

Case Report

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Psychosis in Parkinson Disease

Mervat Wahba*

Associate Professor, USA

*Corresponding author: Mervat Wahba, Associate Professor, 415 Link Building, 855 Monroe Avenue, Memphis TN, USA.

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Abstract

Parkinson disease (PD) affects 1 million Americans with the number anticipated to double worldwide by 2030. There is a growing interest in psychosis and Parkinson's disease [PD], and its impact on treatment. Hallucinations and psychosis occur at any time during the course of Parkinson's disease. The mechanisms underlying drug-induced psychosis in Parkinson disease are not fully understood. Step-by-step approach and excluding other causes for delirium and psychosis such as infection should be considered.

Introduction

Levodopa was introduced in the late 1960s, it offered great success for reversal of symptoms of Parkinson's disease. There are side effects encountered with Levodopa treatment, among which is dopamine-induced psychosis (DIP). This can contribute to increased caregiver, and nursing home work load. Atypical antipsychotic treatments such as Clozapine have offered efficacy in treating this problem. More recently, a newer medication; Pimavanserin (Nuplazid) has been successfully used for this symptom. The antipsychotic effects of this new agent are believed to occur via selective inverse agonist activity at serotonin 5-HT_{2a} receptors. Drug-induced psychosis in patients with Parkinson disease encompasses different distinct syndromes as not all psychotic symptoms are drug-induced. Parkinson disease patients who develop hallucinations and delusions prior to the exposure to Levodopa or other medications arguably have Lewy Body Disease [LBD] or an overlap between LBD and PD.

Incidence and Risk Factors

After introduction of Levodopa, it was apparent that psychiatric syndromes were occurring at a higher frequency thus indicating that Levodopa contributed to this phenomenon. Unfortunately, cases of LBDB and cases of confusion were lumped with other forms of psychosis. In 1971 Goodwin¹ studied the psychiatric side effects in 908 patients with Parkinson's disease using levodopa. And average incidence of 20% was found, with the range of 10-50 %. Delirium was reported in 4.4%, hallucinations and delusions were reported with a frequency of 3.6%. In this modern era of treating psychosis and hallucinations in PD, several publications

have studied the frequency of psychosis in Parkinson's disease and it ranged from 22% to 46% [1-8]. These studies included minor symptoms as delusions and hallucinations. Increased incidence of levodopa related psychosis is seen in patients with premorbid psychiatric illness, dementia, advanced age [9]. Hallucinations in Parkinson's disease can occur at any time during the course of the illness, however they tend to occur late in the diagnosis. Goetz CG et al. [10] have suggested that early-onset hallucinations that occur within three months of the diagnosis onset are not typical of idiopathic Parkinson's disease.

Other anti-parkinsonian medications including non-dopaminergic medications were also recognized to cause dopamine induced psychosis. Acute delirium has been described after withdrawal of Amantadine in patients who have been on the medication at doses over 300 mg per day [11]. Entacapone, a COMT inhibitor that was approved in 1999 to increase the bioavailability of concomitantly administered with levodopa has also been reported to be associated with increased hallucinations [12].

Clinical Features

The clinical features of the DIP in PD have been described in notable reports. Visual hallucinations account for 30% of the symptoms. Visual hallucinations occur with clear sensorium, mostly composed of non-threatening images of people such as family members who have died, also animals, inanimate objects, or children wandering around the house [13,14]. Some patients claim that the images represent an illusion, the term "hallucinosus" is used to describe the occurrence of hallucinations with retained

insight. Other patients claim that the hallucinations are real images, are impacted by their occurrence. Some patients describe that the images may disappear if they move toward them or try to touch them [3].

In contrast to hallucinatory experiences associated with some recreational drugs, no shifting patterns, or distortions of space are seen [15].

Auditory hallucinations may also occur with DIP in up to 40% of patients who experience visual hallucinations⁵. The auditory hallucinations may not be related to the visual hallucinations that is experienced at the same time. Visual illusions and distortions are less likely, but have been reported [16]. It was reported that 3% of PD patients treated with Levodopa for two years or more may experience delusions which are centered around spousal infidelity, or conspiracies by the family or even the healthcare providers [17].

