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REVIEW ARTICLE

Psychosis in Parkinson's Disease: Epidemiology, Pathophysiology, and Management

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Abstract Psychotic symptoms are common in Parkinson's disease (PD) and are associated with poorer quality of life and increased caregiver burden. PD psychosis is correlated with several factors, such as more advanced disease, cognitive impairment, depression, and sleep disorders. The underlying causes of psychosis in PD thus involve a complex interplay between exogenous (e.g., drugs, intercurrent illnesses) and endogenous (e.g., PD disease pathology) factors. Current theories of the pathophysiology of PD psychosis have come from several neuropathological and neuroimaging studies that implicate pathways involving visual processing and executive function, including temporo-limbic structures and neocortical gray matter with altered neurotransmitter functioning (e.g., dopamine, serotonin, and acetylcholine). Treatment of PD psychosis requires a step-wise process, including initial careful investigation of treatable triggering conditions and a comprehensive evaluation with adjustment of PD medications and/or initiation of specific antipsychotic therapies. Clozapine remains the only recommended drug for the treatment of PD psychosis; however, because of regular blood monitoring, quetiapine is usually first-line therapy, although less efficacious. Emerging studies have focused on agents involving other neurotransmitters, including the serotonin 5-HT2A receptor inverse agonist pimavanserin, cholinesterase inhibitors, and antidepressants and anxiolytics.

Key Points

Well-formed visual hallucinations are the most typical psychotic feature associated with idiopathic Parkinson's disease (PD).

Psychosis is more common in advanced disease, and associated with comorbidities including cognitive impairment, sleep disorders, and mood disorders.

Treatment of PD psychosis requires a step-wise process, with initial careful investigation of treatable triggering conditions and possible adjustment of both non-PD and PD medications.

Specific treatment of PD psychosis, without worsening of PD motor symptoms, relies on low doses of the atypical antipsychotics quetiapine or clozapine. Visual hallucinations may respond to cholinesterase inhibitors. Newer agents are in development but comparative efficacy and safety is as yet unknown.

1 Definition and Symptoms

Psychosis is part of the spectrum of neuropsychiatric disorders encountered in Parkinson's disease (PD) patients. The presence of PD psychosis is associated with significant patient morbidity and caregiver burden [1] and is a key factor associated with early mortality [2].

The phenomenology of psychotic symptoms appears to be unique to PD, suggesting a disease-specific rather than drug-induced etiology. Thus, the nature and pattern of

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psychosis can be helpful in defining that the symptoms are associated with PD and not due to other diseases. A decade ago, the National Institute of Neurological Diseases and Stroke (NINDS)/National Institute of Mental Health (NIMH) working group proposed a unified diagnostic criteria for PD psychosis, which consists of the following components: the presence of at least one psychotic symptom (illusions, false sense of presence, hallucinations, delusions); a primary diagnosis of PD that fulfills the UK brain bank criteria; the symptoms occur after the onset of PD and are either recurrent or continuous for 1 month; exclusion of other causes (i.e., dementia with Lewy bodies (DLB), psychiatric disorders such as schizophrenia, schizoaffective disorder, delusional disorder, or mood disorder with psychotic features, or a general medical condition including delirium); and associated features, including with or without insight, dementia, or treatment for PD [3].

Psychotic symptoms in PD are defined as follows [3]:

Delusions are false fixed idiosyncratic beliefs that are maintained despite evidence to the contrary. Delusions in PD are commonly paranoid, consisting of beliefs about spousal infidelity or abandonment/harm, whereas grandiose, somatic, persecutory, and religious delusions are far less common.

Hallucinations are abnormal perceptions without a physical stimulus that can involve any sensory modality, and may be simple or complex in form. There are several types encountered in PD but the commonest, and almost pathognomic are visual. Visual hallucinations (VHs) are typically vivid and well formed, mostly of people or animals with or without minor distortion, but they can also be objects or lines. The hallucinations tend to be stereotyped with similar patterns and disappear when approached, and they often occur during evenings and quiet environments with low ambient stimulation. Auditory hallucinations are less common and consist of people talking, indistinct whispers, music from the other room, and threatening voices. In PD, insight is usually retained initially but often can be lost and a proportion of patients will then go on to develop delusions.

Other types of hallucinations encountered in PD include so-called 'minor' hallucinatory phenomena, which includes the following: presence hallucinations, in which the person experiences the sense that someone is present when there is nobody actually there; passage hallucinations, which consist of fleeting, vague images in the peripheral vision; and illusions, which are misperceptions of real stimuli that are often visual in nature.

Measuring PD-specific psychosis, both in clinical trials and in daily clinical practice, has to date been limited due to a lack of widely used, validated PD psychosis rating scales. In general, scales from non-PD conditions (e.g., schizophrenia) have been used to measure PD psychosis, which clearly do not represent the true phenomenology of the condition. There have been two reviews giving critique on scales that address psychotic phenomena, one by the Quality Standards Subcommittee of the American Academy of Neurology (AAN) [4] and the second from the International Parkinson and Movement Disorder Society (MDS) task force [5]. The AAN subcommittee concluded that a gold standard for diagnosis of psychosis in PD was not available. The MDS Task Force reviewed 12 scales or questionnaires that had been used in published clinical trials focusing on psychosis in PD: Parkinson's Psychosis Rating Scale (PPRS) [6], Parkinson Psychosis Questionnaire (PPQ) [7], Rush Hallucination Inventory [8], Baylor Hallucination Questionnaire [9], Neuropsychiatric Inventory (NPI) [10], Behavioral Pathology in Alzheimer's Disease Rating Scale (Behave-AD) [11], Brief Psychiatric Rating Scale (BPRS) [12], Positive and Negative Syndrome Scale (PANSS) [13], Schedule for Assessment of Positive Symptoms (SAPS) [14], Nurses' Observation Scale for Inpatient Evaluation [15], Clinical Global Impression Scale (CGIS) [16], and Unified Parkinson Disease Rating Scale (UPDRS) Part I [17]. The Task Force labeled the NPI, BPRS, PANSS, and SAPS as 'Recommended,' and the PPRS, PPQ, Behave-AD, and CGIS as 'Suggested.' The NPI and SAPS follow a standardized method of administration for consistency, whereas the BPRS and PANSS are less structured. Nevertheless, a recent systemic review rating scales for sensitivity and specificity concluded that none of the existing scales or questionnaires adequately and comprehensively covers all psychotic symptoms in PD patients; thus, it remains of importance to develop a new, PD-specific instrument for screening psychotic symptoms in PD [18].

2 Epidemiology

The prevalence of psychotic symptoms in PD varies widely owing to differences in methodologies, including lack of consensus in defining each psychotic symptom, assessment period, and place, different sample populations, and effects of medications. The samples of patients collected in earlier studies were mostly cross-sectional with prevalence ranging from 16 % up to 75 % [19–26]. More recently, the prevalence was reported as 60 %, using the NINDS/NIMH criteria for PD psychosis described in Sect. 1, in an outpatient clinic setting with 116 PD patients [27]. The overall prevalence was higher than the definitions used by the authors (i.e., questionnaires and Diagnostic and Statistical Manual of Mental Disorders [DSM] criteria [60 vs 43 %]), owing to the fact that it encompassed the less common

visual illusions (27 %) and minor symptoms (45 %), and emphasized nonvisual hallucinations (35 %). A similar study conducted in 250 community-based PD subjects, using the same scale, reported a lower overall prevalence of 26 % with any psychosis, and 52 % with delusions, and the difference may relate to this study recruiting subjects with higher mini-mental state examination (MMSE) scores (i.e., >24) [28].

In all studies, VHs are the most common psychotic symptom in PD patients and range from 16 to 38 % [29]. Auditory hallucinations are less common and usually co-exist with VHs (0–22 %). Delusions are even less common with a prevalence of 1–7 % of PD patients and are more common in PD patients with dementia, often representing a deterioration of hallucinations, and tend to be the most significant and disabling symptom among all the psychotic features [22].

The less bothersome minor hallucinations (defined above) have gained more attention recently due to the observation that they develop in earlier stages of the disease and may be a 'marker' of progression to more severe bothersome VHs and delusions [30, 31]. The prevalence of such minor hallucinations varies remarkably, again due to methodological differences, and may occur in up to 50–72 % of patients [32, 33].

Studies evaluating progression or changes of psychosis over time have shown that, in general, PD subjects develop psychosis in the more advanced stages of the disease, thus prevalence increases with disease duration. A study of 137 PD patients reported that 60 % had developed hallucinations or delusions after 12 years of follow-up, and higher age at onset and baseline levodopa-equivalent doses (LED), probable rapid eye movement (REM) sleep behavior disorder (RBD) at baseline, and follow-up time were the most important independent risk factors in developing psychotic symptoms [34] (these risk factors are discussed in full in rest of the Sect. 2). Goetz et al. studied 60 non-hallucinating PD patients and assessed the development and evolution of different kinds of hallucinations over 10 years [35]. Whereas isolated VHs dominated in the early profile, nonvisual hallucinations emerged and accounted for a greater proportion over 10 years (0 % at 0.5 years to 60 % at 10 years). Of note, VHs tend to persist in PD, and the existence of VHs at baseline is a strong predictor of their existence at follow-up evaluations [8].

