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Review Article

Psychosis in Parkinson's Disease and Current Management Trends- An Updated Review of Literature

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Abstract

As a neurodegenerative disorder, Parkinson's disease (PD) is characterized by a combination of premotor, motor, and nonmotor symptoms. PD is commonly accompanied by psychosis, which is one of the commonest symptoms in the long run. As a result of Parkinson's disease psychosis (PDP), symptoms can range from minor consequences of the disease (illusions, passage hallucinations, and presence hallucinations), to visual and nonvisual hallucinations and delusions. PDP is associated with a reduction in function and a reduction in quality of life as well. It is commonly believed that PDP is related to economic burden, and it has a significant impact on the utilization of long-term care services. The main focus should be on diagnosing, classifying, and managing PDP in an appropriate manner. As a first step in the management of PDP patients, the emphasis should be on identifying and treating any contributing medical factors, reducing or discontinuing medications that could cause or worsen psychosis, as well as nonpharmacological strategies and considering acetylcholinesterase inhibitors for treatment when dementia is present. A number of medications are being considered for use in PDP, including pimavanserin, quetiapine, and clozapine. The purpose of the current review is to provide a comprehensive understanding of the disorder in the general population with PD, including epidemiology, psychotic symptoms, risk factors, triggers, neuro-signaling pathways, diagnosis, and treatment of PDP.

Abbreviations

PDD: Parkinson's Disease Dementia; LC: Locus Coeruleus; SN: Substantia Nigra; APOE: Apolipoprotein E; VNTR: Variable Number of Tandem Repeats; UTR: Untranslated Region; DR: Dopamine Receptor; CCK: Cholecystokinin; CCKAR: Cholecystokinin A Receptor; CCKBR: Cholecystokinin B Receptor; HOMER1: Homer Scaffold Protein 1; COMT: Catechol-O-Methyltransferase; ACE: Angiotensin-Converting Enzyme; MDS-UPDRS: Movement Disorder Society- Unified Parkinson's Disease Rating Scale; DA: Dopamine Agonist; AAN: American Academy Of Neurology; DDC: Dopa-Decarboxylase.

Introduction

It is known that Parkinson's disease (PD) is a neurodegenerative illness that leads to progressive disability. A loss of striatal dopaminergic neurons in the substantia nigra pars compacta (SNpc), which project to the dorsal striatum, is commonly observed. It is characterized by a decrease in the neurotransmitter dopamine throughout the brain, leading to premotor, motor, and nonmotor symptoms [1-5].

PD patients experience motor features, including resting tremors, bradykinesia, and muscular rigidity with postural instability, often appearing as the disease progresses [6]. Nonmotor symptoms of PD, including cognitive impairments and behavior problems, are generally reported to be more disabling than the motor symptoms of the disease themselves [5,7,8].

There are several non-motor symptoms of PD which include autonomic dysfunction, pain, sleep disruptions, impaired sense of smell/olfactory deficits, gastrointestinal disturbances, cognitive impairment such as subjective cognitive decline, mild cognitive impairment, and dementia, as well as depression, impulse control disorders, and psychosis [9-14]. A summary of all the premotor, motor, and non-motor symptoms can be found in Table 1.

Table 1: Symptoms in PD [4,15].

Premotor symptoms	Anosmia, depression, constipation, rapid eye movement sleep behavior disorder
Motor symptoms	Tremor, bradykinesia, postural instability, shuffling gait, stooped posture, dyskinesia, muscle rigidity, "freezing" episodes, and micrographia
Non-motor symptoms	Flat affect, excessive salivation, anosmia, depression, staring appearance, anxiety, psychosis, sleep disruption, fatigue, autonomic dysfunction, cognitive impairment, constipation, dysphagia, dysarthria, urinary incontinence, diminished speech volume, olfactory dysfunction, unexplained pain

At the histological level, the progressive SNpc degeneration correlates with the accumulation of large intra-cytoplasmic inclusions, namely Lewy body (LB) containing misfolded α-synuclein (α-syn), neurofilaments, and ubiquitin, although α-syn deposition occurs years before motor presentations begin [16-20]. Up to one million Americans and more than 10 million individuals around the world are affected by this disease [21], which is the second most common neurodegenerative disease after Alzheimer's disease [22,23].

There is no exact explanation of the etiology of PD, but it is believed that a combination of both environmental and genetic factors may contribute to the disease [24-26]. Among the general population, it is estimated that the prevalence of the disease is between 0.3 and 1.0% and that the incidence of the disease among those aged over 80 is approximately 3.0% [27-30]. In terms of incidence ratio, it has been observed that PD is more prevalent among males than females by an average of 2:1 [31-35].

It is expected that by 2030 that the incidence of PD will double in the five most populated nations in Western Europe and the 10 most populated countries in the world, including the United States because of the growing elderly population [36-40]. The incidence and prevalence of PD increases with age and is most commonly seen in people over the age of 50 [41-44]. It is estimated that 20% of individuals with PD will be diagnosed before they are 65 years old [45-47].

As the population ages with an increased life expectancy, the prevalence of PD is expected to increase dramatically over the next few decades [38,48]. This will be a consequence of the changing demographics of an aging population. There are approximately 930,000 individuals in the United States over the age of 45 who suffer from PD, and by 2030, that number is expected to rise to 1,238,000 individuals [40,44]. According, to the National Institute for Health, average annual costs related to PD in the United States alone are estimated to be more than $25 billion, taking into account direct and indirect costs such as treatment, Social Security payments, and lost income from inability to work [21].

As one of the greatest challenges in the treatment of PD, Parkinson's disease psychosis (PDP) encompasses a spectrum of symptoms that go beyond just formed VHs and is considered to be one of the major challenges for treating neurologists and physicians [49-54]. It is possible to experience presence or passage hallucinations (i.e., seeing an object or person moving in the periphery of the eye) [51]; complex VHs involving people, animals, or objects [52]; auditory, tactile, gustatory, and olfactory hallucinations, which can occur independently or in combination with VHs [55,56]; and paranoid beliefs involving spouses, family members, or caregivers [57].

The most common symptoms of PDP are VHs, which have been reported in up to 65% - 75% of patients [58,59]. The prevalence of hallucinations has been found to be 50% in patients with PD after 15 years, and 70% after 20 years [60].

For a long time, it has been believed that psychosis is primarily due to the use of dopaminergic treatments in the treatment of PD motor symptoms. In spite of that, it has become increasingly apparent that dopaminergic therapy is neither necessary nor sufficient in order to completely explain how psychosis develops [53,61]. Recently, it has been found that these symptoms may be caused by intrinsic processes within the disease itself [62,63].

As a result of these differences in clinical features observed in PDP, it is important to remember that it differs from other psychotic diseases like schizophrenia or mood disorders associated with psychotic phenomena. Therefore, the current diagnostic criteria that are used in other mental health conditions may not be adequate for describing PDP's diversity [64].

A strong correlation exists between psychosis symptoms in patients with PD and caregiver burden [65-70]. There is no question that PDP has a significant impact on both patients and caregivers alike. There are numerous outcomes associated with this condition, including an impaired quality of life (QOL) [61], placement in a nursing home [71,72], deteriorating patient outcomes, and an increased risk of death even [53,73-75]. If psychotic features are present in a patient, they tend to persist and become recurrent over time [53,76-79].

Although the complex pathophysiology of PDP remains elusive, it is believed that it is associated with abnormalities in visual processing, sleep disturbances, and specific changes in dopamine, serotonin, and acetylcholine signaling [53,80-82]. Increasing levels of sensitivity in the mesolimbic and mesocortical areas of the brain are considered to be one of the factors that contribute to psychosis, according to the dopamine hypothesis. Furthermore, it is also hypothesized that the serotonergic and the acetyl-cholinergic systems also play a role in PDP, either by disrupting the equilibrium between serotonin and dopamine or by causing a deficit in cholinergic neurons [83-88].

Epidemiology

Published data on the annual incidence of PDP are scarce. The authors of a recent study conducted an incident cohort study from 1991 to 2010 in Olmsted County, Minnesota, to investigate the incidence of PDP, as well as to investigate their survival. In this study, they found that the incidence of PDP was 4.28 per 100 person-years in their cohort. There was also an increase in the risk of death by 71% among PDP patients compared to patients with PD. As compared to women, men had a 73.4% higher risk of death when they were PD patients without psychosis, while there were no significant differences in sex between those who were PD patients with psychosis and those who were not. In their study, they found that patients with PDP were more likely to die than patients with PD. In PD without psychosis, the odds of death were higher for men than for women; however, in PDP, the odds of death were comparable regardless of gender [89].

