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Review Article

Pimavanserin: a novel therapeutic approach to treat Parkinson's Disease Psychosis

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Abstract

PDP (Parkinson's disease psychosis) is a neuropsychological nonmotor manifestation that occurs in individuals as a result of Parkinsonism with the advancement of the disease. It is mainly characterized by delusions, hallucinations, and other cognitive features affecting the patient's quality of life. Although the existing treatments for PDP have a lot of clinical experience, they focus mainly on reducing and regulating the cognitive features. Hence, it is difficult to minimize the exacerbation of motor dysfunction along with the existing motor complications of Parkinson's disease (PD). Previous medications also led to tremors and rigidity as undesirable effects with long-term use by blocking dopamine (D2) receptors. Moreover, patients with PD take several drugs to manage their motor symptoms, which may complicate their medication regimen, causing patient burden. Therefore, as an emergent pharmacotherapeutic approach, pimavanserin, which is a selective 5-HT2A receptor inverse agonist, shows promising benefits in managing disease conditions by reducing psychosis while avoiding motor worsening and other non-motor side effects. This distinguishes pimavanserin from other available therapies for PDP. This review analyzes all the previously and recently published research works that have evaluated the efficacy of pimavanserin in the clinical management of PDP with its screening and pharmacological properties.

Keywords: Pimavanserin, Parkinson's disease psychosis, 5HT2A inverse agonist, Parkinson's disease, psychotic disorders, psychosis

1. Introduction

Parkinson's disease (PD) is a neuropsychological disorder primarily impairing motor features within the striatum caused by the deterioration of dopaminergic neurons (D2)[1]. The four cardinal features of Parkinson's disease are tremors, bradykinesia, postural instability, and rigidity[2, 3]. In recent years, non-motor features have gained increased recognition and contributed to the severity of the disease and, hence, to the well-being and functional status of the patient[3]. Over 50% of PD patients experience common psychotic symptoms, such as hallucinations and delusions (i.e., psychosis) at some point of time. These symptoms often have an insidious onset, leading to delayed diagnosis and treatment, thereby worsening their quality of life and increasing the burden on caretakers[4-6].

PDP occurs from a complex correlation between serotonergic, dopaminergic, and cholinergic systems, making its pathophysiology multidimensional[7, 8]. Regardless of its prevalence and effect on society, PDP remains unrecognized or poorly treated due to hesitation in using traditional antipsychotics, as they often aggravate motor symptoms[9]. This longstanding therapeutic problem led to an urgent need for a treatment alternative that controls psychosis without worsening parkinsonian motor symptoms.

Pimavanserin is a selective inverse agonist and antagonist of the 5-hydroxytryptamine receptor subtype 2A (5-HT2A)[10]. It does not affect other G-protein coupled receptors, including dopaminergic, histaminergic, and muscarinic receptors. Because of its specificity, it is the only medication approved by the US Food and Drug Administration to treat PDP[10,11]. The development of pimavanserin was supported by an effective pharmacological basis, as well as preclinical and clinical evidence that confirmed its safety profile and efficacy[12, 13]. Before the FDA approval of this drug, antipsychotic medications like clozapine and quetiapine were used off-label. However, in elderly individuals diagnosed with Parkinsonism, using these drugs increases the risk of fractures, morbidity, and mortality[14, 15].

2. The distinct mechanism of pimavanserin

Pimavanserin selectively modulates cortical–limbic 5-HT2A pathways without producing basal ganglia D_2 receptor blockade, thereby avoiding motor deterioration typically associated with conventional antipsychotics as shown in Figure 1.

