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***Abstract*:** Parkinson's disease (PD) is a progressive neurodegenerative disorder with both motor and nonmotor symptoms (NMS), leading to significant morbidity and caregiver burden. Psychosis is common but is under recognized by physicians. When present, it increases the patient's risk of hospitalization and nursing home placement and caregiver burden. Although the atypical antipsychotic agent, clozapine, has been considered the gold standard treatment, severe agranulocytosis in 0.38% of patients and more commonly milder leukopenia, resulting in frequent blood testing, limit its use. Pimavanserin, a 5HT2A receptor inverse agonist, has been shown to reduce psychosis in PD without worsening motor symptoms. It is therefore a welcome therapeutic option for this devastating NMS.

Keywords: Parkinson's disease, pimavanserin, psychosis

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Introduction

Parkinson's disease (PD) is the second most common neurodegenerative disorder worldwide after Alzheimer's disease. Current estimates report more than one million people in the United States have PD, with an overall incidence of 13.4 per 100,000 individuals/year [Przedborski, 2015]. PD is a progressive disease, and has a mean age of onset at 55 years old. Cardinal motor symptoms include resting tremor, bradykinesia, rigidity, and postural instability. Apart from these motor symptoms, nonmotor symptoms (NMS) such as psychosis, sleep dysfunction, cognitive impairment, depression, anxiety, and autonomic dysfunction are being increasingly recognized. Many of these NMS may predate the development of motor symptoms [Sauerbier and Chauduri, 2015].

Unfortunately, NMS are not recognized in as many as 21–50% of consultations [Chaudhuri *et al.* 2010]. A study of 101 patients with PD from a movement disorders center compared patients' self-reporting of depression, anxiety, sleep disorders, and fatigue, with physicians' impressions, and with formal tests such as the Beck Depression Inventory [Shulman *et al.* 2002]. Overall, the concordance between a physician's evaluation and formal rating scales was low, particularly for behavioral symptoms, and physicians only recognized depression in 21%, compared with 57% by a screening questionnaire. In a study of 242 patients evaluated at a movement disorders clinic, 65% did not disclose delusions, and of the NMS surveyed, psychiatric symptoms had the highest undisclosed rate (50%) [Chaudhuri *et al.* 2010]. Three reasons for nondisclosure were patients and caregivers were unaware they were related to PD; patients were embarrassed; and the majority of the visit centered on motor symptoms [Chaudhuri *et al.* 2010]. Another study of 74 patients with PD and 54 family members confirmed that NMS are not frequently reported [Cheon *et al.* 2008], and less than 10% knew of the relationship between delusions and PD.

Psychosis in PD: definition, clinical manifestations, and epidemiology

An National Institute of Neurological Disorders/National Institute of Mental Health's workshop developed diagnostic criteria for Parkinson's disease psychosis (PDP) [Ravina *et al.* 2007] (Table 1) with specific definitions of delusions, hallucinations, a sense of presence, and illusions (Table 2). These two latter phenomena are termed minor phenomena, occurring in 40% of patients, and are less disruptive [Ravina *et al.* 2007]. Unfortunately, there are no absolute scales for assessment of PDP. Although the Parkinson's Psychosis Rating Scale has been validated, it has not gained

Table 1. Summary of NINDS/NIMH diagnostic criteria for PDP [Ravina *et al.* 2007].

1. Presence of at least one of the following: false sense of presence, illusions, hallucinations, delusions
2. Primary diagnosis of PD according to UK Brain Bank Criteria and symptoms of psychosis occur after PD onset
3. Symptoms of psychosis must be persistent for at least 1 month
4. Other causes must be excluded, such as dementia with Lewy bodies, schizophrenia and related disorders, mood disorder with psychotic features, and delirium
5. Associated features such as presence or absence of insight, dementia, and medications need to be specified

PD, Parkinson's disease; PDP, Parkinson's disease psychosis; NINDS/NIMH, National Institute of Neurological Disorders and National Institute of Mental Health's.

Table 2. NINDS/NIMH definitions of PDP behavioral phenomena [Ravina *et al.* 2007].

1. Delusions are false, fixed beliefs held despite evidence to the contrary
2. Hallucinations are sensory perceptions without a physical stimulus, can involve any sensory modality, and can be simple or complex
3. A sense of presence is a hallucination of someone being present without actually being with the patient
4. Illusions are misrepresentations of real stimuli, which are often visual in nature

PDP, Parkinson's disease psychosis.

universal acceptance. Other rating scales, such as the Brief Psychiatric Rating Scale and the Neuropsychiatric Inventory were developed for other psychiatric conditions [Chou *et al.* 2005].