PDP's prevalence has been difficult to determine, mainly because of the non-uniform methods of defining and measuring symptoms, resulting in a wide variance in how prevalent it is from one part of the world to another [53,90]. It is important to note that the samples of patients collected in earlier studies are generally cross-sectional, with prevalence rates ranging from 16% to 75% [91-103]. According to the NINDS/NIMH (National Institute of Neurological Disorders and Stroke/National Institute of Mental Health) criteria for PDP, 113 patients with PD were evaluated in an outpatient clinic setting and 60 percent of them were found to have psychotic symptoms [104].

As a whole, the prevalence of the disorder was higher than the definitions that the authors used (such as questionnaires and Diagnostic and Statistical Manual of Mental Disorders [DSM] criteria [60% *vs*. 43%), mainly due to the fact that the study included the less common visual illusions (27%) and minor symptoms (45%), as well as non VHs (35%). Using the same scale, a similar study of 250 community-based PD patients found a lower overall prevalence of 26% with any kind of psychosis and 52% with delusions. This result may be due to the fact that this study recruited subjects who had higher mini-mental state examination (MMSE) scores (i.e., > 24) than those in the previous study [105].

Across cross-sectional studies, there is a relatively homogeneous prevalence rate for complex VHs, with a range of 22% to 38% for the prevalence of these types of hallucinations. The values range from 0% to 22% for auditory hallucinations and even higher for minor psychotic symptoms (17% to 72%). Due to a number of methodological differences, and especially the wide variation in the range of psychotic symptoms that were investigated in these studies, it is difficult to compare the total prevalence of hallucinations or psychotic symptoms in general between these studies. There was no assessment of tactile hallucinations, olfactory hallucinations, or gustatory hallucinations, although these types of hallucinations may be more prevalent than previously assumed [106].

According to longitudinal studies of PD patients, a number of longitudinal studies have repeatedly been conducted to assess the prevalence of hallucinations at a given point in time. According to a selected clinic-based sample, the point prevalence rates for the disease in a determined population increased from 33% (n = 89) to 55% (n = 49) after 6 years [76], After 4 years, the prevalence of the disease in a community-based sample jumped from 23% (n = 82) to 56% (n = 68) [107] and in patients who were initially enrolled in a drug trial, the prevalence of the disease increased by 21% (n = 52) to 77% (n = 30) after respectively 15 and 20 years [108].

It is worth noting that two long-term studies included de novo patients participating in drug trials at the start. The prevalence of hallucinations over a period of four years in a four-year trial was 17% during that period [109]. In a 20-year follow-up of patients initially recruited in a bromocriptine trial, the period prevalence was 74% [108]. Analyses of psychotic symptoms among Southeast Asian patients with PD were conducted using a retrospective cohort of 336 patients. According to the study, psychosis was diagnosed in 63 patients with PD, which corresponds to an 18.8% prevalence of psychosis in this population.

In a retrospective study that examined a total of 445 patients who had died with a pathologically confirmed diagnosis of PD, 50% were found to have had a history of VHs and/or minor psychotic symptoms during their lifetimes [111].

In addition to the progressive nature of the disease, it has been reported that minor phenomena such as a sense of presence or visual illusions have an impact on 17% to 72% of patients, while VHs can have a life-time risk of up to 50% [112]. In community-based population studies, it is estimated that up to 60 percent of patients with PD will develop psychosis within 12 years of onset and that 27% of people with PD will experience psychotic symptoms within 19 months of being diagnosed [80]. As the disease progresses, psychotic symptoms often present sequentially in a series of stages, starting with a visual illusion, then transitioning to more severe hallucinations that include insight, hallucinations without insight, and then delusions [113].

Compared to those who are healthy, people with PD are six times more likely to develop dementia during their lifetime than those who are healthy [114]. According to a study by Fenelon and colleagues, 70% of patients with PD who also had dementia reported experiencing hallucinations, as opposed to 10% of those with intact neurocognitive functions. In addition, 55% of those with severe cognitive impairments reported hallucinations, as opposed to 8% of those with mild or absent cognitive impairments who reported hallucinations. An older age at onset and a longer duration of PD are two additional risk factors linked to the occurrence of hallucinations, and the presence of hallucinations for a longer period of time is an independent predictor of VHs [95].

There is a correlation between persistent psychosis and younger age at which PD onset occurs with a longer duration of the disease. An increased prevalence of paranoia has been found to be associated with nursing home placement [115]. Sleep disturbances are prevalent among PD patients and approximately 82% of those with PDP report sleep disturbances during the course of their disease [116]. The presence of VHs has been pointed out as a significant indicator of daytime somnolence [95].

Nature of psychotic symptomatology in PDP

As PD progresses over time, psychosis usually develops

slowly and gradually over the course of the disease [80,117]. In most cases, the prodromal phase of the disorder is characterized by vivid dreams and nightmares [118,119]. During this phase, it is possible to develop illusions (e.g., people hidden behind curtains) as well as a false sense of presence (such as the sense of being in the company of others) [120].

Following this, patients tend to develop hallucinations in which they are still able to make sense of what is happening [58,121]. PDP on the other hand, has been associated with increased severity of motor system dysfunction in patients with hallucinations [50,121,122] Various studies have looked into hallucination by modalities [93,97,103,123,124]. It has been shown that VHs has been linked to retinal pathology, poor visual acuity, impaired color, and contrast discrimination, as well as abnormalities in higher-level processing in PD patients [125].

Typically, the content of these primarily VHs is recurrent in nature [126-129]. In addition, patients can develop hallucinations without being aware of their condition or having delusions [58,121]. Psychosis can occur with or without dementia, as well as spontaneously or due to the use of drugs, and the symptoms can occur either in the presence or in the absence of dementia [53,79,130,131].

There is no doubt that VHs has been considered to be the most characteristic feature of PDP, however, the spectrum encompasses a range of minor phenomena, hallucinations both visual and non-visual, as well as delusions.

It is considered among the minor phenomena that presence hallucinations (the delusion that someone or something is present), passage hallucinations (fleeting images viewed in one's peripheral vision), and visual illusions (the misperception of external stimuli) occur. Minor phenomena are observed in 20% - 45% of individuals with PD [51,55,105,132] and these phenomena are frequently associated with hallucinations in 13%-27% of cases [55,105].

It is important to note that hallucinations in patients with PD can sometimes become a threat, but for the most part, they are not [124]. Despite this, they may still be distressing to some people [103]. The most common hallucination type is VHs [60,101,123,124], which occurs more frequently at night due to the dim lighting in the room [91,101,128]. Most of the time, these incidents are brief (a few seconds) and occur at least once a week [103,128]. The most common form of formed VHs involve people [91,103], but it is also possible for it to involve animals or objects as well [96,103]. The content can be either familiar or unfamiliar [133], black and white or colored [128], and of a normal size or distorted in some way [96,101].

People with non VHs are more prone to these experiences as they age [123] and they often co-occur with VHs [93,124]. The most common type of auditory hallucination is hearing human voices, but they can also include other sounds, such as animal noises [93,124]. In general, tactile hallucinations are predisposed to be stereotyped and are most often related to insects or small animals [124].

Although there are some similarities between the hallucinations caused by primary psychiatric conditions and those caused by PD, there are a number of differences between them as well. Schizophrenia hallucinations are most commonly auditory (although they are frequently multimodal), are more frequent, are more likely to be ego-syntonic, have an associated emotional valence, and are likely to result in a more negative impact on individuals than PDP hallucinations [134].

As opposed to hallucinations, delusions are fixed false beliefs that are less frequent than hallucinations. In general, prevalence estimates range from 3%-14% [105,135-139] and are higher when it comes to Parkinson's disease dementia (PDD; 19%-51%) [140-142]. Infidelity is one of the most common themes of delusions [98], which are most commonly paranoid in nature. It was found that 2.5% of individuals with nontreatment naive PD exhibited delusional jealousy in a large cross-sectional study [143].

Capgras syndrome (the belief that familiar people have been replaced by imposters), Fregoli syndrome (the belief that familiar people appear as strangers), and reduplicative paramnesia (the belief that a person, place, object, or event has been duplicated) have also been described in PD [144,145] and 17% of individuals with PDD were affected by these conditions [146].

It is possible that psychosis can progress along a continuum in which minor phenomena evolve into hallucinations accompanied by retained insight to hallucinations accompanied by the loss of insight and the development of delusions [49].

There is a high probability that psychosis will continue to persist even after it has developed [56]. The results of a longitudinal study showed that, within three years, 81% of individuals who had hallucinations with retained insight began to experience hallucinations with loss of insight or delusions [147]. Based on a retrospective analysis of data from a small nonrandomized study, it appears that while both reducing the PD medications and initiating antipsychotic treatment result in an initial benefit, only the latter significantly delays the progression of hallucinations over time [148].