Several factors may be associated with and contribute to the development of psychosis, though no single variable can be considered the sole culprit and the risk is highest in subjects with all risk factors (see Table 1). These risk factors can be classified into the following: pharmacological, disease-related, genetic, and intercurrent medical conditions.

2.1 Pharmacological Risk Factors

2.1.1 Drug-Naïve Parkinson's Disease (PD)

The majority of studies evaluating psychosis in PD are in subjects already on medication; very few studies report the incidence in drug-naïve PD patients. Due to the association of psychosis with advanced disease, psychosis in early PD is much less common, but does occur. One study reported 4 out of 33 (12 %) untreated PD patients without dementia from Tanzania with a mean disease duration of 7.2 years (versus 4.7 years for non-hallucinators) having VHs [36], and in another study, 8 of 30 (26 %) early (mean duration of PD 22 months, range 11–46 months) drug-naive PD patients experienced well-formed VHs [37]. In one study, using the NPI, 1.1 and 1.2 % of the 175 early untreated PD patients experienced delusions and VHs, respectively [38]. A recent study prospectively analyzed the frequency of minor hallucinations as a 'pre-motor' symptom in drug-naive, 'de novo' PD patients [31]. Forty-two percent (21 of 50) of PD patients experienced minor hallucinations (compared with 5 % in controls), and 33.3 % of these patients developed these minor hallucinations before the first parkinsonian motor symptoms, which only occurred between 7 months and 8 years after the hallucinations.

As part of the ongoing Parkinson's Progression Markers Initiative (PPMI), a recent cross-sectional study of 423 de novo, untreated patients with PD and 196 healthy controls was reported. Screening for PD psychosis was performed using the MDS-UPDRS Part I; and the prevalence of psychosis at the time of enrollment was more common in the PD group compared with the healthy controls (3.0 versus 1.0 %) [39]. The prevalence of psychosis in PD patients increased significantly over time (5.3 and 10 % at 12 months and 24 months, respectively), though none of the demographic or clinical features (e.g., disease stage or severity, duration of disease, tremor or non-tremor type) was able to predict a positive psychosis score [40].

The difficulty in early PD is that all studies, to date, do not have pathological confirmation of diagnosis. Thus, subjects with other causes of hallucinations, such as DLB, may have been recruited. Other non-PD drugs may also trigger psychosis, and as such, differentiating drug-induced from true, spontaneous psychosis in early PD is difficult. Clinical experience has largely suggested a de novo early PD subject is extremely unlikely to experience spontaneous psychosis, and the presence would usually suggest other diagnoses. However, recent studies suggest that hallucinations may occur, and even as pre-motor features. As discussed below, the interplay between RBD and VHs may be the key to the presence of VHs in early PD. Thus, early PD subjects often have RBD and excessive daytime sleepiness. Early PD subjects thus may experience VHs in

Table 1 Risk factors for developing psychosis in Parkinson's disease (PD)

	Importance	Independence	Controversial
Disease-related risk factors			
Disease duration	+++	Y	–
Disease severity	+++	Y	–
Age at onset	++	?	+
PD subtypes			
Idiopathic PD akinetic subtype	+	N	–
Genetic PD	++	Y	–
Non-motor symptoms			
Dementia	+++	Y	–
RBD	+++	Y	–
Visual disorders	++	?	–
Depression	+	N	–
Autonomic dysfunction	+	N	–
Olfactory dysfunction	+	N	–
Genetics	+	N	+
Intercurrent medical conditions	++	Y	–
Medication-related risk factors			
LEDD doses	++	Y	–
Levodopa dose	+	Y	+
Non-levodopa	+	?	+

The table is an overview of the relative risk factors for developing PD psychosis, as reviewed in the accompanying text. The risk factors are divided into disease-related and medication-related factors and graded according to how important the risk factor is (Importance). Importance is graded high (+++), moderate (++), or low (+). The second column (Independence) shows whether the risk factor is sufficiently strong to be an independent risk (yes [Y]) or whether it is usually associated with other factors (no [N]), or unclear (?). The third column (Controversial) is whether the literature is unclear (yes [+]), or not applicable/unlikely (–), as to the importance and/or independence of the risk factor associated with developing PD psychosis, from the literature reviewed in the text

LEDD levodopa equivalent daily dose, *RBD* REM sleep behavior disorder

the day, during periods of going off or waking from daytime sleeps. It is thus extremely important when assessing these early PD subjects to determine the diurnal time course of when these VHs occur in relation to daytime naps and sleep–wake cycle. Further studies are needed to correlate the presence of daytime sleep disorders and PD psychosis in early untreated PD.

2.1.2 PD Medications

The relationship between psychotic symptoms and PD medications continues to be difficult to interpret and separate, as psychosis is more common in PD patients in more advanced stages, and by definition these patients will be treated with dopaminergic drugs for their PD symptoms. Clinically, a very common scenario in which psychosis occurs, or is exacerbated, is in relation to the introduction of, or changes in, PD medications [41–44]; however, no evidence-based data or randomized trials are available to support this.

One method of trying to determine whether dopaminergic drugs, per se, are an independent risk factor for psychosis is to correlate dose with symptoms. However, overall, in most cross-sectional studies, hallucinators did not have significant differences in the total levodopa daily dose or other PD medication usage from non-hallucinators [19, 20, 24, 26, 45–47]. The absence of hallucinations, despite infusion of high doses of levodopa, also suggests that dopamine medication alone is not the sole reason for psychosis [48, 49]. On the contrary, a higher daily levodopa dose emerged as an independent predictor of feeling of presence, a type of minor hallucination, that suggests a specific facilitating role of dopaminergic agents in these milder types of psychosis [50].

Other dopaminergic medications can also trigger psychosis. The suggestion that direct dopamine receptor agonists (DAs) may be more likely to induce psychosis than levodopa remains unclear. While earlier studies suggested that the time to onset of hallucinations was reported to be only weakly linked with the use of ergot type DA [51], DAs were found to have higher odds ratios (OR 0.65–2.01) than levodopa (OR 0.11) when evaluating the occurrence of psychotic symptoms with individual DAs in a more

recent study [52]. Two meta-analyses also showed that hallucinators used DAs more frequently than placebo or levodopa [53, 54]. Interestingly, one study suggested that delusional jealousy, a content-specific delusion characterized by a range of irrational thoughts and preoccupation with a partner's sexual unfaithfulness based on unfounded evidence, is thought to be strongly related to the usage of DA [55], which may occur independently from hypersexuality, the other similar but more common side effect of DAs [56]. A cross-sectional study evaluating risk factors in 775 PD subjects also noted that patients on DAs and catechol-*O*-methyltransferase (COMT) inhibitors were also more likely to have PD psychosis [57]. The potential increased risk of psychosis with DAs over levodopa may reflect the pharmacology of DAs, in which there is binding to non-dopamine receptors, such as serotonin (5-hydroxytryptamine; 5-HT), that may be implicated in psychosis.

Overall, dopaminergic agents are known to trigger psychosis in susceptible PD patients and psychosis can certainly resolve if newly added/increased drugs are reduced. However, many subjects continue to experience psychosis even when potential triggering drugs are altered, suggesting psychosis is not purely a drug-induced effect. The other risk factors—age, presence of comorbid dementia—are likely to trigger psychosis, as not all PD patients get psychosis with dopaminergic drugs. The effect of PD drugs is also not purely dopamine-mediated, and the pharmacological profile (i.e., dopamine, glutamate, serotonin, cholinergic, etc.) of the drugs that are more likely to trigger psychosis is discussed in Sect. 3.3.

2.2 Disease-Related Risk Factors

Multiple pathological changes within the brain due to progressive neurodegeneration in PD are likely the biggest risk factors for developing psychosis. Thus, several disease-related risk factors are important to consider, including disease duration, disease severity, and presence of other disease-related comorbidities including cognitive impairment and mood disorders.

2.2.1 Duration of PD and Severity of PD

The association of PD psychosis with disease duration has been a consistent finding and adds to the suggestion that the cause of psychosis relates to disease-related factors more than drugs per se. Thus, longer duration of PD [19, 58–60] has been correlated interchangeably and associated with psychotic symptoms in PD. Earlier multivariate analyses show that it is the duration of PD rather than the age at onset that is the independent predictor of VHs [19, 46, 61]. In an autopsy-proven study, the onset of VHs in PD typically occurred in the second half of the disease course, while <4 % developed in the first 5 years of PD [62]. Longitudinal studies show that with follow-up, PD psychosis increases over time, which most likely reflects disease progression. Thus, the prevalence of hallucinations of 89 PD patients increased from 33 to 55 % in a 6-year follow-up [63], and, in another study, the corresponding values were 21 % at 15 years versus 74 % at 20 years of follow-up [64]. Another larger study also reported an increase of hallucinations from 23 to 56 % among the 125 PD patients after 4 years of follow-up [65].

