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Psychosis in Parkinson Disease: A Review of Etiology, Phenomenology, and Management

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Abstract

Parkinson disease psychosis (PDP) is a common phenomenon in Parkinson disease (PD) patients treated with dopaminergic drugs, and is associated with high morbidity and mortality. It also correlates with depression and dementia, and can contribute to considerable caregiver stress and burnout. While symptoms can be relieved by decreasing doses or number of anti-PD medications, this may lead to an unacceptable worsening of motor function. When general medical or psychiatric conditions have been ruled out, and decreasing dopaminergic agents is not effective in treating psychosis, therapies include atypical antipsychotics, primarily clozapine and quetiapine. Of these, clozapine is effective but is associated with a poor side-effect profile and the necessity for frequent blood draws. Clinicians prefer quetiapine for its theoretically better safety profile, although there is no evidence for efficacy in treating psychosis. All atypical antipsychotics are associated with increased mortality in this patient population. Cholinesterase inhibitors can ameliorate psychosis symptoms. The serotonin 5-HT_{2A} receptor inverse agonist pimavanserin was recently approved by the US FDA for the treatment of PDP and may prove to be a more targeted therapy without the downsides of atypical antipsychotics.

1 Introduction

Parkinson disease (PD) is classically a neurodegenerative disorder characterized by a motor tetrad: (resting) tremor, rigidity, akinesia/bradykinesia, and postural instability [1]. PD pathology is related to the loss of dopaminergic neurons in the pars compacta of the substantia nigra and ventral tegmental (VT) area [2–4]. PD patients may also experience episodes of hallucinations and delusions, which, prior to the widespread use of dopaminergic drugs as therapy (in the 1910s and 1920s), were assumed to be due to a concomitant epidemic of encephalitis lethargica [5]. After the introduction of levodopa and, later,

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dopamine agonist treatment for PD, hallucinations were reported as medication side effects [6].

Parkinson disease psychosis (PDP), characterized by visual hallucinations and/or other psychotic symptoms, including auditory hallucinations, delusions, or illusions [7], is now considered to be closely associated with PD. In contrast to psychosis due to toxic/metabolic syndromes, PDP presents with a clear (rather than clouded) sensorium [8]. PDP is associated with high mortality, as well as morbidity, for patients, including decreases in health-promoting behaviors and longer nursing home stays [9]. Furthermore, there is a relationship between the development of PDP and other psychiatric diagnoses, including depression and dementia. Finally, PDP is a source of considerable caregiver stress and burnout [10, 11]. Because of its impact on the longevity and quality of life of many PD patients, PDP is a critical treatment target.

Psychosis can be provoked by the drugs used to treat the motor symptoms of PD. Additionally, PDP may be confounded with other conditions associated with psychosis. Therefore, diagnosis and management of psychosis in the setting of PD can be challenging. Treatment may not be indicated for mild hallucinations with retained insight, but becomes necessary in cases impacting quality of life. Atypical antipsychotics, including quetiapine and clozapine, are currently used where therapy for PDP is indicated, although pimavanserin, a novel therapeutic agent targeted to PDP, has been approved in the US. In this article, we review the literature describing PDP phenomenology and risk factors. We also discuss diagnostic and therapeutic approaches to PDP, as well as future directions for research into better treatment options.

2 Clinical Features

2.1 Hallucinations

Visual hallucinations are the most common feature of PDP, in contrast to primary psychotic disorders, where auditory hallucinations are most common. Hallucinations are more frequent in dim lighting or at the end of the day [12]. Patient retention of insight into these hallucinations may fluctuate over time, and may be related to the degree of concomitant cognitive impairment [13]. In a sample of 191 PD patients without dementia to whom the Parkinson Psychosis Rating Scale (PPRS) was administered, 21.5% of participants had psychosis. Visual hallucinations were common in this sample (13.6%). Auditory hallucinations were present in 6.8% of these patients; illusions or misidentification in 7.3%, and paranoid ideation in 4.7% [14].