The amount of time individuals with minor phenomena were followed for a mean of 4.4 +/- 1.5 years in a longitudinal study of de novo PD [132]. There was a resolution of symptoms for 10% of the individuals, a stabilization for 52% of them, and a worsening for 38%. As part of another longitudinal study of de novo, untreated patients with PD, it was found that

minor phenomena preceded formed hallucinations in about 50% of cases [113]. Additionally, it is important to note that the cognitive impairment of those with minor phenomena is not different from that of those without minor phenomena [132,149].

It was found in a cross-sectional study that there was an association between cognitive impairment and hallucinations, but not with delusions [150]. A new classification system for PDP has recently been proposed by Factor, et al. which recognizes different subtypes of PDP and differentiates between them. Symptomatic psychosis has been divided into four classes, class I symptomatic psychosis, class II dopaminergic drug-induced psychosis (mostly delusions), class III psychosis, which is characterized by affective disorders and serotonergic dysfunction, and class IV psychosis characterized by cognitive decline and cholinergic dysfunction. It is important to note that only class IV psychosis is recognized as progressive and associated with a poor prognosis in this classification system [151].

Risk factors and triggers

In PD, the most frequent cause of admission to a nursing home is a psychotic episode, especially when delusions are the primary psychopathological symptom of the disease. It has been shown that there are a number of risk factors associated with PD, including exposure to Parkinson's medications, an increase in executive impairment, an increase in the severity and duration of Parkinson's disease, comorbid depression or anxiety, a comorbid sleep disorder, including rapid eye movement (REM) sleep behavior disorder and insomnia, as well as older age, global cognitive impairment, mild cognitive impairment or dementia, visual impairment, increasing fatigue during the day, and polypharmacy, particularly psychoactive drugs that are either prescribed or not [152,153].

Very well-defined medical conditions can trigger the onset of psychosis or increase the severity of symptoms which includes infection associated with fever, especially in cases of lower respiratory and urinary tract, dehydration, irregular or imbalanced nutrition, psychosocial stress or stressors, deprivation of or overload with sensory inputs such as loss of hearing aid, glasses, single room house, surgical operations, narcosis, metabolic alterations like hypo/ hyperglycemia, electrolyte imbalance (hyponatremia, hypocalcemia, hypomagnesemia), anemia, uremia, hepatic encephalopathy, hypovitaminosis (thiamine, folate, niacin, vitamin B12), hyper-/hypoparathyroidism, hyper-/hypothyreosis, and drugs (amantadine, anticholinergics, benzodiazepines, beta-blockers, corticosteroids, ketamine, lithium, metronidazole, opioids, penicillin, theophylline, etc.) [59,154-157].

Economic burden

Although PD has significant economic costs, those costs are amplified in the case of patients who have also been diagnosed with PDP, in addition to PD. In a recent study, the odds ratio for PDP in form of hallucinations to be in a nursing home is 16 times higher than for PD patients staying in the community [160].

Hue and colleagues (2005) estimated that almost 70% of PD's total economic burden can be attributed to indirect costs including productivity loss and uncompensated care provided by family members during the course of the disease [158]. There is evidence to indicate that productivity loss is greatest in the later stages of the disease and should be considered [159]. Even in the first year after diagnosis, indirect costs associated with lost productivity among the patient and caregiver were responsible for 45% of total expenditures in the first year following diagnosis [160-163].

Impact on long-term care utilization

No matter what the age of a patient is, there is a strong correlation between symptoms of psychosis and placement in a nursing home [76,164]. An analysis of claims data for commercially insured patients with Parkinson's disease under the age of 65 years (n = 1151) over a period of 10 years found that patients who required ambulatory assistance devices and institutionalization had 6 to 7 times the direct costs as those who did not require such devices or institutionalization. A total of 24% of patients with PD were diagnosed with mental disorders, 11% had neuropsychiatric disorders, and 10% had sleep disorders. There was a significant difference between the institutionalized cohort of patients with PD and matched controls in that 57% had mental disorders compared to 10%, and 29% had neuropsychiatric disorders compared to 4% [160].

It has been shown in an analysis of Medicare claim data from 2000 to 2010 that PDP imposes a heavy burden on Medicare. A total of 74.6% of patients with PDP spent 179 days on average in long-term care facilities (LTCs) as compared to 55.8% of patients with PD without psychosis (83 days on average). With regard to LTC in particular, the average annual all-cause cost for patients with PDP was $31,178, compared to $14,461 for those without psychosis who were suffering from PD. In terms of total reimbursement for all causes of care, the average annual reimbursement for patients with PDP was $67,251, while the reimbursement for PD patients without psychosis was $38,742 [162].

Neuroanatomy and neurochemistry

As far as PDP is concerned, the central dogma of the disorder is the overstimulation of the mesocorticolimbic dopamine receptors [165]. Overstimulation is caused by the interaction between the dopaminergic system and the serotonin system. Firstly, LBs that contain alpha-synuclein have been identified in the substantia nigra as well as the cerebral cortex as a significant disruptor of dopamine and serotonin transmission. There is an association between VH and high Lewy body densities in the amygdala and parahippocampal cortex [166-167].

There has been a suggestion since the early 1970s that serotonin and dopamine imbalance might contribute to PDP [168]. There was not much attention given to the possibility of serotonin being an element that could contribute to psychosis until it was discovered that lysergic acid diethylamide (LSD) and LSD-like hallucinogens could activate 5-HT2A receptors [169,170]. Atypical antipsychotics, such as clozapine and quetiapine, are also antagonists of both 5-HT2A/2C receptors, as well as dopamine D2 receptors, in low doses. This property has been suggested as a possible mechanism by which antipsychotics are effective in PD without worsening motor symptoms [171-173].

Using the selective 5-HT2A receptor ligand [18F]-setoperone PET imaging method, Ballager, et al. assessed in vivo changes in 5-HT2A receptor binding between PD patients without dementia with VHs compared with the PD patients without dementia with VHs [174].

It has been demonstrated that PD patients with VHs have increased 5-HT2A binding within the ventral visual pathway, which is composed of bilateral inferooccipital gyrus, right fusiform gyrus, and inferotemporal cortex. In addition, the bilateral dorsolateral prefrontal cortex, medial orbitofrontal cortex, and insula have been affected in PD patients with VHs. In contrast to patients who did not have VHs, another postmortem tissue study revealed that there was an increased binding of [3H]-ketanserin to 5-HT2A in the inferolateral temporal cortex of PD patients with VHs [175].

Nonmotor symptoms are associated with the degeneration of serotonergic neurons within the raphe nucleus, which is part of the limbic system [176-178]. There are two such symptoms associated with PDP, namely depression and anxiety, both of which are common [179-184]. It has been suggested that activities in the temporal cortex and visual pathways are likely a cause of VHs in PDP due to upregulation and overstimulation of cortical serotonin 5-HT2A receptors [84,175,185,186].

In the prefrontal cortex, the upregulation of dopamine receptors affects projections to the ventral striatum, which in turn regulates the release of dopamine from the brain [187-190]. It is known that dopamine binds to a variety of 5HT receptors, suggesting that dopaminergic agents may also play a role in the development of psychosis [191-194]. In comparison to levodopa, there is a higher risk of psychosis with dopamine agonists, which may be due to the stimulation of serotonin receptors, as opposed to levodopa [195-198].

There is no doubt that PD has a known cholinergic deficit that has been linked to psychosis in DLB [199-201]. Furthermore, there have been reports that anticholinergic drugs intended to treat motor symptoms of PD can cause psychosis [155,202]. The cholinesterase inhibitor rivastigmine demonstrated promising results that involved PD patients with dementia and DLB with VHs [203,204].

There is evidence that disrupting the ascending cholinergic transmitter system is associated with the denervation of the cortex frontal and degeneration of central cholinergic structures, such as the nucleus basalis of Meynert and pedunculopontine nucleus, which are responsible for attention, cognition, and RBD [205,206]. In PD patients, altered cortical processing of visual perception due to degeneration of cholinergic structures (i.e., PPN) may be associated with their VHs, and this has also been shown in VBM (Voxel-based morphometry) imaging by the volume reduction of PPN after 2.5 years of follow-up [207,208].

PDP may also exhibit a significant reduction in glutamatergic activity as a result of interactions between dopamine and glutamate in the dorsal striatum and nucleus accumbens of the brain. In patients with PD, it is known that the glutamate antagonist amantadine and memantine lead to VHs [209]. Earlier it was proposed that the etiology of PD was caused by reduced glutamatergic function, resulting in increased dopaminergic activity, leading to the development of psychosis in patients with the disease [210,211].

In a recent study using proton magnetic resonance spectroscopy (1H MRS), which measures metabolites in the brain, it was found that there were lower glutamate levels in the dorsal caudate and putamen of patients with PDP compared to those who did not have psychosis [212]. As compared to healthy controls, several hippocampal subfields in the hippocampal region have been observed to have atrophy in patients with PDP [213,214].