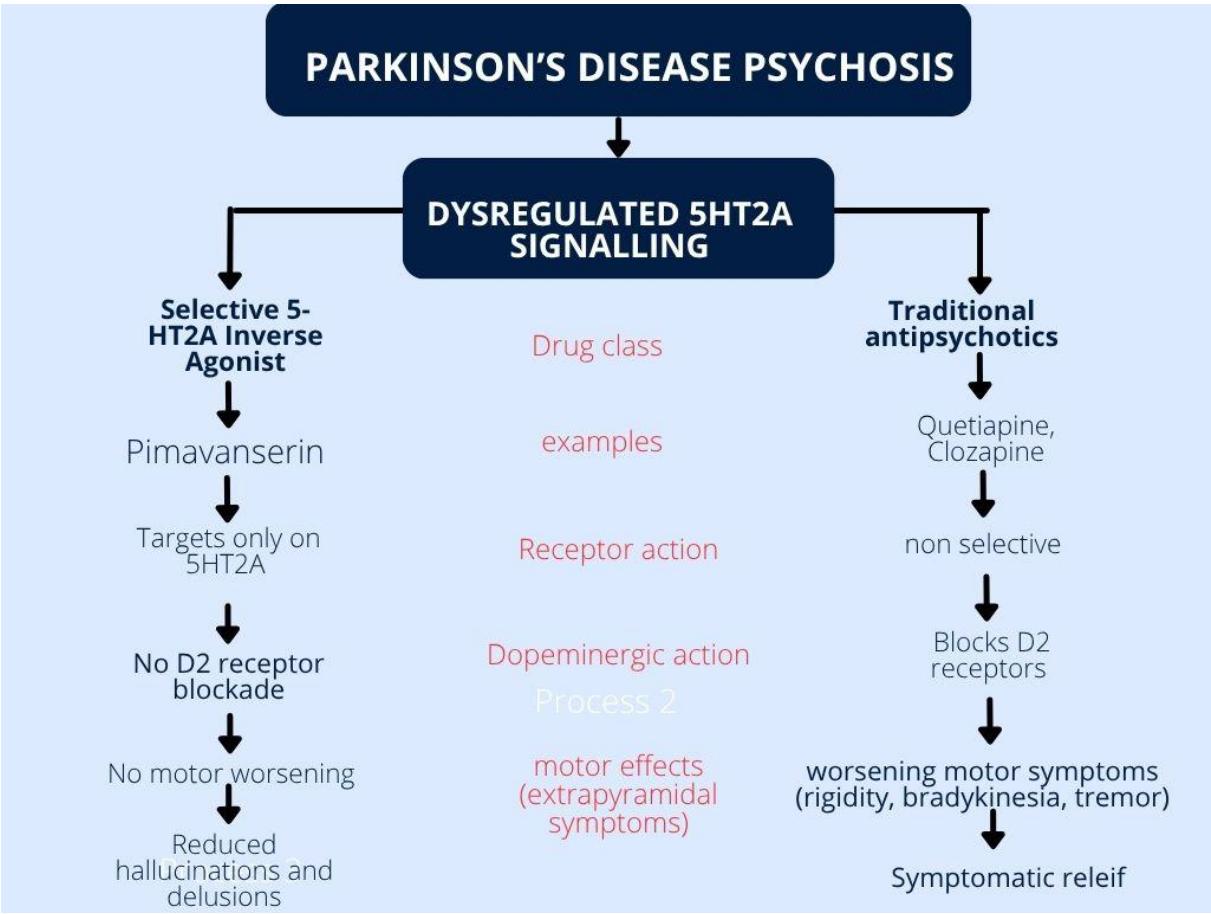

Figure 1: schematic representation of contrasting mechanisms of pimavanserin and traditional antipsychotics in Parkinson's disease psychosis.

3. Pharmacological properties

Pimavanserin, an antipsychotic drug, shows its efficacy without affecting motor symptoms by blocking 5HT2A/2C receptors, but it lacks the blocking of dopamine D2 receptors, whereas all other atypical antipsychotics have both D2 and 5HT2A antagonistic properties. It has 40-fold less affinity to interact with 5HT2C when compared to the 5HT2A receptor[16, 17].

Dysregulation of several neurotransmitters, notably dopamine, serotonin, acetylcholine, and glutamate, is responsible for the development of PD psychosis [18]. There is a notable disturbance between the serotonergic and dopaminergic neurotransmitters; this imbalance is the result of the accumulation of Lewy bodies within the cerebral cortex. This results in the advancement of psychosis in some individuals diagnosed with Parkinson's disease[18, 7].

5HT2a is a subtype of 5HT, serotonin receptors called G protein-coupled receptors distributed throughout the central and peripheral nervous system. Among serotonin receptors, 5-HT2A is the most excitatory one. In the central nervous system, 5-HT2A is responsible for numerous functions, including learning, mood, cognition, anxiety, and memory[19, 20]. Any abnormality in the serotonergic systems leads to various pathological conditions, which include depression, autism, mood disorders, and schizophrenia[20]. It has been hypothesized that atypical antipsychotics have more affinity to 5-HT2A receptors than D2 receptors. Blocking of this targeted receptor results in an antipsychotic effect with low extrapyramidal side effects[21].