Longer disease duration generally implies greater PD disability/severity. Many studies have shown that hallucinators have greater PD severities in terms of UPDRS Part II (activities of daily living) and Part III (motor subscores) and Hoehn and Yahr stage [19, 66].

2.2.2 PD Subtypes

In keeping with an association with more severe disease, the motor phenotype of PD that may be more likely to develop psychosis is with more axial impairment [19, 26, 32], lower tremor scores and higher rigidity, bradykinesia and postural instability scores [46], and freezing of gait [60, 67, 68]. In another study of 206 patients, a trend towards more likelihood of developing VHs was found in the patients with bradykinesia–rigidity onset phenotype compared with patients with tremor phenotype (OR 1.89, $p = 0.065$) [69], which is in accordance with another study of 314 PD patients where a similar trend was found, but only in female patients [70].

Interestingly, both the side and the degree of motor asymmetry seems to correlate with the severity of psychosis, which was shown in a study with 149 PD patients with higher PPRS scores in the extreme right-sided PD group, suggesting damage to the left hemisphere effects PD psychosis over time [71]. However, other studies have reported the opposite. A small study in 31 treated PD patients (disease duration 6–8 years) reported that left-sided (rather than right-sided) onset PD was correlated to the presence of nocturnal hallucinations and daytime dozing [72]; the interpretation was that right-hemisphere neural networks are implicated in the generation and control of visual images, arousal, and vigilance.

2.2.3 Age

To date, older age has been considered a significant risk factor [46, 57, 58], but this is not consistent [8]. A more recent study, with a large group of PD patients enrolled ($n = 500$ patients) reinforced the finding that age was strongly correlated with the occurrence of psychotic symptoms (OR 4.82 in ages 63.8–72.9 years versus OR 6.25 in ages >72.9) [60]. In one study ($n = 331$), the

medication-related risk of psychosis was higher in patients aged ≥70 years, particularly levodopa, DA, and anticholinergics, whereas no significant risk was found in younger patients, suggesting different mechanisms between young and old PD patients [73]. Increased age at onset of PD led to increased risk of developing hallucinations, by about 5 % per year [45].

In terms of the types of PD psychosis associated with age, most studies have evaluated well-formed VHs (as the commonest psychotic symptom). Goetz et al. found that older patients were more likely to have non-visual or mixed hallucinations than purely VHs, which suggested that age may play a role in the phenomenology of hallucinations [74]. Of note, while one study found an association of delusions with younger onset of both PD and psychosis as compared with hallucinations [75], another study failed to show this; with the prevalence of delusions incomparable between the young-onset and later onset PD patients (1.9 and 2.8 %, respectively; $p = 0.527$) [76].

2.2.4 Genetic PD Types

The association of genes that cause PD and risk of psychosis is unclear; but overall the autosomal recessive (AR) genetic PD (e.g., *parkin*, PTEN-induced putative kinase 1 [*Pink1*] and *DJ1*), appears less likely to have psychosis than autosomal dominant (AD) genetic PD (α-synuclein [SNCA] and leucine-rich repeat kinase 2 [LRRK2]) or idiopathic non-genetic PD. An early systematic review on the prevalence of non-motor symptoms in genetic PD [48] revealed that the overall frequency of psychosis in genetic PD does not appear to be higher and may even be lower than in idiopathic PD (3–29 %). With all cases combined, psychotic symptoms appeared to be rare in *parkin*-linked PD (about 3 %) and in other genetic PDs (SNCA, *Pink1*), in comparison with idiopathic PD. More recent studies have shown that *parkin* PD can be associated with psychosis [77]; but comparing *parkin*+ with disease-matched *parkin*− PD reported no real differences [78]. In PD patients with *Pink1* mutations, affective and schizophrenic spectrum symptoms have been described as part of the phenotypic spectrum or even the sole manifestation [79].

Previous studies have reported VHs are common psychotic symptoms in PD patients with SNCA duplications [80, 81], and schizophrenic-like symptoms of delusion and auditory hallucination may manifest as prodromal features [82]. Other studies indicated a high prevalence of psychiatric symptoms in LRRK2, G2019S mutation carriers (26 % of the 23 patients in the Algerian cohort [83] and 33 % of the 25 patients in the Italian cohort [84]); however, a more recent study found fewer hallucinations and antipsychotics required in the LRRK2-PD mutation group than in those with PD without LRRK mutations [85]. In a recent retrospective cohort study of up to 12 years' duration following 215 PD patients, 19 (8.8 %) PD patients with glucocerebrosidase (GBA) mutations developed psychosis significantly earlier and more frequently than those without mutations, with an adjusted hazard ratio of 3.1 for psychosis [86]. Thus, the role of genetics in risk of PD psychosis is complex, and the psychosis seems less due to the gene mutation per se, than possible other co-morbidities/risk factors.

2.2.5 Cognitive Impairment

Cognitive impairment is strongly associated with all psychotic symptoms in PD and is considered to be one of the most important independent risk factors for developing such symptoms [19, 20, 22, 26, 45, 87–89]. Clinical studies have consistently shown that psychosis is more prevalent in PD patients with dementia (PDD) than in PD patients without dementia [19, 45, 46, 90], even in the early stages of PD [91], and this increased prevalence continues over time in longitudinal studies (5-fold in 12 years) [34]. The prevalence of psychosis has been reported in up to 75 % of PDD, and symptoms are more intractable in this group [90]. Nevertheless, in two longitudinal studies, lower MMSE scores or dementia was neither associated with nor predicted future development of psychosis in multivariate models [8, 34], thus suggesting that cognitive impairment and psychosis may just co-exist across a clinical continuum.

The types and severity of psychosis in PDD may be different compared with PD without dementia [90]. In a study analyzing the symptoms in PDD patients, such subjects were reported to have more complex VHs (89 versus 17 %), illusions (65 versus 25 %) and presence (62 versus 31 %) but not passage hallucinations, compared with PD patients without dementia [92].

The close link between PD psychosis and dementia in PD is reflected in the known observation that the occurrence of VHs in PD may be a harbinger of subsequent cognitive decline [93], or the presence of preexisting dementia leads to more rapid decline in cognition with associated psychosis [94]. A longitudinal study reported that 75 % (9/12) of the PD patients with VHs developed dementia during a 2.5-year follow-up, whereas none of the PD patients without VHs met criteria for dementia [95].

Despite many studies, the cognitive profile of PD patients without dementia who develop psychosis compared with those who do not remains unclear. PD hallucinators without dementia have more deficits in executive function, set-shifting, sustained attention, immediate and delayed recalls, verbal memory, phonological and semantic fluency, and visuoperceptual function compared with non-hallucinators [96–104]. Several studies have suggested that

this cognitive profile is key to developing VHs [105, 106], which suggests there may be common neuropathologic processes leading to both hallucinations and cognitive decline [107]. In particular, a temporal–anatomical pattern of correlations in degrees of severities between the cognition deficit and VHs has been reported [99]: patients with minor VHs did not differ from patients without VHs in any cognitive domain; patients with major VHs and retained insight performed worse on the action verbal fluency task, suggesting a predominant frontal-striatal impairment; and patients with VHs and loss of insight showed a greater impairment on the Parkinson's Disease–Cognitive Rating Scale (PD-CRS) posterior cortical score and the clock copying item, suggesting a greater impairment in posterior cortical areas.

In contrast, other studies have reported no significant differences in cognitive profile of PD without dementia, with and without VHs [108, 109]. While an earlier study found delusions to be more frequent in dementia than non-dementia patients [90], a recent study showed that delusions in isolation or coexistent with VHs did not demonstrate any of the cognitive correlations [110, 111].

It is important to remember that despite the important association of dementia with the risk of psychosis, a recent study also reported a high proportion (20–25 %) of PD subjects without dementia developed VHs, emphasizing the importance of other contributors in different sets of patients studied [66].

2.2.6 *Sleep–Wake Disturbances*

Ever since Moskovitz et al. proposed the 'kindling' mechanism that psychotic symptoms progress from early vivid dreams to hallucinations and eventually delusions, sleep disorders have been reported more frequently in PD patients with VHs than those without, suggesting a link with sleep and risk of PD psychosis. Such sleep disorders include sleep fragmentation, vivid dreams and nightmares [112, 113], daytime somnolence [19, 89], and other sleep disorders evident on polysomnography, including decreased sleep efficiency, total REM sleep time, and REM sleep percentage [114–116].

In particular, there appears to be a link, and potential risk factor for PD psychosis, with RBD compared with patients without RBD [23, 117–119]. In one longitudinal study, the presence of vivid dreams or nightmares, but no sleep fragmentations, was correlated with VHs, although it did not predict future development of VHs [63]. Two other longitudinal studies showed higher risks of emergence of VHs in PD patients with RBD compared with those without RBD after 2 years' [120] and 12 years' [34] follow-up. The presence of minor hallucinations was also significantly associated with the presence of RBD [31]. The severity of RBD symptoms also seems to correlate with psychosis in early PD patients without dementia [66]. Recently, Lenka et al. published a review integrating the overlapping factors that are shared by RBD, VHs, and cognitive impairment based on clinical and epidemiological studies, neuroimaging, and electrophysiology, which suggest that they may all be driven by a similar neurobiological process [121].