In a study done by Lenka, et al. abnormalities in white matter were found in patients with PDP who had fractional anisotropy in several areas of the brain, such as the inferior longitudinal fasciculus (ILF) and the inferior frontal-occipital fasciculus (IFOF). In addition to ILF and IFOF abnormalities, there is evidence that they contribute to VHs by disrupting the information processing from the orbitofrontal cortex to the occipital cortex [215].

PDP has a complex pathophysiology that has not been fully understood and is still under investigation. Dopamine receptor antagonists are used for the treatment of psychosis, while many dopaminergic PD medications exhibit high propensities for inducing psychotic symptoms as well [216]. The use of dopaminergic medications by patients with PD does not always result in psychosis, high-dose levodopa infusions do not cause hallucinations [217]. In addition, hallucinations can also occur in people with untreated PD [218], and it is estimated that 3 percent of those with untreated PD will develop psychosis [219,220].

According to the original hypothesis, there is a pharmacological kindling after chronic levodopa treatment, where dopamine is no longer being stored adequately on the presynaptic level. Thus, overflow and overstimulation of mesocorticolimbic postsynaptic dopamine D2 receptors in

limbic areas and the cerebral cortex are thought to be involved in psychosis, similar to motor dyskinesia [221-223].

As evidence accumulates, it appears that D3 receptors have a minor modulatory effect on the function attributed to dopamine D2 receptors in the brain [224-233]. The results of a recent postmortem study using a D3-selective ligand, ^{3}H-WC-10, showed increased D3 receptors in striatal regions of five patients with DLB/PDD, compared with cognition-intact elderly controls, and in patients with DLB/PDD who had hallucinations compared with patients without hallucinations [234].

The clinical features of PDD and DLB are similar, and VH is highly specific for LB parkinsonism (DLB and PD) in contrast to non-LB parkinsonism [111,235,236]. Despite the fact that both conditions are characterized by cholinergic dysfunction, it is possible that this system plays a role in PDP as well [125,237]. It is possible for anticholinergic medication to cause or contribute to impairments in cognitive function. In contrast, the cholinesterase inhibitor rivastigmine can be used to treat both DLB and hallucinations in PDD, as it inhibits cholinesterase activity [203].

VHs is associated with a greater level of amyloid plaque and neurofibrillary tangles in the cortex and amygdala of PD patients, as well as more cortical and amygdalar LB pathology [214]. The work of Ffytche, et al. suggests that the progression of psychosis from the brain stem to the basal forebrain to the cortex is similar to the progression of LB pathology from the brainstem to the cortex [49].

Postmortem studies have investigated potential links between visual hallucinations and pathology within the LC and SN, yet have found no such associations [238]. A study looked at the correlation of brainstem pathologies with PDP in a cohort of 175 patients. They semi-quantitatively analyzed the brains to ascertain the burden of neuronal loss and gliosis and LB pathology within the LC and SN. Around 56% of patients in the whole sample had the diagnosis of psychosis. The authors found out psychosis was associated with severe neuronal loss and gliosis in the substantia nigra but not in the locus coeruleus. Psychosis was not found to be associated with LB score. They concluded PDP is associated with the underlying neurodegenerative process and demonstrated that cell loss and gliosis may be a better marker of psychotic symptoms than LB pathology [239].

Neuro-signaling pathways and network changes in PDP

It has been proposed that various hypothetical frameworks can be used to explain VHs, including the possibility of endogenous imagery being absorbed while dreaming [240], a deficit in reality monitoring that causes the perception [241] to be indestructible, the dysregulation of internal and external imagery [242], the impairment of the interaction between attention and perception [243], and the dysfunction of attentional networks [244].

In the study by Stebbins, et al. it was argued that the top-down, internally driven process of attentional cortex processing is disinhibited when compared to the usual, externally driven, bottom-up process [245].

A decrease in cortical activation was found in the posterior region of the brain (i.e., the middle temporal and occipital regions, parietal regions, and cingulate regions) in the study, which could be associated with reduced visual attention to external perceptions. It was found that patients with PD with VHs demonstrated increased activity in the frontal cortex (the superior and inferior frontal cortex as well as the caudate nucleus). As a result of a disruption of visual signal input, the retinal striatal cortical signals may be impaired due to reduced retinal dopamine and decreased striatonigral input, which, in turn, may result in abnormal activation of visual areas, and difficulty distinguishing between relevant and irrelevant visual information. A second hypothesis, supporting the notion of a bottom-up impairment in perceptional visual cortex processing, was supported by the study conducted by Meppelink, et al. [246].

As a result of impaired bottom-up processing in PD with VHs, the lateral occipital cortex and extrastriate temporal visual cortex were not activated as much as they should have been just before image recognition. However, it was not evident that there was a compensatory 'top-down' cortical response.

It has been found, however, that an impaired "top-down" response may be attributed to decreased activation of the frontal gyri. A reduction in the activation of the occipitotemporal cortex, as well as an impairment in the integration of sensory and mnemonic information, may all contribute to visual impairments in patients with PD as well as a reduction in the activation of the frontoparietal cortex, which can suppress irrelevant stimuli.

A comprehensive assessment of the clinical, demographic, and ophthalmological correlates of VHs in PD has been provided by Gallagher, et al. which supports the hypothesized model of impaired visual processing, sleep/wake disturbance, and brain stem dysfunction, as well as cognitive dysfunction. In PD, there is a variety of impairments, particularly frontal, thereby contributing to the pathogenesis of VHs, which are further bolstered by higher cortical LB counts in areas associated with visuo-perception and executive function that were associated with increased VHs [238].

In a recent study, researchers used a novel experimental priming task that used top-down verbal cues to prime the recognition of partial or ambiguous images from the bottom up, challenging the previous hypothesis, which demonstrated that VHs in PD are normally activated from the top down

as well as interact between the top-down and bottom-up processes [247].

In a study conducted by Firbank, et al. using magnetic resonance spectroscopy in 36 patients with PD, it was found that in patients with VHs, the ratio of aminobutyric acid/creatine in the occipital lobe was lower than in patients who did not exhibit psychotic symptoms; furthermore, gray matter loss was observed in the anterior temporal lobe, as well as the visual cortex in the V4 region [248].

There was a reduced amount of gray matter atrophy in the visuoperceptive areas of patients with PD with minor hallucinations [249,250]. An analysis of neural networks and structure was conducted by Zarkali, et al. using fixed-based analysis. According to their findings, PD patients with hallucinations had degenerated and decreased posterior thalamic projections in the inferior frontal-occipital white matter tracts, suggesting that the splenium and posterior thalamus may play a large role in maintaining network balance and regulating the default mode network in PD [251].

Genes and PDP

There is no clear indication that there is an association between the genes that cause PD and the risk of psychosis. It is noteworthy, however, that with the exception of polymorphisms in genes associated with the cholecystokinin system, most of the conclusions regarding the other studies were inconsistent in regards to predicting the development of any psychotic profile in someone with PD [252].

Autosomal dominant genetic PD synuclein [SNCA] and leucine-rich repeat kinase 2 [LRRK2]) or idiopathic non-genetic PD has been linked to psychosis as compared to autosomal recessive genetic PD ((e.g., parkin, PTEN-induced putative kinase 1 [Pink1] and DJ1). In an early systematic review of the prevalence of non-motor symptoms in genetic PD [48], it was found that the frequency of psychosis in genetic PD does not appear to be greater than in idiopathic PD (3%-29%), and in fact, may even be lower [94].

Taking all cases together, it has been found that psychotic symptoms are relatively rare in parkin-linked PD (about 3%) and other genetic forms of PD (SNCA, Pink1) compared to those resulting from idiopathic causes. Recently, there have been studies that have shown that parkin PD may also be associated with psychosis [253], but comparing parkin+ with disease-matched parkin- PD reported no real differences [254].

VHs have previously been found to be common psychotic symptoms in PD patients with duplications of the SNCA in previous studies [255,256]. In the longitudinal cohort study conducted on 215 PD patients and 126 controls over a period of 12 years, mutations in the glucocerebrosidase gene were identified as a susceptibility factor for early-onset psychosis in PD [257].

Due to the well-established association between psychosis and dementia in PD, as well as the relationship between the advanced stage of the disease and the emergence of psychotic symptoms, it has been proposed that APOE e4 may play a role in the development of PDP [258].

As a result of the presence of the APOE e4 allele in patients with PD without dementia who are taking levodopa, they have a higher risk of VHs [259]. There are, however, four other studies that have not confirmed the association between these two factors [260-263]. In fact, another study was able to show that having the APOE- e4 allele was positively associated with the occurrence of psychosis prior to cognitive decline and independent of age or cognitive status in patients with PD [264].