4. Screening of PDP

Most of the PD patients present with hallucinations and delusions, which are common and enervative, and trouble the patient and caregivers[22]. It is necessary to address these symptoms to enhance the individual's quality of life. The most crucial step to achieve this is to diagnose the targeted patients and provide an effective treatment. The lack of clinical diagnostic tools and treatment guidelines hinders effective treatment[23]. A group of panel members who were experts in psychiatry and neurology were involved in discussions to develop an assessment tool and standardized treatment guidelines for the effective therapeutic approach to PDP[22]. The Non-Motor Symptoms Scale for Parkinson's Disease (NMSS) is a 30-item scale used to assess the severity of non-motor symptoms and the response or progression of PDP patients to a given treatment[24]. MDS-UPDRS (Movement Disorder Society–Unified Parkinson's Disease Rating Scale) was developed based on the original UPDRS (55 items). MDS-UPDRS (65 items) is more comprehensive than the original one; it has four parts that cover both motor and non-motor severity of individuals with Parkinsonism[25]. The Scale for the Assessment of Positive Symptoms for Parkinson's Disease Psychosis (SAPS-PD) is used to assess the severity of positive psychotic symptoms in patients with PDP[6].

5. Summary of animal and human studies for pimavanserin in treating PDP

5.1 Preclinical evidence linking

A summary of preclinical studies assessing the pharmacological and behavioural effects of pimavanserin and its precursor (ACP-103) in animal models of Parkinson's disease psychosis is presented in Table 1.

Table 1: Preclinical evidence supporting the efficacy and safety of pimavanserin in Parkinson's disease psychosis.

STUDY TYPE AND OBJECTIVES	AUTHOR	TYPE AND NUMBER OF PARTICIPANTS	TREATMENT	RESULTS
To establish optimal therapeutic doses of quetiapine, clozapine and pimavanserin in an animal model of PDP[26].	David Hubbard, Uli Hacksell and Krista McFarland	Male Sprague-Dawley rats (225-250 g). Locomotor activity: 10-14/group. Rotometry- 7-10 /group.	Rats were given varying doses of clozapine, quetiapine, and pimavanserin. Efficacy was assessed using amphetamine-induced locomotion (3 mg/kg, SC). Apomorphine-induced rotations (0.5 mg/kg) were used to assess dopaminergic side effects.	Pimavanserin provided an antipsychotic effect at low doses (0.3-1 mg/kg) through 5-HT2A inverse agonism without affecting dopaminergic pathways. Sedation is caused only at very high doses (30 mg/kg), suggesting its tolerability compared to clozapine and quetiapine which can be further confirmed with human studies.
2. Pharmacological and Behavioral Profile of ACP -103 N-(4 Fluorophenylmethyl) -N-(1-methylpiperidin-4-yl)-N-(4-(2 methylpropyloxy) phenylmethyl) Carbamide (2R,3R) Dihydroxybutanedioate (2:1), a Novel 5-HT2A Receptor Inverse Agonist[27].	Vanover KE et al.	8-16 rats/dose. Non-Swiss male albino mice (20-30 g) and Sprague-Dawley rats (200-300 g).	ACP-103 (pimavanserin precursor) given orally or subcutaneously before multiple behavioral test: 1.(-2,5-dimethoxy-4-iodoamphetamine hydrochloride) DOI-induced head twitch experiments. 2.DOI-induced disruption of PPI (percentage of prepulse inhibition): Rats were given one of the 3 doses of ACP-103, MDI 100,150 before the test; after one week, the same rats received the opposite treatment. 3. MK801 induced hyperactivity in mice. 4. Ataxia assessment.	ACP-103 delayed and reduced DOI induced head twitches at 3 mg/kg. restored the PPI disruption at a smaller dose. Low dose (0.1-0.3 mg/kg) reduced hyperactivity ACP-103 (3 mg/kg) PO reduced hyperactivity but not spontaneous activity at any doses. ACP-103 did not induce ataxia at any doses even at a high dose (100 mg/kg) with any route of administration.

5.2 Clinical evidence linking

5.2.1 Phase 1 trial

Two single-centered, double-blind, randomized, placebo-controlled phase 1 studies in healthy males were conducted to evaluate ACP-103's (Pimavanserin) safety, tolerability, and pharmacokinetics.

Single-dose study: Carried out among 25 nonsmoking, healthy males (18–45 years) who were divided into five groups receiving placebo or ACP-103 at 25 mg, 50 mg orally, or 100 mg, 200 mg, 300 mg through the nasogastric route. Fasting was required for 10 hours before dosing. It was well tolerated up to 300 mg, with no maximum tolerated dose established. Oral burning, bitter/acidic taste, and postural disorientation were mild adverse effects.