Mechanisms of Dopamine-Induced Psychosis (DIP)

Several theories exist to explain DIP as symptoms may be merely the unmasking of a premorbid psychiatric diagnosis, Levodopa may precipitate these symptoms by inducing hypersensitivity to the denervated dopamine receptors. The visual hallucinations did not always correlate with the levels of levodopa [18]. Serotonergic mechanisms are also implicated as Levodopa reduces brainstem Serotonin by replacing it in the presynaptic sites, also by interfering with the transport of L-tryptophan across the gut and blood-brain barrier, and by inhibiting tryptophan hydroxylase [19]. Anticholinergic medications that are used to mitigate against tremors may also precipitate hallucinations.

Treatment of Psychosis

A careful analysis of the symptoms with ruling out confounding factors such as infections, hypoxia, hemodynamic abnormalities should be ruled out as possible factors contributing to the patient's decompensation. If no other etiologies are present, gradual reductions of the Levodopa medication as well as other anti-parkinson medications should be tried, one medication at a time, starting with the dopamine agonists.

Pimavanserin is a relatively newly approved medication in treating DIP or Parkinson's disease psychosis (PDP) that has expanded the treatment options for DIP or PDP. Pimavanserin was developed to treat PDP, was approved by the FDA in 2016. Pimavanserin acts as an inverse agonist and antagonist at serotonin 5-HT_{2A} receptors with high binding affinity and at serotonin 5-HT_{2C} receptors with lower binding affinity. Pimavanserin shows low binding to σ_1 receptors and has no appreciable affinity to serotonin 5-HT_{2B}, dopamine (including D₂), muscarinic acetylcholine, histamine, or adrenergic receptors, or to calcium channels [20,21]. These properties account for the non-worsening of Parkinsonism with the use of Pimavanserin.

The efficacy of Pimavanserin was tested in a double-blind 6-week study utilizing a 9-item SAPS-PD (Scale for assessment of Positive Symptoms-Parkinson's Disease). A secondary measure in this trial included the Unified Parkinson's Disease Rating Scale (UPDRS) parts II+III. Among patients who received pimavanserin,

74% experienced an improvement in PDP symptoms, nearly 14% experienced complete resolution, compared to 56% and 1% respectively for patients who received placebo [22]. Pimavanserin may cause prolongation of the QT interval, thus EKG should be obtained prior to initiating the treatment, also caution should be exercised when the patient is also on other medications that may prolong the QT interval. Dosing of Pimavanserin is 34 mg once daily (two 17mg tablets taken together). The half life of Pimavanserin is 57 hours, achieves a steady state plasma concentration in two weeks [22].

Prior to the approval of Pimavanserin, treatment options included quetiapine (Seroquel), clozapine (Clozaril).

Clozaril (CLZ) is the only medication prior to Pimavanserin to show proven efficacy in treating DIP or DPD without worsening Parkinsonism in clinical trials. The concerning adverse effect of CLZ is agranulocytosis that may occur in 1 to 2% [23]. CLZ may worsen dementia, also other less frequent medical complications after use of CLZ were reported such as autonomic dysfunction, venous thromboembolism, myocarditis [24,25]. Quetiapine (QTP) is a reasonable alternative to treat DIP or PDP if Pimavanserin is unavailable. Use of Risperdal (RSP) and Olanzapine (OLZ) and other older generation antipsychotics should be avoided as they worsen Parkinsonian clinical manifestations. Some patients require significant reductions in levodopa. With all treatments of DIP or PDP, the treating physician should carefully monitor the Parkinsonian symptoms, vital signs, QT interval, dementia features, sedative effects as well as fall precautions.

Long-Term Prognosis

Prior to the introduction of Pimavanserin, Factor SA et al. [26] studied 59 patients who were mostly severely affected with DIP who were enrolled in a double-blind trial for CLZ therapy, followed them up for 22 months. At baseline, 12% were living in a nursing home, 95% had hallucinations, and 60% had paranoia. At follow up, 25% were dead, nursing home placement occurred in 42%, psychosis were persistent in 69%. These outcomes cannot be generalized in this new era with the availability of new treatments such as Pimavanserin. We await new follow up registries in this area.

Acknowledgement

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Conflict of Interest

Author declared no conflict of interest.

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