A study published showed that PD patients with the allele APOE-e4 are significantly more likely to develop hallucinations in the first five years of the disease as opposed to PD patients without the allele. However, it should be noted that the presence of APOE e4 was not associated with the occurrence of hallucinations five years after PD diagnosis in the current study [265].

There is an association between polymorphisms of the Dopamine Transporter (DAT) gene and neuropsychiatric disorders such as bipolar disorder and attention defiicit hyperactivity disorder [266]. There has been evidence that the 40-bp VNTR of the DAT gene is related to an increased susceptibility to PD [267-269]. It has been observed that psychosis is more common in levodopa-treated PD patients of Caucasian descent with psychosis than in those without psychosis who carried the nine-copy allele of the 40-bp VNTR of the DAT gene [270]. A recent study conducted in Serbia, however, revealed that there was no significant correlation between the 40-bp VNTR of the DAT gene and the risk of PD [271]. Two recent studies also did not show this association [272,273].

There is evidence that the -839 C > T allele of the 5' UTR of the DAT gene is associated with VHs in patients with PD being treated with levodopa [272]. Among Brazilian PD patients with DAT1 rs28363170, a recent study showed that carrying the 10/11, 10/8, and 10/9 genotypes was more commonly associated with VHs, but there was no association found between DAT1 rs28363170 and VHs in the same study [274]. Additionally, a recent study from Slovenia has demonstrated that the haplotype of the SLC6A3 gene was related to the development of levodopa-induced VHs in patients with PD [275].

There is a significant increase in the risk of PDP associated with the use of dopaminergic agonists. Specifically, apomorphine, which has a higher affinity for DRD4 than DRD2 and DRD3, exhibits a modest hallucinogenic effect, and pergolide, which has a greater affinity for DRD2 and DRD3 than DRD4, is significantly associated with hallucinations. The development of hallucinations in PD has been proposed to be a result of hypersensitivity of the dopaminergic

mesocorticolimbic system, especially those that occur early in the course of the disease and are not generally associated with cognitive decline [276].

In a study conducted among Japanese subjects, it has been reported that the genotypes TT and CT at the -45 locus, which is located in the promoter region of the CCK gene, have been associated with a higher frequency of hallucinations in patients with PD who have been given levodopa for treatment [278]. In a different study looking at the Chinese population, it was found that the T allele at the CCK -45 promoter region was associated with VHs in levodopa-treated PD patients [279]. A similar pattern of association between the CCK T allele and PDP occurrence was observed in another study aiming to confirm these findings in a white population. The CCK T allele as well as the combination of the CCK T and CCKAR C alleles were also found to be associated with PDP occurrence, though the frequency of the CCK T allele was relatively low, preventing statistically significant results from being obtained [280]. In another study, the polymorphisms of the CCK, CCKAR, and CCKBR genes were also not associated with the prevalence of PDP in a large study [281]. Therefore, it has been suggested that the effect of the gene polymorphisms related to CCK on the risk of PDP largely depends on the race and ethnicity of the population [281].

Several genetic variants affecting the HOMER1 promoter at rs4704559 and the C variant affecting the promoter at rs4704560 have been linked with an increased likelihood to develop hallucinations in those with PD [282]. In another study, the rs4704559 G allele of the HOMER1 promoter was shown to protect against the development of VHs in Brazilian patients with PD who were treated with levodopa [283].

PD patients with at least one of the COMT rs165815 C alleles are significantly less likely to have frequent levodopa-induced VHs compared to those without this specific allele, according to a study published recently [275]. In PD patients, it has been shown that the COMT-DDC gene–gene interaction affects the likelihood that they will experience VHs caused by levodopa [275].

The ACE-II genotype has been associated with a higher risk of levodopa-induced psychotic manifestations in Chinese patients with PD [284]. As a consequence, a study of Italian patients with PD found no association between ACE-II polymorphisms and PDP, indicating that any such relationship does not exist [285]. Apparently, the conflicting results of these studies may be accounted for by differences in racial or ethnic backgrounds.

It has been reported that polymorphisms in the Ankyrin repeat and kinase domain containing the I (ANKK1) gene have been associated with alcoholism and other neuropsychiatric disorders, including PD [286]. Another recent study showed that the GG rs2734849 ANKK1 gene polymorphism can lead to PDP among people with PD who have been treated with levodopa [271].

The FDA has approved a 5-HT2AR (serotonin 5-HT2A receptors) inverse agonist/antagonist, known as pimavanserin, as a treatment for PDP, further strengthening the hypothesis that serotoninergic function in the brain is critical to PDP development [287]. The results of another study showed that PD patients with dementia, as well as patients with dementia with Lewy bodies (DLBs), had a prevalence of delusions associated with the L/L genotype of the 5-HTTLPR (5-serotonin-transporter-linked promoter region) gene [288].

There are three genotypes of the MAPT (microtubule-associated protein tau) gene (H1/H1, H1/H2, and H2/H2). Postmortem study results demonstrated that PD cases with the H1/H1 genotype had significantly more hallucinations than non-carriers, regardless of the stage of their disease, compared to non-carriers with the H1/H1 genotype [263]. Another study, however, did not establish a relationship between MAPT gene polymorphisms and psychotic manifestations in patients with PD [260].

There is an association between high plasma levels of CRP (C-Reactive Protein) and the occurrence of hallucinations or illusions in patients with PD, suggesting that excessive systemic inflammation may be one factor that contributes to the development of this disease [289]. It has been demonstrated in a study that the IL-6 rs1800795 gene polymorphism is associated with a lower risk of patients with PD experiencing VHs [290].

Recently, GPX1 (Glutathione Peroxidase 1) rs1050450 gene polymorphism has been associated with a higher frequency of VHs in patients with PD [290]. In a recent study, it was demonstrated that the MAOB (Monoamine oxidase B) rs1799836 polymorphism protected against the development of PDP [290]. The BIRC5 (Baculoviral IAP Repeat Containing 5) rs8073069 polymorphism has been shown to have a protective effect against the development of VHs in patients with PD [290].

It has been demonstrated that the BDNF (Brain Derived Neurotrophic Factor) G196A polymorphism in PD was not associated with any non-motor symptoms, including psychiatric symptoms of the disease [291]. A recent study has shown, however, that BDNF Val66Met polymorphisms are associated with mild behavioral impairment (MBI) in patients with PD. It should be noted that Met carriers displayed a significantly increased level of impairment compared to Val carriers both in the subdomains of mood/anxiety and psychosis, which suggests Met polymorphism may increase the risk for PDP [292].

Diagnosis of PDP

As far as PDP is concerned, there is no standard way to diagnose it. The diagnostic criteria of PDP are summarized in the table below, which includes the NINDS-NIMH and DSM-V criteria. Gordon, et al. developed the modified NINDS criteria for a better understanding of PDP [293]. It is necessary to have both psychotic as well as Parkinson's symptoms present.

The diagnosis of PD is based on the criteria defined by the UK brain bank. The diagnosis of PDP requires that the onset of psychosis occur after the onset of symptoms of the disease. There is also a requirement to establish a symptom duration of more than one month and to exclude other conditions, such as DLBs, schizophrenia, or schizoaffective disorder, as well as other symptoms of schizophrenia [53].

There are several differential diagnoses to be considered, including, but not limited to, other neurodegenerative diseases, psychosis associated with the many causes of delirium, major depression, side effects related to dopaminergic medications, intoxication, and withdrawal states caused by other drugs and drugs of abuse as shown in Table 2 and 3.

Table 2: Modified NINDS criteria score: Assigning scores to each psychotic symptom of NINDS-NIMH diagnostic criteria: (1) Delusions score with 2; (2) Other psychotic symptoms score with 1; and (3) Cut-off sum for PD psychosis equal to or higher than 2.

NINDS-NIMH diagnostic criteria		DSM-V criteria
PD dianosis	(1) United Kingdom Brain Banks criteria; and (2) The onset of PD must be preceded the psychotic symptoms	Prominent hallucinations or delusions
Psychotic symptoms: At least one of the following	(1) Hallucinations; (2) False perceptions; (3) Illusions; and (4) Delusions	There is evidence from the history, physical examination, or laboratory findings that the disturbance is the direct pathophysiological consequence of PD
The duration of psychotic symptoms	(1) Periodically or continuously; and (2) Last more than 1 mo	The disturbance is not better explained by another mental disorder
Exclusion of other probable disorders and conditions	(1) Dementia with Lewy bodies; (2) Primary psychiatric disorders; (3) Extrapyramidal symptoms induced by drugs; and (4) Delirium	(1) The disturbance does not occur exclusively during the course of a delirium; and (2) The disturbance causes clinically significant distress or impairment in social, occupational, or other important areas of functioning

Scales to assess psychosis in PD

The development of several scales has also led to the development of a variety of tools and methodologies for (1) assessing the probability of developing PDP [295], (2) confirming the presence of the disease, and (3) analyzing its severity.