The characteristics of hallucinations in PD were described in a sample of 216 PD patients [5]. Visual hallucinations were categorized into ‘minor’ and ‘formed’ variants. ‘Formed’ visual hallucinations included various content, such as of persons, familiar or unfamiliar, animals, or objects, while ‘minor’ hallucinations included illusions, such as of presence or of an object’s passage [15]. Minor hallucinations were present in 25.5% of patients; formed or ‘non-minor’ visual hallucinations in 22.2% (isolated in9.3%), and auditory hallucinations in 9.7% (isolated in 2.3%).

Although less common than visual hallucinations, auditory hallucinations have been reported in PDP. In another study, among a sample of 121 clinic patients with PD, 8% were reported to have auditory hallucinations [16]. None had auditory hallucinations unaccompanied by visual hallucinations, and all patients with auditory hallucinations were cognitively impaired. Auditory hallucinations were non-command and non-paranoid in this sample.

2.2 Delusions

Erotomanic, jealous, and persecutory delusions have been reported in PD [17], and there are case reports of Cotard syndrome ('nihilistic delusion' or self-negation) and Capgras syndrome (delusion that a friend or family member has been 'replaced') in PD patients [18–20]. Delusional jealousy (Othello syndrome) was observed in 20 of 805 patients with PD (approximately 2%), with a significant association with dopamine agonist therapy, and, in a small sample of five patients, was shown to be treatable with dopamine agonist therapy reduction [21, 22].

3 Diagnostic Criteria

A 2007 National Institute of Neurological Disorders and Stroke/National Institute of Mental Health (NINDS/NIMH) work group composed a consensus diagnostic criteria of psychosis in Parkinson disease [23, 24], which included recurrent or continuous symptoms, namely delusions, hallucinations, or other 'minor hallucinations' in the setting of a diagnosis of idiopathic PD, without another medical explanation, for at least 1 month. These manifestations may occur with or without insight, dementia, or medication-treated PD [24, 25].

4 Risk Factors

Various factors impact the risk of developing psychosis in a patient with PD. In a study of 775 PD patients taken off dopaminergic therapy, disease duration and severity, as well as therapy with dopamine agonists and catechol-O-methyltransferase (COMT) inhibitors, were predictors of increased psychosis risk [26]. These 775 patients were a subset of 1008 patients who were members of a Brazilian non-profit organization related to Parkinsonism. The patients fulfilled the Queen Square Brain Bank criteria for PD and did not have other limitations to the performance of motor examinations (including prior stroke, stereotactic neurosurgery). Of these, those who provided informed consent for withdrawal of dopaminergic medications were included.

Furthermore, there is an association between impairment in all cognitive domains and the presence of visual hallucinations [27].

Cognitive impairment, depression, and treatment with anticholinergics are associated with increased risk for PDP [28, 29]. Moustafa et al. found that while PD patients with and without psychosis were impaired on a working memory task compared with controls, PD patients with psychosis had a specific cognitive deficit in transitive inference, a hippocampal task [30]. Additionally, they found that Mini-Mental State Examination (MMSE) scores

correlated directly with psychosis severity, as measured by the Thought Disorder subscale of the Unified Parkinson Disease Rating Scale (UPDRS); however, psychosis has also been observed in PD patients without dementia. Of a sample of 175 outpatients with early untreated PD without dementia, 2.3% exhibited delusions and hallucinations [31].

The relationship between PD medications and PDP is unclear. Psychosis risk is increased with anticholinergic medications. In contrast, treatment with cholinesterase inhibitors, such as donepezil and rivastigmine, can ameliorate psychosis [28, 32]. Treatment with dopaminergic medications has been implicated as a psychosis risk factor, although the risk is not substantiated. For instance, in a sample of 102 PD outpatients, with more than 80% receiving levodopa therapy, Holroyd et al. found stronger associations between visual hallucinations and patient characteristics, such as disease severity, dementia, depression, and worse visual acuity, than with dopaminergic medication dosage [12]. Even among dopaminergic therapies, it is unclear whether levodopa or dopamine agonists contribute more to psychosis [33, 34]. Psychosis has also been reported in cases of subthalamic deep brain stimulation [35].

