients in the following SAPS delusion domain measures: persecutory delusions ( $P = .009$ , effect size = .41), ideas and delusions of reference ( $P = .05$ , effect size = .36) and global ratings of delusions ( $P = .03$ , effect size = .53). Pimavanserin-treated patients showed greater improvement in the SAPS total domain score ( $P = .09$ , effect size = .52). This showed a 40% improvement in the pimavanserin-treated patients compared with an 11% improvement in the placebo-treated group.

### Safety of Pimavanserin

The most common side effects comparing patients on pimavanserin relative to placebo groups were peripheral edema (7%) and confusion (6%) [19]. Other major adverse drug events were increased risk of fall, urinary tract infections, and hallucinations (5%) and constipation (4%). No drug interactions were found between pimavanserin and carbidopa/levodopa hence clinicians can feel safe prescribing both medications together if necessary. Pimavanserin is not known to be either a cytochrome P450 (CYP450) inhibitor or inducer. When given concomitantly with a CYP450 inhibitor, it is recommended to reduce the dose by 50%. When given with a CYP450 inducer, clinicians are encouraged to watch for decreased efficacy and consider a dose increase if necessary. QT interval prolongation was seen in trials, but the largest observed mean for the 34 mg dose was 9.6 milliseconds, which was insignificant [18].

### Conclusion

After reviewing multiple sources of literature, the approval of pimavanserin for treating hallucinations and delusions associated with PD psychosis seems appropriate. A dose that was shown to be effective in clinical trials was 34 mg daily (usually split into two doses of 17 mg each). Special dose changes must be made when there are strong CYP450 interactions, but not with mild-to-moderate renal impairment. No studies have been done in patients with severe renal or hepatic impairment, so currently, pimavanserin is not recommended in these populations. As with all antipsychotic drugs, pimavanserin has a black box warning on its package labeling, which is mandated by the FDA, as it increases mortality in elderly patients with dementia-related psychosis. The labeling also warns the practitioners against using this drug along with QT prolonging drugs. There was an evidence for QT-interval prolongation in a clinical trial but was not significant. There are few post-market trials being conducted which hypothesize that pimavanserin may replace current antipsychotic therapy (clozapine and quetiapine) for the treatment of patients with PD psychosis.

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### Conflict of Interest

The authors report no conflict of interest.

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