A few of these scales are part of more general scales, such as the MDS-UPDRS [296], but others are incorporated as sub-scores into scales that are more specific to PD. The Parkinson Psychosis Questionnaire (PPQ) [297], the Scale for Assessment of Positive Symptoms (SAPS) [298], and the scale for the evaluation of neuropsychiatric disorders in PD (SEND-PD) [299] have been developed specifically to evaluate PDP.

A recommended selection of the available scales is summarized in the table below. Each scale has its particular strengths. It might be practical to integrate a psychiatric scale into a broader assessment of the patients, but in certain cases, it may be helpful to focus on the neuropsychiatric symptoms (NPS) in particular. For example, there are a number of tests that correlate well with the MDS-UPDRS, such as the SEND-PD, which has been shown to correlate with it [299], or the SAPS score, which also takes the impact of psychosis on the patient's well-being and care.

Several scales were examined by the MDS in 2008 in order to diagnose PDP and concluded that it was impossible to use one scale to diagnose the condition effectively. According to their recommendation, there should be a combination of scales used depending on the patient's needs. It was proposed by a task force of the MDS to begin by using scales geared toward diagnosing psychosis, such as the MDS-UPDRS, and then to use scales geared toward severity, such as the SAPS, both of which tend to focus on the severity of psychosis as shown in Table 4 [120].

Table 3: Differential diagnosis of PDP and how to rule out each differential [294].

Disorder	Psychosis+Symptoms to look for?	How to rule out?
Delirium[13]	Clouding of consciousness Disorientation to time, place and person Sundowning phenomenon Altered sleep-wake cycle Cognitive disturbances If patient has preexisting cognitive disturbances, there if further deterioration	Onset-usually acute and fluctuating course History of disorientation/confusion Mini mental state examination Confusion assessment method Rule out electrolyte disturbances
DLB [20,23]	Onset of dementia with or within 1 year of the onset of parkinsonism symptoms Recurrent complex visual hallucinations (core feature) Delusion most common - Capgras syndrome/delusional misidentification syndrome poor insight; behavioral problems Impairment in activities of daily living High neuroleptic sensitivity High neuroleptic sensitivity	History of onset of cognitive disturbances and chronology of appearance of parkinsonian symptoms Visuoperceptual impairment is often present [24] Brain imaging – reduced occipital uptake in areas of visual cortex [24] High neuroleptic sensitivity
Charles bonnet's syndrome [25]	Visual impairment present with benign visual hallucinations	Sensory deprivation in history and examination Less distress
Psychosis as a part of behavioral and psychological symptoms in AD	Cognitive decline Behavioral problems Fluctuating delusions – not firm beliefs Hallucination – less common Significant impairment in activities of daily living No evidence of motor symptoms	History of gradual and progressive cognitive decline No motor symptoms of PD
Antiparkinsonian drug-induced psychosis	Temporal correlation between onset of psychotic symptoms and starting or increase the dose of antiparkinsonian drugs	Careful medication history

AD: Alzheimer's dementia; PD: Parkinson's desease; DLB: Lewy body dementia.

Table 4: Scales for assessing PDP.

Scale	Objective	References
PD Non-Motor Symptom Scale	Risk of developing psychosis	[294]
Scale for Assessment of Positive Symptoms (SAPS)	Presence, severity, and impact of psychosis	[295]
Parkinson's Psychosis Questionnaire (PPQ)	Presence and severity of psychosis	[296]
MDS-UPDRS I, item 1.2	Presence and severity of psychosis	[297]
Scale for Evaluation of Neuropsychiatric Disorders in Parkinson's disease (SEND-PD)	Presence, the severity of psychosis, and other neuropsychiatric symptoms	[298]

Caregiver burden

An important component of the management of chronic illnesses has been the burden placed on caregivers. Caregiver burden can be attributed to a number of risk factors including female gender, a low level of education, living with the patient, a higher number of hours spent caring for the patient, depression, social isolation, financial stress, and a lack of choice in caring for the patient [300].

A significant caregiver burden is seen in PD patients with NPS such as anxiety, depression, and psychosis [301]. Family members are often the primary caregivers for patients who rely on their loved ones for physical, emotional, and financial support during their illness. Consequently, this places increasing stress on the caregivers, causing them to remain stressed, and as a result, they are at risk of deteriorating both mentally and physically in the long run [162]. It is for this reason that PDP is one of the main reasons for the placement of patients with PD in nursing homes [65,71]. According to Schrag and colleagues, the duration of the disease, the patient's depression, hallucinations, and confusion are among some of the top contributors to caregiver distress.

In a study by Martinez-Martin, et al. which studies a sample of 584 pairs of PD patients and their primary caregivers. Patients' NPS were measured with the SEND-PD scale, and the Zarit Caregiver Burden Inventory was used to quantify caregiver burden. There are strong associations between NPS and caregiver burden in PD, and caregiver burden is related to NPS in dementia patients, which is more prevalent and burdensome in this population [68].

Adelmen, et al. worked extensively in this field and they are of a view that it is possible to develop practical assessment strategies to evaluate caregivers, their care recipients, and the overall care needs of the care recipient in order to evaluate caregiver burden in a practical way. In the past few years, a variety of psychological and pharmacological interventions have been shown to have mild to moderate efficacy in reducing caregiver burden and associated symptoms of caregiver distress. Among the psychosocial interventions available to caregivers of dementia patients are support groups and psychoeducational programs. Researchers have found that caregiver burden-related symptoms (e.g., mood, coping, self-efficacy) can be improved even when caregiver burden itself is minimally improved [301].

Management of PDP

Pharmacological: To determine whether or not it is necessary to intervene in the case of PDP as a means of managing the individual, the initial step is to determine the severity and degree of symptoms. There are some PD patients who may not require treatment of illusions and some VHs, as they are regarded as not bothersome by them. As a matter of fact, some PD patients enjoy the experience and prefer to not receive treatment [302]. It is important, however, that such individuals be closely monitored for any changes in their symptoms, as their condition is prone to deterioration, especially if they suffer from any co-morbidity or intercurrent medical issues at the same time.

In order to treat PDP, the first step is to identify and treat any secondary causes, especially infection or febrile illness, metabolic disorders such as dehydration and electrolyte imbalance, as well as structural brain injuries such as subdural hematomas that may trigger acute psychosis in PD patients.

As a next step, it is necessary to review the drugs that have been prescribed. It is possible to experience psychotic symptoms as a result of taking a single PD medication (dopaminergic or non-dopaminergic) or combination of PD medications combined with many other medications, including those used to treat general medical illnesses [57]. It is therefore recommended that patients discontinue the use of all medications other than those that are essential for managing PD. These may include tricyclic antidepressants, antispasmodics (e.g., oxybutynin), anticholinergics, benzodiazepines, muscle relaxants, and opioids.

If there are possible sequential symptoms, it may be necessary to clarify the time when recent medications were started or changed, and discontinue or reduce the medications if necessary. In order to obtain the best results, it is advised to modify the PD drugs, and to gradually remove them from the patients' system in the following order: anticholinergics, monoamine oxidase B inhibitors (MAOBIs), amantadine, DAs, COMT inhibitors, and finally, levodopa [303].

In any case, it is necessary to always ensure that the motor function remains as normal as possible while stopping any PD medication, and it may be necessary to replace the PD medication with equivalent amounts of levodopa in cases where this is needed. One of the most important things to note is that it is not uncommon for PDP (as discussed above) not to be directly linked to dopamine drugs and some symptoms might not even go away after stopping the medication or reducing its dosage.

Upon examining a cohort of PD patients with psychosis after being adjusted to medications and managed for systemic

illnesses, Thomsen, et al. found 16 (62%) of the 26 subjects who were enrolled in this study had sufficiently resolved their psychotic symptoms in the short term to not require antipsychotic drugs to be prescribed [304].

Having observed these results, it is advisable to investigate whether there is any underlying systemic illness that may cause the psychotic symptoms and determine whether there are any medication adjustments that may be needed to resolve them. Adding an antipsychotic agent is an option if the simplification and reduction of the PD medications to the lowest tolerable dose without resulting in an exacerbation of motor symptoms does not improve psychosis symptoms.

Antipsychotics or dopamine D2 receptor antagonists

A specific pharmacological management of psychotic symptoms using antipsychotics in PD is challenging in light of the potential for worsening of PD motor symptoms as a result of blocking the dopamine D2 receptors, as well as the undesirable side effects. In order to minimize the risk of aggravating parkinsonism, all typical and most atypical antipsychotics with a high risk should be avoided. Several reports have been published indicating that so-called atypical antipsychotic medicines can exacerbate the motor symptoms of PD which includes risperidone [305,306], olanzapine (and with no improvement in VHs) [307,308], ziprasidone [309,310] and aripiprazole [311,312].