2.2.7 *Visual Disorders*

There is a strong correlation between visual perceptive disorders and VHs in PD patients. In general, lack of vision from issues ranging from cataracts to low lighting at night can induce VHs in susceptible individuals. More specifically, PD patients with more marked deficits in visual acuity [20, 92, 122], color and contrast discriminations [123], and retinal nerve fiber layer (RNFL) thinning [124] pose higher risks of having VHs. The theory is that reduced retina–cortical signals with dysfunction in central visual information processing may lead to signal conflicts at the cortical level and the release of previously stored internal images.

In particular, studies have shown RNFL thinning to be correlated with disease severity [125] and VHs in PD patients without dementia [124]. A histopathological study of α-synuclein-positive inclusions found in autopsied inner retinal tissues in PD patients suggested the presence of anterograde trans-synaptic degeneration in nerve fibers from RNFL thinning and progress throughout the visual pathways [126], which results in a higher vulnerability in developing VHs. Another study proposed that PD patients are being functionally 'blind to blindsight,' which implies, with preserved conscious vision, PD patients develop inaccurate guessing and misinterpret peripherally located visual stimuli and motion perception, experiencing illusions and hallucinations [127]. This hypothesis with the involvement of one of the two separate visual pathways, the retino-geniculo-extrastriate pathway, was supported by a functional magnetic resonance imaging (fMRI) result showing microstructural alterations in visual pathways with atrophy in the lateral geniculate body [128].

2.2.8 *Depression*

Mood disorders, such as anxiety and depression, also appear to be risk factors for PD psychosis. Thus, many studies have shown correlations between mood and psychotic symptoms in PD [20, 22, 58, 66, 89, 129–131], although a few studies were inconsistent after multivariate analysis [19, 132]. This appears at all stages of the disease; thus, in a study of early-stage PD with 2-year follow-up, the presence of depressive symptoms and anxiety were more frequently observed in PD patients with psychosis [133].

2.2.9 Autonomic Dysfunctions

The association of autonomic dysfunction and PD psychosis has been reported but may also reflect a more advanced disease stage in general. In a retrospective autopsy study, autonomic dysfunction posed a 3.13 hazard ratio as a predictive factor of VHs in patients with Lewy body (LB) pathology (although there was no separation of idiopathic PD from DLB) [26]. Very little is known, however, about any direct pathophysiological links. One study that evaluated markers of autonomic failure recorded lower psychosis (measured using BPRS) scores between PD patients with blood pressure (BP) fluctuating along with the circadian rhythm ($\geq$10 %, $n = 11$, mean BPRS 27.5 $\pm$ 5.3) compared with PD patients without (<10 %, $n = 10$, mean 34.3 $\pm$ 7.3), indicating that those patients who had a blunted nocturnal BP fall were more prone to psychotic symptoms [134]. Notably, this correlation was also found along with the disease severity. The mechanism remains elusive, but possibly relates to dopamine and its relationship with sleep and circadian rhythms.

2.2.10 Olfactory Dysfunction

In a cross-sectional study, psychotic symptoms were more common in 248 PD patients with olfaction scores below the median (30 versus 12 %) [135]. With the result that prodromal olfactory impairment correlates with memory and executive functions [136], hyposmia may be a possible predictor of non-motor symptoms (i.e., psychosis).

2.3 Genetic Factors

There have been several studies, mostly negative, examining possible genetic correlations with VHs. Studies investigating dopamine receptor and dopamine transporter genes did not show any conclusive associations with VHs [137–139]. To date, there has also not been any associative genetic factors with VHs in 5-HT2A receptor and transporter genes [140], HLA typing [141], apolipoprotein E (APOE) ε2 [142], COMT [142], microtubule-associated protein tau (MAPT) [60], and α-synuclein promoter (SNCA-REP1) [60]. The associations of APOE ε4 to VHs have been either none [142] or positive (OR 5.29) [143]. Studies of cholecystokinin [CT/TT] and a combination of cholecystokinin [CT/TT] and cholecystokinin-A receptor [TC/CC] genotypes found associations with VHs [144, 145], however, the biological implication is unclear.

2.4 Other Factors

Some factors were evident only in single publications. Zhu et al. conducted a prospective study evaluating the risks of hallucinations in 386 PD patients following 5 years, in which female sex, as well as motor fluctuations and dyskinesias, which have not been reported as independent risk factors in previous studies, were shown to be related to hallucinations [89]. In another study, PD patients with dyskinesias also had a significantly higher frequency of hallucinations and delusions with the exception of delusional jealousy [146].

2.5 Intercurrent Medical Conditions

In many PD patients, intercurrent medical illnesses are the commonest reason for first development of psychosis, or exacerbation if already present. It is important to differentiate delirium from psychosis with decreased attention, variable level of consciousness, disorientation, and illogical thinking, which commonly occurs more acutely and is usually related to secondary treatable causes like febrile illness (see Table 1). Many studies have concluded that PD itself is an independent risk factor for the development of delirium and more so from adverse drug events and syncope, falls, mobility complications, pneumonia, genitourinary infections, and trauma [147, 148]. The reason PD patients appear so susceptible to developing delirium is not known but clearly relates to the pathological processes, and adds to the idea that psychosis is not a purely dopamine drug-induced effect. Similar to its relationship with dementia, delirium is likely to interface with PD on many levels: a marker of vulnerability of the brain, it unmasks unrecognized neurodegeneration, mediates the effects of noxious insults, and leads to permanent neuronal damage and hypoxia [149].

The pathophysiology of PD and delirium appears to occur from a number of overlapping concepts [150]. Systematic inflammatory events trigger the release of inflammatory mediators by tissue macrophages and brain vascular endothelial cells, which may affect neurons either directly but reversibly and induce acute neuronal synaptic or dendritic damage, or via the activation of microglial cells that have become primed by neurodegenerative disease or ageing and may contribute to accumulating damage. Individual studies have reported that there are many causes that contribute to delirium in PD.

1. Elevated pro-inflammatory cytokines, including interleukin-6 [151], nitric oxide that is involved in oxidative stress [152], elevation of plasma C-reactive protein [153], and subsequent excessive responses to systemic inflammation response, have been demonstrated in ageing and in animal PD models [154].
2. Neurotransmitter ‘imbalance’, including cholinergic deficiency with elevated serum anticholinergic activity, is independently associated with delirium [155], as

are imbalances in glutamate, γ-aminobutyric acid, and melatonin [156].
3. α-Synuclein pathology, which was found to be independently related to postoperative delirium within gastrectomy samples.
4. Genetic factors, particularly APOE ε4 carriers that had an adjusted OR of 1.7 for delirium [150].

3 Pathophysiology of PD Psychosis

Traditionally, due to the triggering effects of PD medications and its role in non-PD psychosis, the dopaminergic system is considered to play a pivotal role in the pathophysiology of PD psychosis. However, as discussed in Sect. 2.1, the link with medications is inconsistent. More likely, there is a complex interplay between the risk factors discussed in the previous sections, both exogenous and endogenous (e.g., disease process itself), associated with signaling pathways involving several brain functions mediated by multiple neurotransmitter systems (e.g., dopamine, serotonin, and acetylcholine).

Most work has so far focused on VHs rather than delusions. In general, studies point towards alterations in pathways involved in visual processing and reality monitoring with neurodegeneration of temporo-limbic structures and neocortical gray matter, including the prefrontal cortex, as being important in the development of VHs in PD patients. Attention, alertness, and sleep–wake cycle functions are also implicated. Investigating the pathophysiology of psychosis in PD has been hampered by a lack of validated PD-specific preclinical models of psychosis. Some attempts have been made using PD models, such as the 1-methyl-4-phenyl-1,2,3,6-tetrahydropyridine (MPTP)-primate model of PD. In this established model of motor symptoms of PD, behavioral changes termed 'psychosis-like behaviors' in response to chronic levodopa can be predictive of pharmacological interventions, both pro- and anti-psychotic [157], and have enabled studies into the pharmacology of PD psychosis. However, due to the complex interaction of disease–related features, most information on understanding PD psychosis has required human studies. Here, we provide an overview of the current knowledge of the pathophysiology of psychotic symptoms in PD through evidence from neuropathology, structural and functional neuroimaging, neurotransmitter studies, and finally neuropathway signaling models.

3.1 Neuropathology

To date, there are limited clinic–pathological studies primarily investigating VHs in PD due to the many confounders that impact interpretation of pathological studies, such as co-morbidities, particularly pathological changes due to co-existent dementia. Earlier studies focused on the presence of LBs/α-synuclein as the marker of pathology while more recent studies have looked at other pathological findings, such as tau, plaques and tangles, and inflammatory markers that may also be linked to PD psychosis.

The most consistent finding has been that the temporal lobe and, more specifically, the inferolateral temporal region, seems to play an important role in VHs of PD, with studies reporting high densities of LBs in the amygdala and parahippocampus in PD hallucinators compared with non-hallucinators [158]. The temporal cortex is part of the ventral visual stream involved in recognition of objects and faces [159, 160] as well as in auditory and visual integration [161, 162]. Another study also found additional LB burden in the frontal and parietal cortical areas in PD subjects with VHs [163], whereas the strong relation of α-synuclein burden in the amygdala to VHs was only found in PD patients with concomitant dementia [164]. A study focused on PD patients without dementia found double the amount of LB-containing neurons in the basolateral nucleus of amygdala in patients with VHs than without VHs, which suggests the contribution of this specific sub-nucleus of amygdala to VHs [165].