Visual hallucinations (VH) are the most common type of hallucination, and occur in as many as 90% with PDP [Ravina *et al.* 2007]. They are often well formed, with images such as animals or people, lasting seconds to minutes, and can occur several times per day, particularly in the evening or when the patients are alone or in quiet environments. Auditory hallucinations, often whispers or threatening voices, typically co-occur with VH in 8–13% of cases in various series, and are rarely isolated. However, in one study, Chou and colleagues found that 48% of individuals with PDP had a mix of visual and auditory hallucinations [Chou *et al.* 2005]. Tactile, olfactory, and gustatory hallucinations are rarer and are not isolated. Delusions are often paranoid in nature, particularly of spousal infidelity. Other rare delusions include somatic, religious, grandiose, and persecutory. Early on, insight is retained, but can progressively be lost. Minor phenomena can remit for sustained periods, but can also recur and persist [Ravina *et al.* 2007].

Estimates of incidence and prevalence vary, ranging from 16% to 75% of patients with PD across studies [Mack *et al.* 2012], with an average of 25–30% [Goetz *et al.* 2006; Rabey, 2009]. Neither minor nor major phenomena are benign since symptoms typically progress [Goetz *et al.* 2006]. In a study of 48 patients followed over 3 years, 39 progressed from hallucinations with insight to hallucinations without insight or to delusions as defined by the Unified Parkinson's Disease Rating Scale (UPDRS) single item subscore, with average time to conversion of 2 years. The remaining nine who did not progress had reduced dopaminergic medications or were given antipsychotic medications [Goetz *et al.* 2006]. Another study comparing progression of sleep disorders with hallucinations demonstrated that overall prevalence of hallucinations increased from 33% to 63% over 10 years [Goetz *et al.* 2010], with the greatest risk factor being time. Medication dose, sleep fragmentation, vivid dreams, and baseline age were not associated with progression in this study. Other associated findings are listed in Table 3.

Pathophysiology of PDP

The pathophysiology of PDP is not entirely understood but is likely multifactorial. Higher PD medication doses have been implicated, and hypersensitization of dopaminergic receptors in the striatum due to chronic stimulation by medications may cause limbic dysfunction and misattribution of internal stimuli originating from the external world [Ravina *et al.* 2007; Zahodne and Fernandez, 2008]. However, the finding of associated structural abnormalities as well as the recent report of minor hallucinations predating motor symptoms and administration of medications supports the premise that the intrinsic disease itself leads to PDP [Pagonabarraga *et al.* 2016]. Interestingly, in addition to REM sleep behavior disorder [Zahodne and Fernandez, 2008], fragmented rapid eye movement sleep may lead to the intrusion of dream imagery during wakefulness

Table 3. Associated risk factors with the development of psychosis.

Cognitive impairment or dementia [Chou *et al.* 2005; Goetz *et al.* 2010]
Higher levodopa equivalent dose at baseline [Zahodne and Fernandez, 2008]
Worse ADL function [Goetz *et al.* 2010]
Poor quality of life [Chou *et al.* 2005]
Depression [Chou *et al.* 2005]
Higher age at onset of motor symptoms [Zahodne and Fernandez, 2008]
Follow-up time [Goetz *et al.* 2010]
Probable RBD (mild activity during sleep) [Zahodne and Fernandez, 2008]

ADL, activities of daily living; RBD, REM sleep behavior disorder.

Table 4. Current treatment guidelines for PDP [modified from Pagonabarraga *et al.* 2016; Jakel and Stacy, 2014].

1. Treatment of any underlying metabolic abnormalities or infections
2. Reduce medications with neurologic side effects such as sedatives, antidepressants, anxiolytics, hypnotics, and bladder medications
3. Evaluate whether adjunctive PD medications such as amantadine, monoamine oxidase-B inhibitors, anticholinergic medication, or entacapone are worsening PDP without providing significant motor benefit, and adjust as clinically appropriate. Dopaminergic medications can be reduced if possible without worsening mobility
4. Start pimavanserin 34 mg daily
5. Consider starting low doses of quetiapine (12.5 mg) or clozapine (6.25 mg daily) and titrating slowly in patients with contraindications to pimavanserin or who are unable to obtain pimavanserin

PD, Parkinson's disease; PDP, Parkinson's disease psychosis.

from reduced cholinergic disinhibition of dream images [Zahodne and Fernandez, 2008].