In a study of 87 patients with advanced PD, including 50 patients diagnosed with psychosis, carrying the apolipoprotein E (ApoE) epsilon4 allele was a risk factor for earlier appearance of psychosis [36]. Epsilon4 (in contrast to epsilon2) is associated with smaller hippocampal volumes in carriers, which is also associated with earlier onset of Alzheimer's disease [37]; smaller hippocampal volumes are also associated with primary psychotic disorders [38, 39]. A recent comprehensive review implicates polymorphisms in the cholecystokinin (CCK) gene in PD psychosis [40].

5 Pathophysiology

Extrinsic (drug-related) and intrinsic (neurotransmitter dysfunction-related) causes of PDP have been suggested. One hypothesis is that degeneration and overstimulation of mesolimbic dopaminergic neurons (specifically in the substantia nigra and VT area) contribute to degeneration in linked areas associated with different neurotransmitters, including locus coeruleus (norepinephrine), nucleus basalis (acetylcholine), and dorsal raphe nuclei (5-hydroxytryptamine [5-HT]) [41]. The functions of dopamine and acetylcholine may be linked because of the role of limbic nicotinic cholinergic receptors in dopamine release [42].

5.1 Neurotransmitter Hypotheses

Although the precise pathophysiology of PDP has not been elucidated, various neurotransmitter systems are being studied.

5.1.1 Dopamine—Degeneration of dopaminergic neurons in the ventral dopaminergic pathway is implicated in PDP because of disruption in limbic and cortical projections from the VT area. Dirnberger et al. found altered pallidal-frontal dopamine processing in six non-depressed, non-demented PD patients, compared with healthy controls, on an executive function task [43]. Overstimulation of striatal/mesolimbic dopamine receptors may be associated with the generation of visual hallucinations [42]. These studies suggest the possibility of striatal dopaminergic impairment influencing frontal regions, providing a

pathway for psychosis induction in PD. Therefore, withdrawing or decreasing levels of dopaminergic medications may alleviate psychotic symptoms in PDP.

5.1.2 Acetylcholine—Loss of cholinergic neurons in the nucleus basalis of Meynert is associated with PD progression [44], while cholinergic deficits may be associated with visual hallucinations in PDP [45]. The pedunculopontine nucleus pars compacta (PPNc) is a cholinergic nucleus whose degeneration is associated with PD pathology. Some investigators have found increased volume loss in PPNc in PD patients compared with both normal controls and dementia with Lewy bodies (DLB) patients with visual hallucinations [46, 47].

5.1.3 Serotonin—Serotonin has been implicated in psychosis generation because of the action of 5-HT_{1A} receptor agonists, including lysergic acid diethylamide (LSD), in producing visual hallucinations. The history of serotonergic drug use in PD dates to initial studies using methysergide (a serotonin antagonist with concerning side effects, including retroperitoneal fibrosis) ineffectively for the treatment of PD [48]. More recently, atypical antipsychotics, which block 5-HT as well as dopamine receptors, have been considered for reducing PDP symptoms. Pimavanserin, a new 5-HT_{2A} receptor inverse agonist, has been approved for the treatment of PDP [24, 49]. Part of the antipsychotic action of pimavanserin may be attributable to the role of 5-HT_{2A} receptor inverse agonists in preferentially releasing dopamine in the cortex, rather than the limbic system [49]. It is promising, in conjunction with risperidone, for the treatment of schizophrenia, allowing for decreased use of risperidone for this indication and reducing the risk of extrapyramidal symptoms [50].

5.2 Functional and Structural Imaging Studies

Visual hallucinations may be related to visual pathway disruption. This includes ocular dysfunction, including color discrimination, alterations in visual acuity, retinal dysfunction, diplopia, and blindness (monocular or binocular) [8, 51–53].