Likewise, as in other neurodegenerative diseases, mixed pathologies have been reported in subjects who experienced PD psychosis (i.e., vascular disease with underlying proteinopathy); thus plaque and tangle densities in frontal, parietal, and hippocampal areas have been reported to be associated with VHs in PD [166]. Other recent pathological findings include associations to tau pathology including agyrophilic grain, which showed a strong association with dementia [167] but unclear links to psychosis in PD [168, 169]. Inflammatory markers related to proteinase activity that have been linked to other neurodegenerative disorders (e.g., Alzheimer's disease) were investigated in a recent post-mortem study in PD [170]. It was suggested that the changes of increased serpin-A5 expression in locus coeruleus, substantia nigra, and primary motor cortex, and reduced trypsin-2 expression in anterior cingulate cortex and increased in primary motor cortex may be linked to the presence of PD psychosis, but this was not clear and further studies are needed.

3.2 Neuroimaging

Neuroimaging studies have been one of the largest areas of research used to investigate the underlying substrates of VHs in PD patients, including structural brain imaging with voxel-based morphometry (VBM), positron emission tomography (PET) and single photon emission computerized tomography (SPECT), and fMRI (see Tables 2, 3, 4 for summary of

Table 2 Structural neuroimaging studies using Voxel-based morphometry (VBM) in Parkinson's disease patients with visual hallucination

Study	Aim of study in PD patients with VHs	Results in PD patients with VHs vs PD patients without VHs
Ramírez -Ruiz et al. [171]	The pattern of cerebral atrophy	More GM volume reductions in left lingual gyrus and bilateral superior parietal lobe
Ibarretxe-Bilbao et al. [172]	The hippocampal GM density	More hippocampal volume reduction (also in PDD)
Ibarretxe-Bilbao et al. [173]	Correlation in progression of cognitive deficits and brain atrophy	More GM reductions in neocortical, limbic, and para-limbic region with cognitive impairment
Meppelink et al. [174]	GM volume changes	No differences
Janzen et al. [175]	GM volume of PPN region	More GM volume reductions in PPN region and its thalamic projections
Shin et al. [176]	Neuroanatomical basis in PD patients without dementia	More GM volume reductions in right orbitofrontal, left temporal, substantia innominata, and thalamic area
Watanabe et al. [177]	Regional brain volume changes	Atrophy in bilateral DLPFC and primary and secondary visual cortex, left rostral PFC, ventral part of cingulate cortex, and fusiform gyrus
Pagonabarraga el al. [178]	GM volume with minor hallucinations	More GM volume reductions in superior parietal lobule, superior occipital gyrus, cuneus, precuneus, superior colliculus
Gama et al. [179]	Cerebral volume	More volume reduction in opercular part of left inferior frontal gyrus
Goldman et al. [180]	GM volume	More GM reduction in lingual, cuneus, fusiform gyri, middle occipital lobe, inferior parietal lobule, paracentral and precentral gyri in PD hallucinators without dementia
Fioravanti et al. [181]	GM volume	More GM volume reductions in right putamen and parietal cortex and additional at PPN and mesencephalic locomotor region (MLR) after 2 years

DLPFC dorsolateral prefrontal cortex, *GM* gray matter, *PD* Parkinson's disease, *PDD* Parkinson's disease dementia, *PFC* prefrontal cortex, *PPN* pedunculopontine nucleus, *VH* visual hallucination

studies). This use of imaging as the primary modality for investigating PD psychosis reflects the difficulties in defining single neurotransmitters or single regions involved, and the multiple factors that likely cause PD psychosis from visual to cognitive to attention functions. However, due to the fluctuating and variable nature of VH symptoms, and heterogeneity of patients recruited, there are currently no consistent imaging findings, although themes have emerged.

3.2.1 Voxel-Based Morphometry (VBM)

VBM imaging helps examine regional patterns of atrophy. To date, studies have reported inconsistent results when comparing gray matter volume in PD patients with and without VHs. The discrepancies in these results may be due to differences in methodology, statistical analysis, or steps of image processing. Table 2 summarizes key VBM-based studies in PD patients with VHs. Overall, these studies have shown atrophy can occur in all areas involving the visual processing pathways (i.e., parietal, temporal, and occipital lobes) and cognitive pathways of cholinergic pedunculopontine nucleus (PPN) in PD subjects with VHs, compared with those without VHs.

3.2.2 Positron Emission Tomography (PET)/Single Photon Emission Computerized Tomography (SPECT) for Blood Flow

Several studies using PET and SPECT have shown hypoperfusion or hypometabolism in areas involving cortical visual pathways, mainly frontal and temporo-occipital gyri. Table 3 summarizes studies using PET and SPECT in PD patients with VHs.

3.2.3 Functional Magnetic Resonance Imaging (fMRI)

Functional connectivity analysis shows activation using different cognitive and motor tasks to represent pathways of interest. As with other imaging modalities, there have been inconsistent results in PD patients with VHs. Table 4 summarizes the results of fMRI studies in PD patients with VHs.

Table 3 Positron emission tomography (PET) and single photon emission computerized tomography (SPECT) studies in Parkinson's disease patients with visual hallucination

Study	Aim of study in PD patients with VHs	Results in PD patients with VHs vs PD patients without VHs
PET studies		
Nagano-Saito et al. [182]	Pattern of glucose metabolism	Increased in frontal regions
Boecker et al. [183]	Pattern of glucose metabolism	Decreased in occipito-parieto-temporal region sparing the occipital pole (left > right)
Park et al. [184]	Pattern of glucose metabolism	Decreased in ventral visual pathways
SPECT studies		
Okada et al. [185]	Cerebral blood flow	Lower in left temporal regions
Oishi et al. [186]	Cerebral blood flow	Decreased in right fusiform gyri and increased in right superior and middle temporal gyri
Matsui et al. [187]	Cerebral blood flow	Decreased in bilateral inferior parietal lobule, inferior temporal gyri and precuneus gyri, and occipital cortex
Kiferle et al. [188]	123I-FP-CIT retrospective comparison	Lower in right caudate

PD Parkinson's disease, *VH* visual hallucination

Table 4 Functional MRI (fMRI) studies in Parkinson's disease patients with visual hallucination

Study	Aim of study in PD patients with VHs	Results in PD patients with VHs
Stebbins et al. [189]	Activation after visual stimulation	Increased frontal and subcortical and decreased visual cortical activations
Holroyd and Wooten [190]	Activation pattern	Increased in visual association areas and decreased activations in primary visual cortex
Ramírez-Ruiz et al. [191]	Cortical activation using face detection task	Decreased in anterior cingulate and superior, middle, and inferior frontal gyri
Meppelink et al. [192]	Activation pattern	Decreased in lateral occipital cortex for several seconds and extrastriate temporal visual cortices just before the image recognitions
Yao et al. [193]	Alteration in DMN	Increased functional connectivity in DMN in right middle frontal gyrus, bilateral posterior cingulate gyrus, and precuneus
Yao et al. [194]	ALFF in resting state	Decreased ALFF in bilateral lingual gyrus and cuneus and increased ALFF in temporo-parietal regions, medial temporal gyrus, and cerebellum
Franciotti et al. [195]	Alteration in DMN in both early and severe PD	Increased functional connectivity in DMN in bilateral middle frontal gyrus, posterior cingulate gyrus in severe PD
Yao et al. [196]	Alteration in hippocampus	Decreased hippocampal functional connectivity in the visual cortices and increased in frontal regions

ALFF amplitude of low-frequency fluctuations, *DMN* default mode network, *MRI* magnetic resonance imaging, *PD* Parkinson's disease, *VHs* visual hallucinations

3.3 Neurotransmitters

A number of neurotransmitter systems, including the dopaminergic, cholinergic, glutamate, and serotonergic systems, have been implicated in the pathophysiology of PD psychosis.

3.3.1 Dopaminergic System

Dopamine is known to play a key role in PD psychosis. This was initially recognized when patients treated with levodopa developed or had exacerbations of psychosis, with clinical features that shared some similarity with other

dopamine-excess syndromes such as schizophrenia, and that the symptoms were reversed by dopamine receptor antagonists [197]. The original proposed hypothesis was the pharmacological 'kindling' after chronic levodopa treatment, where dopamine is no longer adequately stored at the presynaptic level and thus overflow and overstimulation of mesocorticolimbic postsynaptic dopamine D2 receptors in limbic areas and cerebral cortex, analogous to motor dyskinesia, leads to the production of psychosis [198–200]. This hypothesis coincided with the basis of dopamine supersensitivity leading to psychotic reactions in schizophrenia [201]. Yet, this increased dopamine D2 receptor function in schizophrenia has shown inconsistent results [202, 203]. No studies in PD patients with psychosis have, to date, linked 'hypersensitivity' of dopamine D2 receptors with psychosis.