There is evidence for the involvement of multiple structures and pathways in PDP. Neuropsychiatric testing suggests impairments in the frontal-striatal networks in those with hallucinations but retained insight, whereas posterior cortical damage is suggested in those without insight [Jakel and Stacy, 2014]. Reduced volumes of the pedunculopontine nucleus, thalamic gray matter, and inferior frontal gyrus have been noted in those with VH [Broadstock *et al.* 2014]. Minor hallucinations may be due to loss of gray matter in the visual stream, but formed hallucinations may result from extensive loss of gray matter in the ventral and dorsal streams, prefrontal cortex, limbic system, and anteromedial temporal areas [Pagonabarraga *et al.* 2016]. Functional imaging studies suggest reduced metabolism in the visual association pathways [Broadstock *et al.* 2014]. Cortical Lewy body (LB) pathology in the ventral temporal region, including the amygdala and parahippocampal gyrus, is likely involved [Ravina *et al.* 2007; Zahodne and Fernandez, 2008; Broadstock *et al.* 2014], and an autopsy study of 744 patients with various causes of parkinsonism demonstrated a specificity of VH for LB pathology of 92.9%, and a positive predictive value of 93.4%, supporting a direct link between VH and LB pathology [Williams and Lees, 2005].

Dysfunction in serotonergic and cholinergic function may contribute to PDP [Ravina *et al.* 2007; Jakel and Stacy, 2014]. The role of serotonin is suggested by improvement in psychotic symptoms with atypical antipsychotic agents (clozapine) that have serotonergic antagonism. The serotonergic system is known to be affected in PD, with ongoing degeneration of the raphe nuclei altering inputs to the cortex and striatum, and indirectly affecting the cholinergic system. Moreover, stimulation of the 5HT2A receptors on cortical glutaminergic neurons leads to increased dopamine release in the nucleus accumbens (NA) and ventral tegmental area (VTA). This activation of the VTA and NA can lead to hallucinations. Subsequently, these subcortical areas project to other cortical areas *via* the thalamus causing disruptions in the cortico-striato-thalamo-cortical circuitry and in thalamic gating of cognitive and sensory input. Further support for serotonergic dysfunction in the development of PDP comes from two small open-label studies of ondansetron, a 5HT3 antagonist, which demonstrated attenuation of VH and paranoid delusions *via* inhibition of serotonin receptors in the entorhinal and limbic areas [Zoldan *et al.* 1993, 1995]. Additionally, cholinergic deficits in the nucleus basalis of Meynert are prominent in those with cognitive dysfunction that has been associated with PDP [Zahodne and Fernandez, 2008].

Finally, impaired vision, from glaucoma or cataracts, retinal pathology associated with PD [Lee

et al. 2014], and impaired visuospatial processing, particularly for color and contrast vision, may be associated with psychosis due to reduced suppression of internal visual imagery [Ravina *et al.* 2007; Zahodne and Fernandez, 2008].

Effect of psychosis on patients and caregivers

PDP has considerable impact on both patients and caregivers. A case–control study of patients with PD admitted to nursing homes (NH) over 4 years from a tertiary care movement disorders practice revealed that hallucinations were the biggest risk factor for placement [Goetz and Stebbins, 1993]. A 2-year follow-up study [Goetz and Stebbins, 1995] of these NH patients and controls revealed 100% mortality rates for the NH patients as opposed to 32% for community dwellers, with a mean survival time for NH residents of 15.6 months. A study of community-dwelling patients with PD, in which 47/178 were admitted to NH at a mean of 25 months, revealed at 4 years after the initial assessment that the most significant predictors for NH admission were dementia, hallucinations, functional impairment, and age [Aarsland *et al.* 2000].

PDP is also a major risk factor for acute hospital admission. In a retrospective study of 143 patients with PD admitted to a neurology ward in a community hospital in a 6-year period, 37% were admitted for motor complications and 24% for psychosis [Klein *et al.* 2009]. Mean duration of hospitalization was 11 days compared with 7 days in age-matched controls without PD.

Tremendous persistent stress and impaired psychosocial functioning are found in caregivers leading to patient institutionalization [Schrag *et al.* 2006]. Psychiatric burden is common among caregivers. Worsening disease progression and impairments in patient's cognition can further add to the caregiver's poor quality of life. A study of 116 caregivers revealed increased physical fatigue, deterioration in their health, poor relationships with other family members, and a deterioration in their social lives. Depression was noted among 27% of caregivers [Schrag *et al.* 2006], with hallucinations, cognitive dysfunction, depression, and falls contributing to caregiver burden [Schrag *et al.* 2006].