It is also important to remember that antipsychotics carry a 'black box warning' from the US Food and Drug Administration (FDA), for use in elderly patients, especially those with underlying dementia, due to increased risks of all-cause mortality and cerebrovascular events as a result of their use [313]. The risk of death is reported to increase with an increase in the daily dose and/or with an increase in the duration of use, indicating that there is a dose-response effect [314]. There has been a 1.53-fold increase in ventricular arrhythmias and/or sudden cardiac death with the use of antipsychotic drugs, according to one study [315]. It is always a good idea to perform an electrocardiogram to ensure that the QTc interval is normal in all cases.

The use of neuroleptics is also associated with serious complications, such as neuroleptic malignant syndrome in patients who are considered neuroleptic sensitive (e.g., those with advanced PD or DLB), and increased mortality rates with reports of prevalence of up to 40% have been reported in those who are exposed to such medications [316].

The counter argument for treating significant disabling symptoms with appropriate antipsychotics is that, regardless of these issues, psychotic symptoms are considered to be independent predictors of mortality in people with PD during a 12-year follow-up (HR 1.45) [317]. Also, earlier detection of mild hallucinations and the use of antipsychotics may help to reduce the risks of later deterioration of mental health [318].

Brexiprazole

As a new partial agonist of D2 dopamine and serotonin 1A receptors, brexpiprazole is called a serotonin-dopamine activity modulator (SDAM), and as a potent antagonist of serotonin 2A receptors, noradrenergic alpha 1B and 2C receptors, it has a wide range of actions. In addition to being approved to treat schizophrenia, brexpiprazole can also be used as an adjunctive treatment for major depressive disorder (MDD). The study by Akimasa, et al. showed that brexpiprazole was effective in the treatment of PDP without any serious side effects. However, maximal dose should not exceed 4mg/day because of the risk of developing extrapyramidal symptoms [319].

Clozapine

A dibenzodiazepine, clozapine is a drug that has weak antagonism of the dopamine D2 receptor in the striatum as well as significant activity over the dopamine D4 receptor and the 5-HT2 receptor, especially at relatively low doses that are used in the treatment of PD [320]. Several studies have been conducted to test the efficacy of clozapine in PDP, both double blind and placebo-controlled. Currently, it is the only antipsychotic medication consistently found to be effective without worsening motor function, and it carries an acceptable safety risk when monitored regularly [321,322].

AAN evidence-based guidelines published in 2006 state that clozapine is currently the only antipsychotic with a recommendation level B recommendation that can be used in PDP [323]. There are similar conclusions to those found in the meta-analysis of 2007 [324] and the evidence-based medicine review by the MDS in 2011 [325]. At daily doses as low as 6.25 mg [322], PD patients can experience therapeutic benefit; the average effective dose for PD patients is usually between 25 and 50 mg per day.

Furthermore, it has been suggested that clozapine does not worsen motoric symptoms in PD as compared to other antipsychotics due to its fast-off dissociation from striatal dopamine D2 receptors, a phenomenon that is also associated with preferential dopamine D2 receptor occupancy in the temporal cortex compared to the putamen and the substantia nigra [326,327].

There are rare cases of non-dose-related agranulocytosis (prevalence 0.38%) [328] to be associated with clozapine use, which can be fatal. Because of this, absolute neutrophil counts need to be monitored and agranulocytosis can be reversed by stopping the medication immediately. There was an incidence of 8.3% of transient neutropenia observed in an eight-year follow-up study all of which resolved once the clozapine had been discontinued. [329]. In addition, the use of these low doses of the drug for long periods of time appears not to induce metabolic syndrome, which is commonly seen with the higher doses of the drug being used for schizophrenia.

[330]. Postural hypotension and sedation are two of the more common side effects of this medication [331,332].

Quetiapine

As a dibenzothiazepine compound, quetiapine has a similar chemical structure to clozapine. It is also known to have moderate affinity for both dopamine D2 and 5-HT2 receptors with a much higher affinity for 5-HT2A receptors than for dopamine D2 receptors [333]. Aside from clozapine, it is also one of the medications commonly used to treat the psychoses associated with PD. It has been found, however, that quetiapine's efficacy in clinical trials has been inconsistent [334-336].

Even so, low doses of quetiapine (25-75 mg/day) continue to be widely prescribed due to its low propensity to significantly worsen motor function during clinical trials, as well as the fact that it does not require regular blood screening. Accordingly, quetiapine has been classified as having Level C evidence, or evidence that lacks sufficient support, is associated with an acceptable safety risk, does not require specialized monitoring, but has implications for the practice of investigational drugs [337,338].

An open-label randomized trial found that a small percentage of patients taking quetiapine with severe parkinsonism who experienced mild exacerbations of the disease were elderly people with PDD, and who received a high dose of quetiapine. Therefore, patients with PDD are advised not to take quetiapine above 100 mg per day [339].

To compare the efficacy of clozapine and quetiapine in the treatment of psychosis in people with PD, two clinical trials have been conducted. Despite the fact that in one study the efficacy of quetiapine and clozapine appeared to be equal [339], the other study indicated that clozapine had a greater efficacy over quetiapine [340].

5-HT2A receptor ligands

Mianserin: Mianserin is a non-selective, clinically-available, anti-depressant that blocks 5-HT2A receptors [341]. Adjia, et al. looked at the effect of mianserin on the severity of psychosis and dyskinesia in the MPTP-lesioned common marmoset. They found mianserin was effective to alleviate both PDP and dyskinesia but with hinderance of L-DOPA antiparkinsonian action which was a limitation of its usefulness [342].

The non-selective inhibition of 5-HT2A-dependent mechanisms may be effective in treating PDP without worsening the motor symptoms of PD. It has been demonstrated that mianserin is the first non-selective 5-HT2 receptor antagonist that has been found to be effective at treating PDP after eight weeks in patients who have PD (n = 12) without showing signs of motor dysfunction [322].

Mirtazapine: Adija, et al. looked at the anti-psychotic potential of mirtazapine in the 1-methyl-4-phenyl-1,2,3,6-tetrahydropyridine (MPTP)-lesioned common marmoset. The results of the study showed that mirtazapine had antipsychotic and antidyskinetic actions that did not interfere with L-DOPA's anti-parkinsonian activity [343]. Several case reports also found out the efficacy of mirtazapine on nocturnal VHs and auditory hallucinations in PD patients without worsening the motor symptoms [344,345].

Pimavanserin: It must be noted that 5-HT2A receptors are constitutively active even in the absence of a 5-HT agonist, which means that an inverse agonist can be more effective at inhibiting such receptors than an antagonist can. The treatment of PDP can be made more effective by using 5-HT2A inverse agonists, which were suggested as potential therapeutic drugs [346,347].

With its low affinity for 5-HT2C and negligible binding to dopaminergic, adrenergic, histaminergic, and muscarinic receptors, pimavanserin is a selective inverse 5-HT2A receptor agonist, thus sparing atypical antipsychotics from the adverse effects of sedation and hypotension [348].

Using SAPS, a phase II study in 46 patients reported good tolerability over 28 days and a small reduction in psychosis compared to placebo [349]. After 6 weeks of taking pimavanserin 40 mg daily, a phase III randomized, double-blind, placebo-controlled study of 185 patients with PD showed significant improvements in SAPS scores (37% *vs.* 14%) as well as caregiver burden, daytime somnolence, and sleep quality [350].

A baseline ECG is needed before treating a patient with pimavanserin because it has the potential to cause QT interval prolongation. As many as eleven percent of the patients in the treatment group withdrew due to worsening psychotic symptoms during the trial. A meta-analysis of four RCTs (including two unpublished ones) evaluating pimavanserin's antipsychotic efficacy in PD has been conducted by Yasue, et al.

The findings of this study indicate that pimavanserin is less likely to cause orthostatic hypotension and does not show significant differences in the incidence of all-cause discontinuation, adverse events, or death in this study. The researchers concluded that pimavanserin is effective in treating PDP with a good level of tolerability [351]. Recently, pimavanserin was approved by the FDA [322].

There is a recent post hoc study that used clinical trial data from 459 PD patients enrolled in the randomized controlled trials (RCTs) for pimavanserin in the treatment of PDP. A study reported a higher mortality rate (incidence rate ratio, [IRR] 4.20, 95% confidence interval, 2.13-7.96) in patients who used antipsychotics in comparison with those who did not [353]. In addition to this, other common side effects, such as sedation and orthostasis, should also be monitored closely.