Patients with visual hallucinations may also have structural anomalies of the cortical visual processing system, such as gray matter atrophy in several cerebral and cerebellar areas [54–57]. Another notable pathologic marker of visual hallucinations in PDP is the presence of Lewy bodies in the temporal lobe. Well-formed visual hallucinations are associated with the presence of brainstem Lewy bodies, especially in the amygdala and the parahippocampal region [58]. PD patients with visual hallucinations have demonstrated functional imaging differences compared with controls. In a visual processing task, Stebbins et al. found a shift in the processing of strobe stimuli from posterior (visual cortical, including occipital, temporal, parietal posterior cortex) to anterior (attention-related, superior frontal) brain areas in 12 PD patients with visual hallucinations compared with matched PD non-hallucinators, suggesting altered functional visual pathways [59]. Ramirez-Ruiz et al. demonstrated hyperactivation of the inferior frontal gyrus in PD patients with visual hallucinations during a one-back task [60], while Kiferle et al. showed increased caudate uptake in 18 patients with visual hallucinations in a single-photon emission computed tomography (SPECT) study [61]. The results of these and similar studies suggest a derangement in attention and vision networks. Deficits in bottom-up processing and abnormalities in fronto-striatal networks in PD patients may be the basis for hallucinations.

6 Management Approaches

6.1 Assessment

No rating scales have yet been validated for the measurement of PDP, although the Brief Psychiatric Rating Scale (BPRS) for PD, the PPRS, the Neuropsychiatric Inventory (NPI), the UPDRS Thought Disorder subscale, and the Scale for Assessment of Positive Symptoms (SAPS) for PD have been used clinically as well as in research contexts [62]. The pareidolia test assesses for a subject's propensity for, and ability to perceive, complex visual illusions. Patients with DLB tend to experience pareidolias more often and this test may also help differentiate PD patients with psychosis from healthy controls [63, 64]. Currently, the diagnosis of PDP is made on the basis of clinical presentation of recurrent delusions and hallucinations for at least 1 month.

6.2 Diagnostic Work-Up

Diagnosing PDP entails ruling out other causes of the presenting symptoms. Laboratory tests, including clinically appropriate workup for causes of possible delirium or exclusion of occult infection (which might include a complete metabolic panel, complete blood count [CBC], thyroid-stimulating hormone level, liver function tests, ammonia, vitamin B12 and folate levels, as well as rapid plasma reagin and urinalysis) may be considered. Brain magnetic resonance imaging (MRI) should be considered for investigating other intracranial processes when psychosis is acute, persistent, and accompanied by other neurological deficits. Patient medications should be reviewed, with special attention given to recent medication changes. Any Beer's list medication (medications to avoid in the geriatric population, corresponding to the screening tool of older people's prescriptions/screening tool to alert to right treatment [STOPP/START] tool kit in the UK) should be assessed for necessity [65–67]. Concomitantly, a good caregiver history should be obtained. Clinicians should be alert for the possibility of depression or a primary psychotic disorder as a cause of the presenting hallucinations, and clinically assess for these. Chronology and careful history taking are essential; the onset of psychotic symptoms early in life and/or prior to Parkinsonism point to a primary psychiatric disorder. Acute onset of psychotic symptoms early in the course of Parkinsonism suggests DLB, while psychosis in the context of well-established PD suggests PDP. The Lewy Body Composite Risk Score is a new, rapid scoring method that may improve sensitivity of DLB detection [68].

In addition, the impact of psychotic symptoms on the patient's life should be determined; very mild symptoms with preserved insight may not require pharmacologic treatment [69]. Subsequently, medications for PD should be adjusted because of their potential to worsen psychosis. A suggested order in the literature for discontinuation of medications is to, first, stop adjuvant medications for PD, including anticholinergics, selegiline, and amantadine; second, stop dopamine agonists and COMT inhibitors; and, lastly, reduce levodopa only if these measures fail [70]. Complete removal of all dopaminergic medications should be avoided to prevent significant worsening of parkinsonian symptoms and, in rare instances, development of neuroleptic malignant syndrome [71, 72].