Current treatment of PDP

In April 2016 the US Food and Drug Administration (FDA) approved pimavanserin for treatment of hallucinations and delusions associated with PD (Table 4). Prior to that, general treatment guidelines were limited in use of pharmacotherapy, mainly relying on use of quetiapine and clozapine [Zahodne and Fernandez, 2008; Jakel and Stacy, 2014]. A recent evidence-based paper from the International Parkinson's Disease and Movement Disorders Society, and a position paper from the European Federation of Neurological Societies (EFNS) and the Movement Disorders Society–European Section (MDS-ES) position paper report that clozapine is efficacious but requires close monitoring, while quetiapine is likely inefficacious [Seppi *et al.* 2011; Ferreira *et al.* 2013]

Support for clozapine comes from several open-label studies, and a large multicenter randomized, double-blind, placebo-controlled study [The Parkinson Study Group, 1999]. However, its use is limited by side effects (orthostatic hypotension, sialorrhea, and rare but severe agranulocytosis requiring weekly evaluations of blood counts for the first 6 months). Low doses of clozapine were given to determine its antipsychotic effects using the Clinical Global Impression (CGI) Scale for psychosis, the Scale for Assessment of Positive Symptoms (SAPS), and the Brief Psychiatric Rating Scale in a randomized, double-blind, placebo-controlled trial. Doses of 6.25–50 mg per day were given over 4 weeks. Out of 60 patients initially recruited, 54 completed the study. Clozapine demonstrated improvements in all measures of psychosis without worsening UPDRS motor scores. Severe leukopenia requiring discontinuation occurred in one patient, whose blood cell counts returned to normal after stopping clozapine [The Parkinson Study Group, 1999]. A subsequent 4-week randomized, double-blind, placebo trial of clozapine compared with placebo followed by a 12-week clozapine open period and a month of drug discontinuation in 60 patients with PD also demonstrated that a mean dose of 50 mg/day improved CGI and positive and negative symptoms scale scores without significant changes in Mini Mental State Exam (MMSE) and UPDRS [Pollak *et al.* 2004]. Those in the open-label period who had received placebo earlier also had significant improvement in their PDP and one-third of patients tolerated higher doses of levodopa or agonists with their PDP better controlled. Interruption of therapy led to resumption of symptoms [Pollak *et al.* 2004]. In general, severe agranulocytosis was noted in 0.38% of over 90,000 patients receiving

the medication [Goldman and Holden, 2014]. Quetiapine is more readily used in practice due to its ease of administration and superior side-effect profile despite inconsistent evidence of efficacy in treating PDP [Goldman and Holden, 2014]. While one open-label study [Juncos *et al.* 2004] and two retrospective studies [Reddy *et al.* 2002; Fernandez *et al.* 2003] suggested improvement in PDP, three moderate sized randomized controlled trials [Ondo *et al.* 2005; Rabey *et al.* 2007; Shotbolt *et al.* 2009] did not show significant improvement in PDP. A small under-powered study [Fernandez *et al.* 2009] and another which assessed psychosis in those with dementia and parkinsonism [Kurlan *et al.* 2007] also did not show benefit with quetiapine. Interestingly, two open-label studies [Morgante *et al.* 2002, 2004] and one rater-blinded prospective study [Merims *et al*. 2006] all comparing quetiapine with clozapine, using the Brief Psychiatric Rating Scale and CGI Severity scale (CGI-S), demonstrated that both were efficacious in treating PDP. The American Academy of Neurology (AAN) [Miyasaki *et al*. 2006] gave clozapine a level B recommendation, stating that it should be considered but side effects must be monitored closely, and gave quetiapine a level C recommendation, suggesting only possible utility [Miyasaki *et al.* 2006]. Moreover, quetiapine has associated side effects of somnolence, dizziness, headache, weight gain, and orthostasis [Goldman and Holden, 2014].