Anti-dementia drugs

There seems to be a correlation between VHs and a faster rate of decline in cognitive function. Thus, it is logical to hypothesize that cholinesterase inhibitors may offer greater therapeutic benefits to PD patients with severe dementia who suffer from high levels of VHs. It is however important to note that to date, no double-blind, placebo-controlled studies have been carried out with the primary endpoint being the reduction of VHs. The majority of studies have been conducted using smaller groups, case studies, and open-label trials to assess the effectiveness of cholinesterase inhibitors in the treatment of PDP [354-357], while others have used VHs as secondary outcomes in studies where the primary outcome is to measure changes in cognitive abilities [358-361].

A number of studies have demonstrated the positive effects of cholinesterase inhibitors in the treatment of cognitive impairment, with subtle effects only observed on VHs but not on delusions, and without a significant impact on motor function. A significant number of patients, 7% - 10% of them, also reported worsening of their tremors as a side effect [362]. According to studies conducted to date, rivastigmine appears to be more consistently effective than donepezil in treating psychosis [359,361,363.

Anxiolytics and antidepressants

The psychological symptoms of depression and anxiety are often present in patients with PDP. It has therefore been suggested that either selective serotonin reuptake inhibitors (SSRIs) or serotonin-norepinephrine reuptake inhibitors (SNRIs) could be used to treat both of these symptoms through an enhancement of serotonergic activity. It has been noted in a case series of eight patients with psychosis that acute reversal of psychotic symptoms can be observed with SSRI (citalopram) or SNRI (venlafaxine), either monotherapy or as an adjunct to PD treatment in patients with comorbid depression or anxiety [364].

Several case reports have reported that clomipramine helped reduce the symptoms of PDP, indicating that reducing co-existing anxiety and depression may have a separate effect on the symptoms of PDP as well [365]. Furthermore, there have been case reports of patients with PD suffering from acute psychosis as a result of taking fluoxetine [366] as well as mirtazapine [367]. At the present time, however, no RCTs have been conducted to identify the specific role that any antidepressant class plays in the treatment of PDP.

Other pharmacological therapies

The use of Yokukansan, a traditional Japanese medicine that consists of medicinal herbs, is approved in Japan for the treatment of anxiety and insomnia, as it has effects on the function of serotonergic receptors (5-HT1A and 5-HT2A). Studies have also shown that yokukansan has beneficial effects on neuropsychiatric symptoms associated with dementia, with good tolerability as well [368,369].

It has also been reported in a recent study that there is a tendency to improve delusions alongside significant improvements in hallucinations. It is important to note that motor functions did not undergo a significant change as a result of the treatment. Hypokalemia, listlessness, and drug allergies were some of the adverse effects associated with this medicine [370].

A study looked at the role of yokukansan for treating behavioral and psychological symptoms of dementia (BPSD) in patients with PD (n = 7) and those with PDD (n = 7). PD and PDD patients were treated for 4 weeks with yokukansan and the same patients were observed without yokukansan for 4 weeks. Psychological symptoms were evaluated every 4 weeks according to the Neuropsychiatric Inventory (NPI) scale. There was a significant improvement in psychological symptoms in the majority of patients with PD and PDD after 4 weeks of yokukansan treatment, especially in the incidence and duration of hallucinations [371].

Further, it is also reported that gabapentin was effective in treating an advanced case of PD with episodic VHs like insects and worms over the trunk and genital areas as well as asynchronous pain over the inguinal area. Despite the absence of any motor deterioration after gabapentin use, the disappearance of VHs suggests that there may be a possible involvement of the glutamic acid neuron system and/or the amino butyric acid neuron system in the VH disappearance and can be used as an alternative option in advanced PD [372]. During the course of taking gabapentin 300 mg orally five times a day for neuropathic chest pain following a coronary artery bypass graft surgery three years prior, a 65-year-old woman with no history of psychiatric illnesses developed VHs. A discontinuation of gabapentin led to the resolution of her hallucinations and was absent at 1 year of follow up. Taking gabapentin as a treatment for elderly patients must be done with the greatest care [373].

Nonpharmacological

Electroconvulsive therapy: It has been reported that there have been several small case series which have demonstrated that electroconvulsive therapy (ECT) has a beneficial effect on patients with refractory PD psychotic symptoms [374-376], as well as no change, or even improvement in symptoms related to motor function [377]. A meta-analysis looked at the role of ECT in non-motor symptoms especially NPS in PD. There was a significant improvement in depression and psychosis following ECT. It can be a useful tool in treating complicated PD patients [378].

In another study, it has been found that all patients who received ECT showed a statistically significant improvement in their Brief Psychiatric Rating Scale (reduction of 52%

points) and Hamilton Depression Rating Scale (reduction of 50% points), irrespective of whether or not they were experiencing psychosis or depression at the time. As an effective treatment for refractory NPS associated with PD, ECT has shown great promise [379]. Several case reports have shown the usefulness of ECT in drug induced psychosis especially caused by levodopa and other dopaminergic agents when used in idiopathic PD for longer duration and also in psychosis caused in cases secondary parkinsonism [380-384].

However, a case report also found out that there was a marked increase in parkinsonian symptoms and dystonia after ECT was administered to a patient with schizoaffective disorder and anticholinergic-refractory neuroleptic-induced parkinsonism. There has never been a report in the literature about this kind of unusual reaction of parkinsonian and dystonic symptoms to ECT [385]. One should continuously monitor for these uncommon side effects in PD patients when ECT is used.

DBS surgery

Several researchers have suggested that reducing the amount of dopaminergic medication after bilateral subthalamic DBS surgery may improve psychotic symptoms in PD patients 87[252]. A number of reports have also been published of stimulation-induced psychotic symptoms as well as transient manic psychosis following DBS surgery, which are likely to occur more frequently in older patients [386-388]. However, a recent case report described an acute-onset and reversible psychosis following DBS to the globus pallidus internus (GPi) [389].

Transcranial direct current stimulation

A shortage of well-designed, adequately powered RCTs is present for treating PDP. It was found that repeated consecutive sessions of occipital cathodal transcranial direct current stimulation (tDCS) and parietal anodal tDCS did not help in VHs associated with both PDD and DLB. Cognitive stimulation (attentional and visuoperceptual tasks) did not improve the condition [390].

Psychological approaches

It is also important to discuss non-pharmacological methods for managing psychosis and its behavioral and emotional consequences with the patient and his/her family. There is a tendency that PDP persists, and aggressive pharmacological treatments may not be able to resolve it. Additionally, psychosis is linked to other mental health conditions such as depression that are associated with disturbing emotions. An important element in optimizing psychosis management is the acquisition of self-management skills and the implementation of structured psychological interventions, despite the fact that both areas are understudied.

The effectiveness of psychotherapy as a primary intervention for PDP has not been studied in detail. However, clinical experience suggests that applications of cognitive behavioral therapy (CBT) techniques, such as stimulus control, caregiver skills training, family psychoeducation, and, to a lesser extent cognitive reframing, may be useful in treating the condition. In addition to CBT, caregiver management techniques may also help so as to improve the QOL for people with PDP by addressing modifiable risk factors such as healthy sleep habits, circadian rhythms, inaccurate beliefs about the meaning and cause of PDP, and the medications used to treat it, and by enhancing caregiver skills [390].

According to Diederich and colleagues, 36 out of 46 hallucinating PD patients who were surveyed reported using self-driven coping strategies in order to manage their symptoms, such as cognitive, interactive, and visual means. There was no formal measure included in the study to evaluate the effectiveness of these coping strategies, however patients who used these strategies found their hallucinations to be bothersome or depressing only 39% of the time, whereas patients who did not use these strategies found their hallucinations to be bothersome or depressing 60% of the time [391].

An array of psychosocial interventions has also been successfully used to treat the psychosis of PD patients, including CBT, supportive therapy, and psychoeducation [391-396]. Due to the fact that early psychosis in PD is often accompanied by retained insight, these patients are likely to benefit even more from such techniques as those described above.

Conclusion

The present review suggests that PDP is an important non-motor symptom that can predict a poor outcome in patients with PD. It has been suggested that dyshomeostasis of neurotransmitters, disruption of neuro-signaling pathways, and cognitive impairment contribute to the development of PDP. In the course of PD, onset and progression of psychosis are both associated with the side effects of anti-Parkinsonism medications and the patient's specific characteristics. A number of therapeutic approaches are available to treat PDP, including the reduction or cessation of dopaminergic drugs, the use of antipsychotics, cholinesterase inhibitors, NMDAR agonists, and nonpharmacological interventions. It is still important in clinical practice to develop pharmacological interventions for PDP.

Future research should assess whether antiparkinsonian medications have any impact on the development and progression of PDP in a cohort of patients receiving different kinds and doses of antiparkinsonian medications, in order to determine whether antiparkinsonian medications have any significant impact. The emerging research on future targeted therapies which are based on new biomarkers and genetic factors may provide useful information for tailoring therapeutic strategies to each individual.

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