6.3 Drugs with Promise in the Treatment of Parkinson Disease Psychosis

6.3.1 Quetiapine and Clozapine—Atypical antipsychotics can be used if, after other steps are taken, psychosis symptoms are still troubling and persistent. Clozapine is recommended and is the only antipsychotic with proven efficacy in PDP [73]. Although in a randomized open-label trial of 45 patients with PDP, clozapine and quetiapine were shown to be equally effective in reducing psychotic symptoms, as measured by the BPRS, several subsequent randomized clinical trials (RCTs) demonstrated no change in psychotic outcomes with quetiapine [74–77]. Neither worsened motor symptoms on the UPDRS.

Although there is insufficient evidence for the efficacy of quetiapine, clinicians tend to prefer low-dose quetiapine over clozapine because of the extensive need for monitoring for clozapine-induced agranulocytosis, including weekly CBCs for 6 months, followed by biweekly CBCs, which are then administered monthly after 1 year [70]. Additionally, patients and providers must both be registered with the FDA for clozapine to be prescribed. A recent retrospective chart review of clozapine use in PDP patients at a single center over the course of 8 years demonstrated a low overall retention rate on clozapine, in large part due to the inconvenience of frequent blood testing [78]. However, a danger of using quetiapine is the possibility of sedation and subsequent falls in geriatric patients [79]. Both are atypical antipsychotics and carry the risk of weight gain and the metabolic syndrome. The FDA has also determined that available data show increased mortality with the use of atypical antipsychotics in elderly patients with dementia, and this risk appears to carry into the PD population [80]. However, it is of note that low-dose clozapine can be used to good effect in PDP, and this may allay concerns about the metabolic syndrome in association with clozapine [81]. While maintenance doses of 50–200 mg/day may be typically required for the treatment of psychosis associated with schizophrenia, doses<50 mg/day can be used to good effect in PDP [82, 83]. Generally, clozapine may have a fast onset of action, over a few days to 1 week [84]. In a study of 32 patients with PD and psychosis, over 5 years, the major side effect of clozapine that limited dose uptitration was somnolence [85].

In 2006, the American Academy of Neurology (AAN) released guidelines for the treatment of PDP with atypical antipsychotics. These guidelines recommended the use of clozapine over quetiapine (level C evidence) on the basis of a double-blind prospective cohort study (level B evidence) because clozapine may improve both psychosis and motor function [82, 86, 87]. Clozapine is considered the gold standard in the treatment of PDP. The National Institute for Health and Care Excellence (NICE, UK) 2006 guidelines agree with the use of clozapine and quetiapine, and new guidelines are currently in draft form and are expected in 2017 [88].

6.3.2 Other Antipsychotics—Other antipsychotics have been examined in the treatment of PDP, notably olanzapine, risperidone, ziprasidone (all atypical antipsychotics), and melperone (typical antipsychotic). In double-blind studies, olanzapine has not been shown to be effective in treating psychosis but has resulted in significant motor worsening when compared with placebo or clozapine [89, 90]. Consequently, the AAN does not recommend olanzapine for the treatment of PDP (level B evidence). Risperidone is effective in treating psychosis but has variably resulted in worsening motor symptoms [91]. There is

no AAN guideline on the use of risperidone in PDP, while NICE guidelines also recommend against the use of olanzapine [88].

In a very small, open-label, prospective trial, ziprasidone has been shown to ameliorate psychosis symptoms, as assessed by SAPS and BPRS, in 14 patients over 4 weeks [92]; however, it carries a possibility of QT prolongation and an unfavorable extrapyramidal symptom side-effect profile. Melperone may not have the side effect of metabolic syndrome. However, results of an unpublished double-blind, placebo-controlled trial in 2011 suggest that it is ineffective in the treatment of PDP, as assessed by the SAPS, although it did not worsen motor function [93].