Other atypical antipsychotic agents are not typically used in PDP. Despite positive results in a cohort of 15 patients with PD without dementia [Wolters *et al.* 1996], olanzapine in later studies was ineffective and intolerable in subsequent studies due to worsening of motor UPDRS scores [Brier *et al.* 2002; Ondo *et al.* 2002; Nichols *et al*. 2013]. In a small study comparing clozapine and olanzapine, several in the olanzapine cohort could not complete the study due to worsening UPDRS motor scores [Goetz *et al.* 2000]. Although the D2 receptor affinity of olanzapine is less than 'typical' neuroleptics, it may still be sufficient to block nigrostriatal pathways even at low doses, and positron emission tomography studies demonstrate less D2 receptor occupancy for clozapine compared with olanzapine or risperidone [Goetz *et al*. 2000]. As a result, the AAN [Miyasaki *et al.* 2006] and EFNS/MDS-ES [Ferreira *et al.* 2013] do not recommend the use of olanzapine or risperidone in the treatment of PDP. Reports of ziprasidone in PD are limited but suggest reduction in psychosis. However, psychiatrists have reported that motor symptoms worsen, making ziprasidone less useful [Weiden *et al.* 2002]. Aripiprazole has mixed results with worrisome side effects. Studies involving cholinesterase inhibitors rivastigmine and donepezil have been mixed. Some studies suggest benefit, but further studies are needed to clarify the role of this class of medications in treating PDP. Two small studies utilizing electroconvulsive therapy for refractory PDP reported benefits [Zahodne and Fernandez, 2008; Jakel and Stacy, 2014]. Cognitive behavioral therapy has been used in PDP but needs further research into its efficacy [Zahodne and Fernandez, 2008].

Mechanism of action of pimavanserin

Pimavanserin is a 5HT2A receptor inverse agonist, defined as an antagonist with negative intrinsic activity. Thus it antagonizes the full activity of agonists, and simultaneously lowers the basal level of receptor signaling [Garay *et al.* 2016]. The 5HT2 group of serotonin receptors are Gq G-protein coupled, and modulate phosphoinositide hydrolysis and protein kinase C activation. These receptors are abundant in the cerebral cortex, where they are located on most pyramidal neurons, especially above and below layers IV, and on many GABAergic interneurons known to specialize in the inhibition of pyramidal cells [Meltzer *et al.* 2012].

VTA dopamine neurons are under excitatory control of the medial prefrontal cortex 5HT2A receptors. Blocking these receptors may treat psychosis, and it is thought that clozapine's blocking activity at the 5HT2A receptors likely contributes to its beneficial effects in PDP [Meltzer *et al.* 2012, 2013]. Inverse agonists also potentiate the effects of dopamine blocking agents, suggesting a possible interplay between cortical serotonergic inputs and the dopaminergic neurons of the NA [Meltzer *et al.* 2012].

Pimavanserin is approximately 30-fold more selective for 5HT2A receptors over other 5HT receptors and has no effect on dopamine receptors. Preclinical data revealed favorable pharmacokinetic and side-effect profiles. In rats, pimavanserin has a similar affinity for 5HT2A receptors as clozapine. It reduced drug-induced head twitches, exaggerated startle, and N-methyl-D-aspartate receptor antagonist induced hyperactivity, without ataxic or myorelaxant side effects. The compound was readily bioavailable at 10 mg/kg

orally [Vanover *et al.* 2006]. It has also been studied in rodent models of PDP [McFarland *et al.* 2011; Vanover *et al.* 2008]. Pimavanserin reduced psychotic behaviors (increased or altered head twitches) after treating rats with fenfluramine, a serotonin releasing agent [McFarland *et al.* 2011]. Pimavanserin was also studied in combination with olanzapine and risperidone, leading to improvements in psychotic features in rats such as novel object recognition [Snigdha *et al.* 2010], and it allowed for dose-sparing of antipsychotic agents [Gardell *et al.* 2007]. There is evidence to suggest that reduced dopaminergic tone may potentiate the activity of 5HT2A pharmacologic manipulation, particularly in the striatum. Thus it may exhibit different potencies in PD and schizophrenia [Vanover *et al.* 2008]. Dopaminergic signaling was altered in lesioned parkinsonian animals compared with those without nigrostriatal lesioning, and interestingly it was more sensitive to pimavanserin administration. Compensatory excessive dopaminergic signaling in response to striatal degeneration was impacted by pimavanserin. However, the normal dopaminergic response to amphetamine in nonlesioned animals was not impaired [McFarland *et al.* 2011].