Multiple-dose study: Comprised 24 healthy males (19–35 years) who were split into three groups receiving placebo or ACP-103 at 50 mg, 100 mg, or 150 mg once daily for 14 days. The maximum tolerated dose was considered to be 100 mg once daily. Common adverse events reported were nausea, vomiting, and gastrointestinal discomfort, where 150 mg caused vasovagal episodes.

These findings indicate ACP-103 is a dose-proportional, safe, and selective 5-HT2A inverse agonist, with good tolerability in single dosing up to 300 mg; however, there

is a possible maximum dose of 100 mg/day for prolonged use, which supports further clinical development[28]. These results provided the pharmacokinetic and tolerability basis for taking pimavanserin into further studies.

5.2.2 Phase 2 trial:

This was a Phase 2, multi-centre, randomized, double-blind, placebo-controlled 28-day trial conducted in patients with L-DOPA–induced Parkinson's disease psychosis (PDP). Patients with an NPI psychosis severity score ≥4 were randomized (1:1) to pimavanserin (n=29) or placebo (n=31). And the doses were titrated from 20 mg (Day 1) to 40 mg (Day 8) and 60 mg (Day 15).

Safety: Motor scores (UPDRS II, III, and V) remained stable, and adverse event rates were comparable across groups, confirming pimavanserin does not worsen Parkinsonian symptoms.

Efficacy: Pimavanserin produced significant improvement in SAPS global hallucination and delusion scores, UPDRS Part I, and secondary measures, PPRS, and CGI-S, compared with placebo.

Overall, the study showed that pimavanserin was well tolerated and significantly improved psychosis without compromising motor control in PDP[29]. Although the short 28-day duration limits conclusions about the long-term safety and durability of response, these results provided proof for the efficacy of pimavanserin, making way for larger phase 3 trials.

5.2.3 Phase 3 trials:

A 6-week, randomized, double-blind, placebo-controlled trial in 54 centres (2 in Canada, 52 in the USA) examined Pimavanserin 40 mg daily in 199 individuals (≥40 years) with Parkinson's disease psychosis. Pimavanserin significantly improved psychosis at day 43 compared to placebo, as assessed by SAPS-PD, SAPS-H+D, CGI-I, and CGI-S scores, while also reducing caretaker burden. Common adverse events were urinary tract infections and falls, although no impairment of motor function or drowsiness was reported. Sustained response beyond 6 weeks was not evaluated[30].

Another study evaluated the motor and cognitive safety of pimavanserin in PD-related psychosis. A pooled analysis of three 6-week trials, including the HARMONY study, assessed pimavanserin motor and cognitive safety in PD psychosis. Motor ratings were comparable between 202 patients using pimavanserin 34 mg and 231 on placebo. Pimavanserin caused fewer occurrences of orthostatic hypotension but increased gait disturbance and disorientation, with no motor or cognitive impairment, indicating acceptable tolerance even in PD dementia[31].

5.2.4 Phase 4 trials`

An overview of clinical studies (Phase 4 and associated extension trials) evaluating the effectiveness, safety, relapse prevention, and cognitive/motor outcomes of pimavanserin in Parkinson's disease psychosis is presented in Table 2.

Table 2: Clinical studies evaluating pimavanserin in Parkinson's disease psychosis: Phase 4 trials and open-label extension analyses.

STUDY TYPE AND OBJECTIVES	AUTHOR	TYPE AND NUMBER OF PATIENTS	TREATMENT	RESULTS
Randomized controlled trial (international, multicentre, randomized discontinuation study) To estimate the time to psychosis relapse and effect on motor symptoms and cognitive functions[32].	Daniel Weintraub et al.	Patients with moderate-to-severe Parkinson's disease psychosis and aged 50-90 years. Out of 392 enrolled patients, 59 had PDD. 49/59 completed open label. 36/49 were randomized (16 to pimavanserin and 20 to placebo).	Patients received pimavanserin 34 mg/day for 12 weeks (open label). Patients who tolerated Pimavanserin at 8 and 12 weeks were randomized to proceed with Pimavanserin or to be assigned to a placebo during the double blinding phase.	When compared with placebo, pimavanserin reduced the risk of psychosis relapse in individuals with PDP without worsening of motor or cognitive function.
Randomized controlled trial (open-label extension trial) To assess the effectiveness and tolerability of	Isaacson SH et al.	Patients having psychotic manifestations of not less than moderate severity according to the clinical diagnostic criteria used for PDP, but patients who had improved symptoms during the core study were omitted.	Core study: Pimavanserin (34 mg) or placebo over 6 weeks. OLE: eligible patients continued with 34 mg pimavanserin orally	The efficacy and tolerability response was maintained among patients who proceeded with pimavanserin over the course of 10 weeks, and the response improved in patients who switched from placebo to pimavanserin.