6.3.3 Cholinesterase Inhibitors—Because of the close association between severe hallucinations in PD and dementia, cholinesterase inhibitors have been investigated as a therapeutic for PDP. These may be effective in the context of pre-existing visual hallucinations or PD with dementia. In several randomized, placebo-controlled, double-blind trials of donepezil to evaluate cognitive outcomes, psychiatric symptoms as assessed by the NPI were a secondary outcome that did not change between treatment and control groups [94]. However, a 24-week study of rivastigmine for PD dementia among outpatients found improvement in visual hallucination incidence [95]. Of note, hallucinations may be treated with cholinesterase inhibitors in DLB, with a current ongoing clinical trial in PDP [96–98]. Studies with cholinesterase inhibitors are needed, with psychotic symptom reduction in PDP as a primary outcome measure.

6.3.4 Serotonin Agonists/Antagonists—Because of the need for dopaminergic therapy for motor symptoms of PD, there has been strong interest in serotonergic agents for PDP [99]. Both clozapine and quetiapine, which are currently used to treat PDP, are 5-HT_{2A} receptor antagonists. Ondansetron, a 5-HT_3 receptor antagonist, has shown some efficacy in the treatment of PDP [100], while pimavanserin, a 5-HT_{2A} receptor inverse agonist, has been approved for PDP in the US. Two double-blinded RCTs have compared pimavanserin with placebo in reducing psychotic symptoms. The first, over the course of 28 days, showed patient improvement on SAPS-based measures, and no decline in motor or cognitive function was seen [101]. In addition, a 6-week-long trial of nearly 200 outpatients showed patient improvement on psychotic symptoms versus placebo on a modified version of the SAPS—the SAPS-PD—without significant adverse effects [102]. Pimavanserin and atypical antipsychotics have not been directly compared.

6.3.5 Other Treatments—Case reports for various antidepressants, including clomipramine, citalopram, and mirtazapine have demonstrated potential efficacy in PDP with comorbid depression or insomnia [103–105]. Electroconvulsive therapy has been shown in a few case reports to benefit PDP patients [106].

Non-interventional treatments for psychosis, including psychoeducation and cognitive behavioral therapy, have shown some benefit in schizophrenia and could also be explored in the setting of PDP [107]. Music therapy has been used with benefit for the affective and behavioral symptoms of PD [108]; however, these therapies would pose challenges in patients with cognitive impairment as some degree of insight would be required.

7 Conclusions

PDP, often manifesting with visual hallucinations, is a common complication of PD. Generally, it is comorbid with significant cognitive impairment, with severe social and occupational consequences for the patient. The pathophysiology of PDP is only partly understood. Therefore, available treatments for PDP are suboptimal. There is a conflict between the need for dopaminergic treatment in PD and the anti-dopaminergic mechanism of most antipsychotics. Of the atypical antipsychotics, clozapine has shown effectiveness in an RCT but its side effects and the need for monitoring are undesirable. Pimavanserin, a 5-HT_{2A} receptor inverse agonist, has recently been approved by the FDA for use in the US [109].

Next steps will likely include investigating similar serotonergic drugs in comparison studies with atypical antipsychotics, as well as further elucidating the role of cholinesterase inhibitors in treatment. Ongoing studies include [A Study of the Safety and Tolerability of Pimavanserin (ACP-103) in Patients With Parkinson's Disease Psychosis] and [Cholinesterase Inhibitors to Slow Progression of Visual Hallucinations in Parkinson's Disease], as well as an observational study, [Understanding Hallucinations (Part I)], among others. Further research is needed to identify imaging, genetic, and other clinical biomarkers for PDP, which, in turn, could lead to more targeted therapies.

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Key Points

Parkinson disease psychosis (PDP) is associated with increased morbidity and mortality in Parkinson disease patients.

Decreasing the number and dosage of anti-Parkinson disease drugs, which could alleviate PDP symptoms, might also worsen motor function.

Atypical antipsychotics, including clozapine and quetiapine, have problematic side effects. Clozapine is proven to be effective in PDP, with fewer side effects than quetiapine.

Pimavanserin, a serotonin receptor inverse agonist, has been newly approved in the US to treat PDP.