Clinical trials of pimavanserin in PDP

Preliminary studies assessing adverse effects and bioavailability in healthy controls suggested minimal issues with tolerability and long half life of pimavanserin 20–50 mg without interference from food [Vanover *et al.* 2007a, 2007b]. The high affinity of pimavanserin for 5HT2A receptors [Nordstrom *et al.* 2008] stimulated great interest in its potential for treating PDP. To date, pimavanserin was studied in phase II, phase III, and open-label extension clinical trials, with encouraging results as described below.

A phase II, multicenter, randomized, placebo-controlled, double-blind 4-week trial [Meltzer *et al.* 2010] with patients with PDP was performed in those with hallucinations or delusions of moderate to severe frequency, as measured by a score of 4 or higher on the Neuropsychiatric Inventory (NPI). Inclusion criteria were symptoms for at least 4 weeks and stable PD medications for 1 week prior to and throughout the study period. No other antipsychotic medications were permitted. Patients with premorbid psychiatric conditions other than depression, and myocardial infarction within the past 3 months were excluded. Participants started pimavanserin 20 mg daily, with doses increased to 40 and 60 mg based on clinical response. The Hoehn and Yahr (H&Y) and UPDRS assessed motor symptoms, and psychotic symptoms were assessed using the SAPS, the Parkinson's Psychosis Rating Scale (PPRS), and CGI-S. Daytime sleepiness was assessed using the Epworth Sleepiness Scale (ESS). In the pimavanserin group, the mean age was 72.3 years [standard error (SE) 1.43], 26 (89.7%) were men, 28 (96.6%) were white, mean NPI score was 10.2 (1.05), and mean H&Y was 3 (0.17). In the placebo group, the average age was 69.6 years, 20 were men, all were white, NPI score was 11.6, and the mean H&Y score was 3. One of the patients in the pimavanserin group and three from the placebo group did not complete the 28-day trial. Twenty of the remaining pimavanserin-treated group and 24 from the placebo group completed the full safety analysis at 57 days. At day 28, those treated with pimavanserin had a statistically significant reduction in the mean global rating of hallucinations (3.5–2.4 points) and following SAPS measures for persecutory delusions (1.3–0.7 points), and global ratings of delusions (1.9–1.2 points). The pimavanserin-treated group had a 40% reduction in the SAPS total domain score. The UPDRS part I thought disorder subscore also significantly improved in the pimavanserin group, with a total mean difference of 1.45 points. Nonsignificant improvements *versus* placebo in the PPRS, CGI-S, and ESS were also noted in the pimavanserin group. There were no significant differences in adverse events between the two arms. The most commonly reported adverse events in the pimavanserin group were somnolence, edema, and increase in blood urea nitrogen, each reported at 10.3%. Among those in the placebo group, the most common side effects were: hallucinations (16.1%), dizziness (12.9%), and falls, headache, and confusion (each 9.7%). Treatment-related motor adverse events were mild. Although there were benefits noted in hallucinations and delusions, the principle measures of psychosis (total SAPS, PPRS, CGI-S) only showed a trend towards improvement. In summary, primary endpoints of safety and tolerability were met, and the duration was similar to previous clozapine trials [Meltzer *et al.* 2010].

The first phase III clinical trial of pimavanserin has only been published in abstract form [Friedman *et al.* 2010], although it has been described by the first author of the abstract in a subsequent review, [Friedman, 2013]. In this study of 259 subjects

with PDP, randomized to placebo, pimavanserin 10 mg daily, or pimavanserin 40 mg daily, benefit in the primary outcome measure [change in Scale For Assessment of Positive Symptoms-Parkinson's Disease hallucinations and delusions (H+D) score)] was not statistically significant. However, a large placebo response had been observed, and interestingly this was less at US sites than elsewhere. A subsequent *post hoc* analysis of sites within the USA was therefore undertaken and detected statistically significant benefit for pimavanserin 40 mg daily at 2 weeks.