pimavanserin through an open-label extension (OLE) trial[6].		Out of 176 eligible patients after core study, 171 entered OLE, 87 switched from placebo to receive pimavanserin and 84 continued with pimavanserin.	once daily for the first 4 weeks.	
Clinical trial (multi-centre, open-label extension study) To estimate the duration of maintained response with pimavanserin among participants with PDP for an additional 4 weeks of treatment[4].	Isaacson SH et al.	Subjects who completed one of the three double-blinded, placebo-controlled core studies. Out of 538 patients completing one of the core study, 459 were enrolled into OLE, out of which 424 patients were assessed for efficacy after 4 weeks.	Pimavanserin 8.5 mg,17 mg ,34 mg or placebo during the core study. In OLE, all participants received pimavanserin 34 mg once daily for 4 weeks.	Those subjects who switched from placebo to pimavanserin showed improvement compared to patients who received pimavanserin for the entire 10 weeks. Thus, pimavanserin shows additional efficacy in treating hallucinations and delusions associated with PDP.
Clinical trial (6-week randomized, double blinded, placebo-controlled phase 3 trial) To investigate the differential effect of pimavanserin among PDP patients with versus without cognitive impairment among those who receive or do not receive cognitive-enhancing medications[5].	Espay AJ et al.	Adults aged ≥40 years with PDP for ≥1 month. 185 subjects were included in the efficacy trial (95 pimavanserin, 90 placebo). and 198 individuals in a safety study (104 pimavanserin, 94 placebo).	Patients received Pimavanserin 34 mg once daily or placebo over 6 weeks period.	• Pimavanserin demonstrated superior efficacy to placebo in both cognitively impaired and cognitively normal subgroups. • Greater improvement observed in patients with cognitive impairment • Benefits were maintained in patients receiving cognitive-enhancing medications.

6. Discussion

Pimavanserin is a well-tolerated option that targets the 5-HT2A receptor and works uniquely as an inverse agonist. It is one of the treatment options with a distinct mechanism for addressing psychotic symptoms in Parkinson's disease. Due to its significant effectiveness compared to other antipsychotics and limited treatment options for psychosis associated with Parkinson's disease, the Food and Drug Administration approved it in April 2016[27, 30]. The approval of this drug was based on the excellent results demonstrated in a phase III trial[33]. Most animal models establish that effective doses of pimavanserin reduce psychosis-like behaviour without impacting motor symptoms[26, 34]. The results of the phase 1 trial show that ACP 103 (Pimavanserin) is tolerable up to 300 mg with fewer adverse events[26]. The phase 2 and 3 trials confirmed pimavanserin's efficacy and safety in treating psychotic symptoms without worsening motor symptoms, thereby reducing caregiver burden and being well tolerated[28, 29, 31]. According to a 2022 meta-analysis by Mansuri Z et al., pimavanserin was associated with a lower incidence of orthostatic hypotension than a placebo. As a result, this study also emphasizes the advantages of pimavanserin for positive psychotic features of PD and its safety profile, particularly with regard to adverse effects such as headaches, falls, and confusion[35]. A study conducted by Alipour-Haris G et al. 2023, suggested that pimavanserin demonstrates potential benefits over quetiapine in reducing the likelihood of hospitalization[36]. The FDA's Adverse Event Reporting System (FAERS) suggests that pimavanserin demonstrated a lower risk of mortality than other antipsychotics[37]. The restricted mechanism of action of pimavanserin is that it may not address all underlying causes of Parkinson-related psychosis because of its restricted mode of action, and its exact pharmacological pathway remains unclear[16]. Further prospective studies are needed to assess the long-term safety and efficacy of pimavanserin with other available antipsychotics and their generalizability to all patients with PDP, making it an attractive treatment option for PDP.

7. Conclusion

Pimavanserin, a novel therapy for Parkinson's disease psychosis, is more efficacious than current antipsychotics

like olanzapine and quetiapine in reducing the severity of psychotic symptoms without interfering with or worsening other motor or cognitive functions, thus providing a safer alternative to existing medications. It has demonstrated a unique mechanism of action with no blockage of dopamine D2 receptors, restoring motor function. Thus, it provides a non-dopaminergic approach in treating psychosis in patients who are very sensitive to the adverse effects of dopamine-blocking drugs.

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