Although classically, the dopamine D2 receptor is linked to psychosis in general, there are five different dopamine receptor subtypes, which are members of the large G-protein coupled receptor superfamily. In vitro, dopamine receptor subtypes are divided into two groups and constitute the two main pathways that have been studied in the basal ganglia, the dopamine D1-like receptors (D1 and D5) located on the so-called 'direct' striatopallidal pathway and the dopamine D2-like receptors (D2, D3, and D4) on the 'indirect' striatopallidal pathway. The classic model predicts a balance between these two pathways, direct (stimulatory) and indirect (inhibitory) networks, that facilitates the execution of movements, and imbalance leads to bradykinesia in PD, and dyskinesia following levodopa therapy [204]. Dopamine D1 and D2 receptors are expressed in high density, not only in the nigrostriatal, but also in the mesolimbic and mesocortical dopaminergic systems (i.e., nucleus accumbens, amygdala, hippocampus, and cerebral cortex), hypothalamus, thalamus, and cerebellum [205–207]. Thus, dopamine D2 antagonists influence not only mesolimbic/mesocortical circuits that likely play a role in psychosis, but also the nigrostriatal pathway, thus resulting in motor side effects, including parkinsonism.

Other dopamine receptors (D3, D4, and D5) have thus been investigated as possible targets for treating psychosis without affecting dopamine D2 motor circuits. The dopamine D3 receptor has a more limited pattern of distribution with the highest level of expression in the limbic areas, and thus is a potentially useful target. Several preclinical studies in animal models of PD have shown increased expression of dopamine D3 receptors in the ventral striatum following chronic levodopa therapy that correlates to the expression of levodopa-induced dyskinesia, suggesting there are increased D3 receptors in advanced PD [208]. Evidence has accumulated that D3 receptors exert minor modulatory influence on functions attributed to dopamine D2 receptors [209, 210], but the potential role of dopamine D3 receptor in PD psychosis is as yet unclear. A recent postmortem study using a D3-selective ligand, [^{3}H] WC-10, showed increased D3 receptors in striatal regions in five DLB/PDD patients compared with cognitively intact elderly controls, as well as in DLB/PDD patients with hallucinations compared with patients without [211]. To date, no clinically available dopamine D3 selective antagonists have been evaluated in PD psychosis [209]. Of interest, newer agents are in development; for example, cariprazine is a new dopamine D3 selective ligand that has been investigated in schizophrenia [212]. Dopamine D4 receptors have the lowest level of expression in the brain and are found in the hippocampus and frontal cerebral cortex [213]. Dopamine D4 antagonists have been previously investigated for schizophrenia but with no benefit [214].

One recent finding in dopamine receptor pharmacology is the discovery of so-called 'heterodimers' that seem to be linked to both the effects of nigrostriatal dopamine depletion and then chronic levodopa in PD, and result in altered distribution, and hence function, of dopamine D2 and D1-like receptors [215]. Thus, heterodimers have been described in animal models of advanced PD between dopamine D1/D3 receptors; D2/D4 receptors; glutamate NMDA/dopamine and adenosine A2A/dopamine receptors in the striatum. Altered function of these neurotransmitter systems may thus be involved in PD psychosis but further studies are needed.

The treatment of PD psychosis still relies on the use of dopamine D2 receptor antagonists that were originally developed to treat schizophrenia, and this is discussed in the section on management.

3.3.2 Serotonin (5-hydroxytryptamine; 5-HT)

The serotonin system has been implicated in PD psychosis. While an imbalance in serotonin and dopamine as the contribution to PD psychosis was first suggested in 1975 [216], it was not until the discovery of the activation of 5-HT2A receptors secondary to lysergic acid diethylamide (LSD) and LSD-like hallucinogens [217, 218] that more attention was given to serotonin as a possible element inducing psychosis. Of interest, the atypical antipsychotics, clozapine and quetiapine, at low doses, are also 5-HT2A/2C receptor antagonists as well as dopamine D2 antagonists, and this property has also been suggested as a mechanism underlying antipsychotic efficacy in schizophrenia without causing parkinsonism [219, 220] and in PD without worsening motor symptoms [221–223].

Advances in radioligands for 5-HT2A receptor binding enable a better understanding of its distribution and effect in human function. Ballanger et al. assessed in vivo

changes in 5-HT2A receptor binding using the selective 5-HT2A receptor ligand [18F]-setoperone PET among PD patients without dementia with VHs compared with the PD patients without VHs [224]. The PD patients with VHs demonstrated an increased 5-HT2A binding in the ventral visual pathway (i.e., bilateral inferooccipital gyrus, right fusiform gyrus, and inferotemporal cortex) and the bilateral dorsolateral prefrontal cortex, medial orbitofrontal cortex, and insula. Another postmortem tissue study showed an increased [3H]-ketanserin 5-HT2A binding in the inferolateral temporal cortex in PD patients who had VHs when compared with those who did not [225]. Both of these studies suggest alterations in pathways mediating visual and cognitive processing and a role for 5-HT2A receptors in PD hallucinations.

In PD, there is an extensive loss of serotonergic raphe neurons and a reduction of serotonergic projections to the frontal cortex, temporal cortex, and putamen [226–228]. The increase in 5-HT2A receptor function in PD may come from a 'hyperstimulation' after dopamine administration, in which dopamine is metabolized and released into the striatum by serotonergic terminals and acts as a 'false neurotransmitter' [229]; or compensatory postsynaptic serotonergic up-regulation from reduced dopamine [230, 231] or serotonin [232]. Further studies are needed to fully evaluate the role of 5-HT receptors in PD psychosis.

Nevertheless, the comparative lack of serotonergic activity of non-ergot DAs versus ergot DAs, but with similar propensity to induce VHs, shows that other neurotransmitter systems are clearly contributing to psychosis in PD.

3.3.3 Cholinergic System

The role of the central cholinergic system in PD psychosis is suggested from the following findings: (1) cholinergic-based cognitive impairment is correlated with psychotic symptoms, as mentioned previously; (2) a therapeutic benefit of the cholinesterase inhibitor rivastigmine in PD patients with dementia and DLB with VHs [233]; and (3) cessation of VHs after reducing anticholinergic drugs. The disruption of ascending cholinergic transmitter system leads to frontal cortical denervation and degeneration of central cholinergic structures, such as the nucleus basalis of Meynert and PPN, which are involved in attention, cognition, and RBD [234, 235]. Alterations in the cortical processing of visual perception, secondary to degeneration of cholinergic structures (i.e., PPN), may be related to VHs in PD patients [236], and has also been shown in VBM imaging by the volume reduction of PPN after 2.5 years of follow-up [237].

3.3.4 Glutamate Pathway

Glutamate antagonists amantadine or memantine are known to cause VHs in patients with PD. The etiology was previously proposed to reflect a loss of glutamatergic function causing dopaminergic overactivity that results in the occurrence of psychosis in PD [238]. Recent studies using a proton magnetic resonance spectroscopy (1H-MRS) that measures metabolites showed reduced glutamate levels in the dorsal caudate and putamen in the PD psychosis group compared with the PD without psychosis group [239]. However, the exact mechanism remains unclear.

Subtypes of glutamate receptors appear to have variable predilection to inducing psychosis. The initial attempts to pharmacologically oppose glutamate hyperactivity by antagonizing the ionotropic glutamate receptors (iGlu) produce debilitating side effects in humans; thus, focus has now turned to the modulatory role on glutamatergic transmission in metabotropic glutamate (mGlu) receptors in the basal ganglia [240]. Nevertheless, the therapeutic potential of mGlu receptor activation on the psychiatric part of PD has not been investigated so far.

3.4 Neuro-Signaling Pathways Involved in PD Psychosis

Several hypothetical frameworks for VHs have been proposed, including the intrusion of endogenous imagery produced during dreaming [118], a 'reality monitoring deficit' that leads to the inability to judge the source of a perception [241], the dysregulated gating of internal and external imagery [106], the impairment of interactions between attention and perception [104], and the dysfunction of attentional networks [242].

Two distinct hypotheses have been proposed with supportive evidence from functional connectivity analysis.

First, the disinhibition of the internally driven 'top-down' attentional cortical visual processing over the usual, externally driven, 'bottom-up' process was proposed in the study by Stebbins et al. [243]. The study showed a decreased cortical activation in the posterior region (i.e., middle temporal and occipital, parietal, and cingulate) that may represent possible reduced visual attention to external perceptions and an increased activation in the frontal region (i.e., superior and inferior frontal cortex and caudate nucleus) in PD patients with VHs. Through reduced retinal dopamine with decreased striatonigral input, a disruption of visual signal input may lead to impaired retinal striatal-cortical signals, which further induces an aberrant activation of visual areas and inability to distinguish relevant from irrelevant visual information.