A subsequent phase III, randomized, double-blind, parallel-group, placebo-controlled trial was therefore performed in 52 centers in the USA and two in Canada [Cummings *et al.* 2014]. This trial incorporated changes in design, including a specific psychotherapy approach aiming to decrease placebo effects, and the use of centralized raters. Participants with PDP were at least 40 years old, and had PD for at least 1 year, psychosis after PD diagnosis, a MMSE score of at least 21/30, and a caregiver present for all visits. Subjects had psychosis for at least 1 month with distressing symptoms present at least weekly, warranting treatment with atypical antipsychotic agents. Medications and deep brain stimulation settings were stable for 1month before study entry. Exclusion criteria included psychosis due to a toxic or metabolic injury, dementia prior to or developing soon after PD diagnosis, antipsychotic medication use, myocardial infarction in the past 6 months, stroke, serious medical illnesses, congestive heart failure, prolonged QT syndrome, or baseline prolongation of QTcB. There were 199 subjects enrolled, with 94 assigned to placebo and 105 to pimavanserin 40 mg once daily. In the placebo group, 87 completed the study *versus* 89 in the treatment arm. During screening a combined score of six or an individual score of four on the NPI was required. A period of psychotherapy was then given, using the brief psychosocial therapy for PD (BPST-PD), with the intended aim of reducing placebo response, with assessments of patients and caregivers at day 3 and 7. Eligibility at baseline was then defined by a SAPS score of 3, and a nonmotor item on SAPS-PD of 3. Assessments were made at baseline by central raters, to eliminate the evaluator bias. The primary endpoint of a reduction in SAPS-PD score at day 43. Of note, SAPS-PD was adapted from the schizophrenia SAPS scale [FOX, 2014].] Although not yet validated in PDP, this scale was used in the original studies of clozapine and is sensitive to changes in PDP.

The SAPS-PD score showed significant improvement in the pimavanserin group compared with placebo, with a mean reduction of 37% from baseline compared with 14%. Pimavanserin was also superior in improving scores on the SAPS-H+D scale, and on separate delusions and hallucinations domains. Subgroup analysis demonstrated pimavanserin's efficacy regardless of age, sex, or MMSE score. Those assigned to pimavanserin also had statistically significant improvements in the CGI-S [1.02 compared with placebo (0.44)], and Clinical Global Impression-Global Improvement [2.78 compared with placebo (3.45)] scales. Exploratory analyses found that caregivers of those receiving pimavanserin reported less burden using a mixed model repeated measures analysis for observed cases, but there was no correlation with improvement in psychosis, suggesting a broad range of positive effects. Importantly there was no worsening of UPDRS motor scores in the pimavanserin group, with a nonsignificant small improvement in motor function. SAPS-PD correlated with both CGI-S and CGI-I scores but not with improvements in sleep, suggesting that the sleep benefit is independent from the effect on PDP.

Adverse events occurred in less than 5% of either group. The most common for the pimavanserin *versus* placebo groups were peripheral edema (7% *versus* 3%), urinary tract infection (13% *versus* 12%), falls (11% *versus* 9%), confusion (6% *versus* 3%), headache (1% *versus* 5%), and hallucinations (7% *versus* 4%). The dropout rate was higher in the pimavanserin group but similar to those rates previously observed in other antipsychotic medication trials using similar scales. Those who discontinued did so due to psychosis.

Putting these results into context, the 6-week study period is in accordance with FDA standards set for other psychosis studies but longer than other studies for PDP. Although the benefit of pimavanserin is less robust than clozapine, the clozapine trials were shorter in duration and enrolled patients with more advanced disease, thus any comparison between these trials must be considered with caution [Fox, 2014].

Assessment of long-term impact of antipsychotics compared with pimavanserin on the morbidity of patients was performed in an open-label extension of the phase III study. Eligible patients were between 30 and 80 years and had PD with moderate to severe psychosis. Those who used antipsychotic agents before the first dose or within

30 days after the last dose of open-label pimavanserin were excluded. Study visits were conducted at 2 weeks, 1 month, 3 months, 6 months, 9 months, 12 months, and then monthly thereafter. Evaluations for safety, vital signs, and UPDRS Part II and III were performed at each visit. Out of a total of 459 patients, 36 were excluded either for pre- or post-study antipsychotic medication use. Of the 423, 66 had an antipsychotic agent added to their regimen, at a mean duration of 247 days from baseline. The other 357 never had antipsychotic agents added to their regimen. Both groups were matched according to age, PD duration, severity of psychosis, and cognitive impairment. Of those receiving an additional antipsychotic to pimavanserin, 52 received quetiapine at 25–50 mg daily. Ten of these individuals received a different adjunctive antipsychotic to pimavanserin at a later time: four received clozapine and another four received risperidone. The remaining six received other antipsychotic medications. Those receiving concurrent antipsychotic agents had a higher rate of statistically significant serious adverse events. The exposure-related incidence rate in the antipsychotic group was 52.5 per 100 person years compared with 17.8 per 100 person years in the pimavanserin only group. There were significant increases in the rates of any antipsychotic-related events, cognitive-related events, infections, and edema. There were nonsignificant increases in the rates of cerebrovascular and thromboembolic events, falls, and sedation. UPDRS motor scores also worsened with concurrent antipsychotic medications. There was also a significantly higher rate in mortality in the concurrent antipsychotic medication group with a rate of 18.8 per 100 person years compared with the 4.5 per 100 person years in the pimavanserin alone group. Also the mortality difference was not noted during the first 12 weeks of therapy but during months three to six. None of these adverse events were reported previously in those taking pimavanserin, making an additive effect less likely [Ballard *et al.* 2015]. Although this study noted more serious side effects in those receiving concurrent antipsychotics, it is important to note that the sample size of this group is small and it is a *post hoc* analysis. It is possible that despite the age, duration of PD and severity of PDP not being significantly different between the pimavanserin alone and concomitant antipsychotic drug group, the small sample size of the latter may have played a role in the final results. It is also possible that those requiring further antipsychotic medications may have had worse underlying disease and a poor outcome from the beginning, thus the results should be interpreted cautiously.