On the other hand, the second hypothesis of impaired 'bottom-up' perceptional visual cortical processing was supported by the study from Meppelink et al. [244]. While the impaired 'bottom-up' processing was evident from reduced activation of the lateral occipital cortex and extrastriate temporal visual cortices for several seconds just before the image recognitions in PD with VHs, a compensatory 'top-down' cortical processing was not shown. Instead, an impaired 'top-down' processing via decreased activations of the frontal gyri was shown. Impairment of visual processing via reduced activation of the occipitotemporal cortex with additional impairment in the integration of sensory and mnemonic information image recognition and suppression of irrelevant stimuli via reduced activations of the frontoparietal cortex may all contribute VHs in PD patients.

By assembling comprehensive assessments of the clinical, demographic and ophthalmological correlates of VHs in PD, Gallagher et al. supported the hypothesized model of impaired visual processing, sleep–wake dysregulation and brainstem dysfunction, and cognitive, particularly frontal, impairment all independently contributing to the pathogenesis of VHs in PD, which were reinforced by pathological results of higher cortical Lewy body counts in areas implicated in visuoperception and executive function [245]. By using novel experimental priming tasks in which top-down verbal cues were used to prime the bottom-up recognition of partial or ambiguous pictures, a recent study challenged the previous hypothesis with the results demonstrating that VHs in PD have normal top-down activation as well as interactions between top-down and bottom-up processes [246].

4 Management

The initial step in managing PD psychosis is to determine the degree and severity of symptoms, and whether there is a need for intervention. Thus, in some PD patients, illusions and some VHs are non-bothersome and may not necessarily require treatment. In fact, some PD patients enjoy the experience and prefer not to be treated [247]. However, such individuals should be closely monitored for any changes as they are at risk and susceptible to worsening symptoms, especially if they experience any comorbidity or intercurrent medical issues.

The first step in treating PD psychosis is then to look for and treat any secondary causes, particularly infection or febrile illness, metabolic abnormality (e.g., dehydration, electrolyte imbalance), or structural lesion of the brain (e.g., subdural hematoma) that can trigger acute psychosis in PD patients.

The next step is to review drugs. Single or combination PD medications (dopaminergic and non-dopaminergic) and many non-PD medications, including those for general medical illness, may all trigger psychotic symptoms [248]. Thus, discontinuing any non-essential non-PD medications, including tricyclic antidepressants, bladder antispasmodics (e.g., oxybutynin), anticholinergics, benzodiazepines, muscle relaxants, and opioids, is recommended. Clarification of timing of recent initiation or change of medications and possible sequential symptoms, and discontinuation or reduction of medications may be necessary. The next step is to modify PD drugs, and a gradual removal of PD medications has been suggested in the following order: anticholinergics, monoamine oxidase B inhibitors (MAOB-Is), amantadine, DAs, COMT inhibitors, and lastly, levodopa [249]. It is important to always make sure that the motor function is maintained while stopping any PD medications and it may be necessary to substitute with equivalent levodopa dosage if needed. The important fact is that often PD psychosis (as discussed above) is not directly linked to dopamine drugs and some of the symptoms may not vanish even if the medication is stopped or reduced.

Thomsen et al. reported that, in evaluating a cohort of PD subjects with psychosis after adjustment of medications and managed systemic illnesses, 16 (62 %) of the 26 enrolled subjects had sufficient resolution of their psychotic symptoms in the short term to preclude them from the need to use antipsychotics [250]. These results reinforced the fact that in a majority of cases, psychotic symptoms may be solved with careful investigation of any underlying systemic illnesses and evaluation of any adjustable medications. If the simplification and reduction of the PD medications to the lowest tolerable dose without the exacerbation of motor symptoms does not improve psychosis, then addition of an antipsychotic agent should be considered.

In Table 5, we list some of the current drugs available to treat PD psychosis and the consideration of their usages, including dose titrations, side effects, and safety issues.

4.1 Antipsychotics or Dopamine D2 Receptor Antagonists

Specific pharmacological management of psychotic symptoms using antipsychotics in PD is challenging due to the potential of worsening of PD motor symptoms by blocking dopamine D2 receptors, and side effect profile. Thus, all typical and most atypical antipsychotics that have a high risk of aggravating parkinsonism should be avoided. The reported so-called atypical antipsychotics that are predisposed to worsening motor symptoms in PD include

Table 5 Drugs used to treat PD psychosis

Drug	(Starting dose; titration) and effective maintenance dose	Side effects	Safety issues
Clozapine	(6.25 mg/day; 6.25 mg every 4–7 days) 10–50 mg/day	Sedation; postural hypotension	Mandatory blood monitoring with ongoing treatment. Absolute neutrophil count must be $\geq$2000/mm^3 and white blood cell count $\geq$3500/mm^3 Baseline ECG for QTc interval prolongation
Quetiapine	(12.5 mg/d; 12.5 mg every 4–7 days) 12.5–150 mg/day	Sedation; postural hypotension	Acceptable risk without specialized monitoring. Baseline ECG for QTc interval prolongation
Pimavanserin	40 mg/day	Sedation; postural hypotension	Acceptable risk without specialized monitoring. Baseline ECG for QTc interval prolongation
Rivastigmine	1.50–6 mg orally twice daily or 4.6–9.5 mg transdermally daily	Nausea; vomiting; worsening PD tremor	Caution in history of seizure, COPD or asthma, and peptic ulcer; baseline ECG
Donepezil	5–10 mg/day	Nausea; vomiting; worsening PD tremor	Caution in history of sick-sinus syndrome, bradycardia or conduction abnormalities, syncopal episodes; Baseline ECG

COPD chronic obstructive pulmonary disease, *PD* Parkinson's disease

risperidone [251, 252], olanzapine (and with no improvement in VHs) [253, 254], ziprasidone [255–257], and aripiprazole [258, 259].

In addition, 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 risk of all-cause mortality and cerebrovascular events [260]. A positive dose–response effect is reported, that is, the risk of death increased with increasing daily dose and/or increasing duration of use [261]. One study reported a 1.53-fold increased risk of ventricular arrhythmia and/or sudden cardiac death with antipsychotic drug use [262]. In all cases, a baseline electrocardiography (ECG) should be performed to ensure normal QTc interval. Another potential risk in patients who are so-called neuroleptic-sensitive (i.e., advanced PD or DLB) is serious complications such as neuroleptic malignant syndrome; and increased mortality rates with prevalence up to 40 % have been reported when exposed to these medications [263]. In PD psychosis patients specifically, a recent post hoc study using clinical trial data from 490 PD subjects enrolled in the randomized controlled trials (RCTs) for pimavanserin (see Sect. 4.2) reported increased mortality (incidence rate ratio, [IRR] 4.20, 95 % CI 2.13–7.96) in those patients using antipsychotics compared with no antipsychotics [264]. Other common side effects, such as sedation and orthostasis, also need close monitoring.

Despite these issues, the counter argument for actively treating significant disabling symptoms with suitable antipsychotics is that in PD, psychotic symptoms are considered independent predictors of mortality during 12-year follow-up (HR 1.45) [265]. In addition, earlier detection of mild hallucinations and use of antipsychotics may reduce the risks of later deterioration [266].

4.1.1 Clozapine

Clozapine is a dibenzodiazepine with weak antagonism of striatal dopamine D2 receptors and prominent activity at dopamine D4 receptors and 5-HT2 receptors, especially at the low doses used in PD [267] (see Table 3). Double-blind, placebo-controlled and open-label trials have been conducted using clozapine in PD patient with psychosis, and currently it is the only antipsychotic medication that has consistently been found to be efficacious without motor worsening and carries acceptable safety risk with regular monitoring [268, 269]. In 2006, the AAN evidence-based guidelines stated that clozapine is the only antipsychotic with a recommendation level B that should be considered in PD patients with psychosis [4]. Similarly, a meta-analysis in 2007 [270] and an evidence-based medicine review from the MDS in 2011 [271] had similar conclusions. PD patients can experience therapeutic benefit at daily doses as low as 6.25 mg [269]; average effective daily dose is usually 25–50 mg/day; thus doses are significantly lower (10-fold lower) compared with doses of 300–900 mg per day used in schizophrenia. Other reasons for the lack of PD motoric worsening have also been suggested: the so-called 'fast-off dissociation' of clozapine from striatal dopamine D2 receptors compared with other antipsychotics [272], and preferential dopamine D2 receptor occupancy in the temporal cortex compared with the putamen and the

substantia nigra [273]. The rare, non-dose-related agranulocytosis (prevalence 0.38 % [274]) associated with clozapine use may be fatal, therefore, absolute neutrophil count must be monitored, and agranulocytosis is reversible with immediate discontinuation. An incidence of 8.3 % of transient neutropenia was reported in an 8-year follow-up of clozapine use, though all were resolved upon discontinuation [275]. Also, long-term use at these low doses do not seem to induce the metabolic syndrome that is commonly seen with the higher doses used in schizophrenia [276]. More common side effects include postural hypotension and sedation.

4.1.2 Quetiapine

Quetiapine is another dibenzothiazepine compound with similar structure to clozapine that has moderate affinity for the dopamine D2 and 5-HT2 receptors with a higher 5-HT2A relative to dopamine D2 receptor binding [277], and is the other antipsychotic medication that is commonly used for the treatment of PD psychosis. Quetiapine, however, has shown inconsistent efficacy in clinical trials [9, 278–280]. Despite this, quetiapine low dose (25–75 mg/day) is still widely used because it does not require regular blood test monitoring and has a low propensity to significantly worsen motor function in clinical trials. Therefore, quetiapine has been regarded as having Level C evidence [4] or having "insufficient evidence, acceptable safety risk without need for specialized monitoring, but investigational practice implications" [271]. In a randomized, open-label trial, the small amount of patients who showed mild exacerbation of parkinsonism with quetiapine were elderly PD patients with dementia who received a higher dose of quetiapine; hence, it was suggested to keep quetiapine no higher than 100 mg/day in PDD [281].

Two clinical trials have been conducted to compare clozapine and quetiapine in treatment of psychosis in PD patients. While, in one study, quetiapine and clozapine appear equally efficacious [281], the other study showed a greater efficacy of clozapine over quetiapine [282].

4.1.3 5-HT2A Receptor Ligands

As noted previously, the efficacy of atypical antipsychotics, clozapine and quetiapine, without worsening of PD motor symptoms, has been suggested to involve 5-HT2A receptor binding. More recent evidence, as discussed above, from imaging and post-mortem studies has also suggested a role for 5-HT2A receptors in PD psychosis. Thus, selective 5-HT2A antagonism is a potential target for PD psychosis without worsening of PD motor symptoms.

Table 6 Comparisons of the binding potential profiles of clozapine, quetiapine, and melperone to 5-HT2A and dopamine receptors (D2, D3, and D4) [284]

	D2	D3	D4	5-HT2A
Clozapine	++	++	+++	++++
Quetiapine	++/+	++/+	+	+
Melperone	++	++++	++	++

Relative binding affinity: + low, ++ moderate, +++ high, ++++ very high

Mianserin was the first non-selective 5-HT2 receptor antagonist that showed improvement in treating PD psychosis after 8 weeks in patients with PD ($n = 12$) without motor deterioration [268]. An unpublished result from a multi-centered, double-blind, placebo-controlled trial stated that melperone, another 5-HT2A antagonist, was ineffective for the treatment of PD psychosis as measured using SAPS ($n = 90$) [283]. No further information is available to determine reasons for the negative results. Table 6 compares the binding potential profiles of 5-HT2A and dopamine receptors (D2, D3, and D4) for clozapine, quetiapine, and another antipsychotic drug, melperone.

5-HT2A receptors are constitutively active even in the absence of a 5-HT agonist, and an inverse agonist is thus able to effectively inhibit such a receptor more effectively than an antagonist. Thus, 5-HT2A inverse agonists were proposed as a potential therapeutic drug for PD psychosis [285]. Pimavanserin is such a selective inverse 5-HT2A receptor agonist with low affinity for the 5-HT2C and negligible binding to dopaminergic, adrenergic, histaminergic, or muscarinic receptors, therefore, theoretically sparing the adverse effects of sedation and hypotension associated with atypical antipsychotics [286]. Overall, four RCTs have evaluated efficacy, but only two have been published. A phase II study in 46 patients reported good tolerability over 28 days with a small reduction in psychosis versus placebo using SAPS [287]. A phase III randomized, double-blind, placebo-controlled study in 185 PD subjects demonstrated a significant antipsychotic efficacy in terms of improvement in SAPS scores (37 vs 14 % in placebo) as well as caregiver burden, daytime somnolence, and sleep quality after 6 weeks of pimavanserin 40 mg daily [288]. There were no motor side effects. Pimavanserin can induce QTc interval prolongation, thus a baseline ECG is needed before use. Eleven percent of patients in the treatment group withdrew from the trial because of worsening psychotic symptoms.

Yasue et al. conducted a meta-analysis of the four RCTs (including the two unpublished studies) evaluating antipsychotic efficacy of pimavanserin versus placebo in PD, and showed less orthostatic hypotension and no

significant differences in incidence of all-cause discontinuation, adverse events, and death, and concluded that pimavanserin has benefit for treating PD psychosis with good tolerability [289]. Pimavanserin has recently received FDA approval.

In the schizophrenia field, other potential antipsychotic agents in development that have 5-HT2A receptor binding include asenapine, blonanserin, iloperidone, and lurasidone [290]. To date, no studies are ongoing using these agents in PD psychosis.

4.2 Anti-Dementia Drugs

As stated previously, VHs appear to predict a more rapid cognitive decline; therefore, it is logical to hypothesize the possibility of a greater therapeutic benefit from cholinesterase inhibitors on VHs in PD patients with dementia. However, to date there have been no double-blind, placebo-controlled trials to specifically evaluate reduction in VHs as the primary endpoint. Instead, there have been smaller studies, case series, or open-label trials evaluating cholinesterase inhibitors in the treatment of psychosis in PD patients [291–294], while other studies have reported VHs as secondary outcomes where the primary outcome is to measure changes in cognitive impairment [233, 295–297]. These studies have generally shown positive effects of cholinesterase inhibitors on cognitive impairment, with subtle effects only on VHs, but not delusions, and without significant negative impact on motor functions. Notably, the most common side effect, in 7–10 %, was worsening of tremor [298]. To date, rivastigmine has been more consistently efficacious in psychosis [233, 294, 295, 299] compared with donepezil [296, 297].

The other clinically available drug used to treat dementia is the NMDA antagonist, memantine. Although memantine has been shown in clinical trials to improve several behavioral complications (i.e., agitation and irritability) in patients with dementia, it has been reported to worsen psychotic symptoms in PD [300] and DLB [301]. Due to the glutamate antagonism, this is likely to exacerbate VHs, and as such is not recommended for PD patients with psychosis.

4.3 Anxiolytics and Antidepressants

Anxiety and depression are often present in subjects with PD psychosis. Thus, a suggestion has been that either selective serotonin reuptake inhibitors (SSRIs) or serotonin-norepinephrine reuptake inhibitors (SNRIs) may help both symptoms via enhancement of serotonergic activity. A case series of eight patients reported acute reversal of psychotic symptoms in response to a SSRI (citalopram) or SNRI (venlafaxine) either as monotherapy or as an adjunct in PD patients with comorbid depression or anxiety [302]. In case reports, other classes of antidepressants, including mirtazapine [303, 304] and clomipramine [305], reduced PD psychosis, suggesting a reduction in co-existent anxiety and depression could have an additional separate effect on reducing the symptoms of PD psychosis. On the other hand, there have been case reports of acute psychosis caused by fluoxetine [306] and mirtazapine [307] in PD patients. However, to date, no RCTs have been conducted to further evaluate the specific role of any antidepressant class in the treatment of PD psychosis.

4.4 Other Therapies

Yokukansan is a traditional Japanese medicine made up of medicinal herbs that has effects on serotonergic (5-HT1A, 5-HT2A receptor) function, and is approved for use in anxiety and insomnia in Japan [308]. Clinical studies have also shown beneficial effects of yokukansan on neuropsychiatric symptoms in dementia, with good tolerability [309]. A recent study in PD patients [310] also reported significant improvements in hallucinations, with some tendency to improvement in delusions; importantly, there was no significant change in motor functions and adverse effects included hypokalemia, listlessness, and drug allergy.

Additionally, a case report reported beneficial effects of gabapentin in a patient with advanced PD with episodic VHs of insects and worms over the trunk and genital areas and asynchronous pain sensation over the inguinal area [311]. The disappearance of VHs after the use of gabapentin without motor deterioration suggests the possible involvement of the glutamic acid neuron system and/or γ-amino butyric acid neuron system and an alternative option in advanced PD.

There have been several small case series evaluating the beneficial effects of electroconvulsive therapy on refractory PD psychotic symptoms [312–314] as well as no change, or even improvement in motor symptoms [315]. This recommendation warrants further investigations with a larger population of patients and long-term follow-up.

5 Conclusions

Psychotic symptoms are common in PD and are associated with poorer quality of life and increased caregiver burden, and can be a significant management challenge. Psychosis in PD is highly correlated with several factors, such as advanced disease stage, cognitive impairment, depression, and sleeping disorders. The pathogenesis of psychosis is complex and interrelated; advances in understanding have

come from neuroimaging technologies, neuropathology, and understanding neurotransmitter systems. The main areas responsible for psychosis have focused on pathways involving visual processing and executive function, including temporo-limbic structures and neocortical gray matter. Management of psychosis requires a step-wise process to initially remove trigger factors, modify risk factors if possible, and rationalize PD and other non-essential medications. Finally, specific drugs may be required that reduce psychosis without worsening PD motor symptoms. Pharmacological studies suggest serotonin and cholinergic neurotransmitter systems as likely the best non-dopaminergic targets. To date, the atypical antipsychotic clozapine, with a mixed pharmacology involving 5-HT2A and low striatal D2 binding, remains the most effective option for severe PD psychosis; while reducing VHs can be achieved with cholinesterase inhibitors. Newer agents targeting 5-HT, such as pimavanserin, are in development. However, prevention of psychosis is also a key to management, and recognition of 'at-risk' patients is critical.

Compliance with Ethical Standards

Conflicts of interest Dr Fox and Dr Chang both report no conflicts of interest relating to the content of this review.

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