A meta-analysis assessing blinded and nonblinded randomized controlled trials of 5HT2A antagonists and inverse agonists, including pimavanserin, nafazedone, mirtazapine, cyproheptadine, trazodone, eplivanserin, and volinanserin, was recently performed. The primary endpoint was changes in the SAPS-H+D scale scores. Secondary endpoints were changes in the motor UPDRS, SAPS hallucinations (SAPS-H), and SAPS-delusions (SAPS-D), adverse events and discontinuation of treatment due to all-cause adverse events and death. After evaluating 349 possible reports, four were included and all of these were trials of pimavanserin *versus* placebo. These four studies included 680 patients with PDP, with average age 71 years, and three were at least 6 weeks in duration. Pimavanserin significantly reduced the SAPS-H+D scores compared with placebo. Likewise, the SAPS-H and SAPS-D scores were also significant reduced, but UPDRS motor scores remained similar between groups. The discontinuation rates and number of adverse events were also similar. Interestingly, the rate of orthostatic hypotension was lower in the pimavanserin group. An open-label study of mianserin and two case reports of mirtazapine also reported benefit, suggesting that 5HT2A receptor antagonists may be beneficial, but of this group of medications only pimavanserin had undergone testing in randomized controlled trials [Yasue *et al.* 2016].

Finally, pimavanserin has been studied in combination with other antipsychotic agents. In a large randomized controlled study of 423 patients, those who received low doses of risperidone (2 mg) and pimavanserin and low doses of haloperidol (2 mg) and pimavanserin had augumentation of the antipsychotic agents with comparable psychosis control to standard doses of risperidone (6 mg/day) and haloperidol (2 mg/day) alone. Those groups receiving pimavanserin also had fewer cases of metabolic syndrome, hyperprolactinemia, and movement disorders [Garay *et al.* 2016; Abbas and Roth, 2008].

Clinical use of pimavanserin

Pimavanserin (Nuplazid; Acadia Pharmaceuticals Inc., San Diego, CA, USA) is newly approved by the FDA, at the time of writing, for treating the delusions and hallucinations associated with PDP and therefore should be considered first-line

treatment. It is recommended at a dose of 34 mg by mouth daily, without titration. When evaluating a patient with PDP, there are however certain conditions that need to be considered. Since pimavanserin prolongs the QT interval, it should be avoided in individuals taking other medications with QT-prolonging activity and also in those with baseline of, or at risk for, prolonged QT interval (Nuplazid package insert). Although there is no direct evidence of increased mortality with pimavanserin, the 'black box warning' is derived purely from the use of dopamine-blocking antipsychotic agents in older people with dementia, which have a markedly different pharmacological effect than pimavanserin. Nevertheless, this warning will need to be discussed in the clinic as some patients with PDP will also have dementia. Its role in emergencies remains to be defined, and this and other questions may be further addressed as the medication is more widely used.

Conclusion

Psychotic symptoms are a devastating feature of PD, increasing NH admission, mortality, and caregiver burden. There is strong evidence that pimavanserin is effective in the treatment of PD without worsening motor symptoms, and it has been newly approved by the FDA for treating the delusions and hallucinations of PDP. Long-term data are emerging supporting its use for a long period of time in this population. Continued study of its side effects, particularly electrocardiogram changes, is necessary as autonomic dysfunction in PD can lead to alterations in cardiovascular function. Despite still unanswered questions, at this time pimavanserin will fill a void in the management of PDP and is predicted to dramatically change the landscape of management options for individuals with PDP.

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