Chapter 6
Psychosis in Parkinson's Disease

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Introduction

Psychosis is one of the most disabling non-motor symptoms of Parkinson's disease (PD). Non-motor symptoms are common, occur at higher prevalence than in age-matched controls, and have significant impact on quality of life [1]. In the present chapter, we will consider the psychopathology, the epidemiology, the pathophysiology, the risk factors, the prognosis, and the management of psychotic features in PD. Before doing so, we provide the historical background of psychosis in PD (PDPsy).

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Historical Background

In James Parkinson's original description of the disease he concluded, "…by the absence of any injury to the senses and to the intellect, we are taught that the morbid state does not extend to the encephalon" [2]. This view of PD as a process that spares the intellectual and psychological functioning was held for many decades.

Especially in the era before the discovery of levodopa treatment, reports regarding psychotic symptoms in PD were limited. Initial reports were regarding patients suffering from parkinsonism who developed psychotic symptoms. In 1882, Ball probably referred to the signs of rapid eye movement (REM) sleep behavior disorder in postencephalitic parkinsonism when describing a man with visual and auditory hallucinations occurring only at nighttime [3]. In 1906, Regis categorized the mental disorders associated with parkinsonism and specifically mentioned hallucinations as a symptom associated with advanced disease [4].

One of the first reports of psychotic symptoms in "paralysis agitans" was in 1923, when Jackson presented a case series of patients with prominent symptoms of psychosis [5]. Early features, such as sleep disturbance, withdrawal from social situations, and suspiciousness, were also mentioned. In this report, more dramatic symptoms such as paranoid delusions and hallucinations that were "generally limited to the organic sensations and tactile sense" were also discussed [5]. In 1949, Mjönes described two patients with tactile hallucinations, one of which also had visual and auditory hallucinations [6]. In 1950, Schwab described a number of psychiatric symptoms including "paranoia" and "schizoid reactions" [7].

Thus, it appears that psychotic features may be an inherent though rare part of the disease itself [8]. However, a number of these cases reported might have had secondary forms of parkinsonism, especially postencephalitic [9].

In the levodopa treatment era, it became apparent that various psychiatric syndromes were occurring with a much higher frequency in treated patients than in untreated patients [9]. Even in the first reports, it was highlighted that apart from higher levodopa dose, psychotic symptoms were much more likely to occur in patients with certain predisposing characteristics, including older age, cognitive impairment, and premorbid psychiatric pathology [10–12]. Newer reports added in these other predisposing factors such as depression, sleep disorders, and visual impairment [13–16]. However, risk factors are discussed in more detail in a separate section.

Signs and Symptoms

The basic psychopathological terms and their correspondent definitions that will be used in this chapter are summarized in Table 6.1

Psychotic symptoms have long been recognized as a feature of PD as well as a complication of PD therapies. PDPsy can occur in non-demented subjects but is also a common feature in patients with PD dementia (PDD) and in patients with

Table 6.1 Summary of the basic psychopathological terms and their correspondent definitions [17, 18]

Term	Definition
Illusions	Misinterpretations of real perception stimuli
Hallucinations	Spontaneous aberrant perceptions without a physical stimulus
Elementary auditory hallucinations	Unstructured sounds, for example, rattles or whistling
Elementary visual hallucinations	Crudely formed flashes of light or color
Complex visual hallucinations	Range from more organized patterns and shapes to full visual perceptions of people and scenes
Passage hallucination	The sensation of a person or animal passing in the periphery of someone's visual field
Sense of presence	The vivid feeling that somebody is present nearby when nobody is actually there

Table 6.2 Characteristics of psychosis in Parkinson's disease [24, 25, 28]

Psychotic feature in PD	Clinical profile in PD	Prevalence
Psychosis	Encompasses hallucinations, delusions, and the "minor" phenomena of illusions, "passage hallucinations," and "sense of presence"	26–60 % [24, 25]
Visual hallucinations	Abnormal visual perceptions without a physical stimulus. Typically stereotyped, and colorful images of familiar people or animals. Associated with older age, duration of PD, cognitive impairment, depression, and sleep disturbances [25, 26]. May be more likely to occur during times of low ambient stimulation and share some characteristics of hallucinations in the visually impaired [27]	13–50 % [24, 28]
Delusions	False, fixed, idiosyncratic beliefs that are maintained despite evidence to the contrary. Often paranoid delusions pertaining to spousal infidelity or fear of abandonment. Distinct from clinical profile of schizophrenia as delusions of thought insertion or broadcasting and delusions of grandeur or of external control and religiosity, which are hallmarks of schizophrenia, are rarely seen in PD psychosis [29]	3–7 % [24, 25]

dementia with Lewy bodies (DLB). PDPsy is known to reduce quality of life and increases caregiver distress [19]. It is an independent risk factor for poor prognosis, nursing home placement, and development of dementia [20, 21], and it is also associated with increased risk of mortality [20, 22, 23]. The characteristics of PDPsy are summarized in Table 6.2.

The prevalence and severity of hallucinations, the commonest manifestation of PDPsy, increase over time [30]. Higher levels of thought disorder and hallucinations are positively associated with disease severity and impairment. Features of PDPsy are more common in late-stage disease but can occur throughout the disease course [31, 32]. Early hallucinations occurring before or shortly after starting a dopaminergic treatment in a patient with a recent diagnosis of PD may be part of the DLB syndrome [33]. However, the cutoff between both conditions, although theoretically well defined, may be more difficult to establish in clinical practice, and the phenomenology of visual hallucinations linked to PD and DLB is similar [34].

Mental disturbances in PD range from comparatively subtle symptoms such as non-disturbing visual hallucinations, vivid dreams, and mild illusions to a psychotic state with disturbing hallucinations and paranoid frightening psychotic delusions [35]. The classic hallucinations in long-term treated PD are usually chronic and repetitive in their content.

Diagnostic Criteria

Diagnostic criteria for psychosis in PD have been proposed by a NINDS/NIMH working group [36]. These require the presence of at least one of illusions, false sense of presence, hallucinations, or delusions, a primary diagnosis based on UK brain bank criteria for PD; symptoms occurring after the onset of PD, symptoms that are recurrent or continuous for at least 1 month, and the psychotic symptoms are not better accounted for by another cause of parkinsonism such as DLB. Furthermore, Duvoisin's classical description perfectly illustrates the panoply of psychotic phenomena in PD patients [37]: "…Visual illusions are especially frequent. Familiar objects may be mistaking for something else. The patient may mention seeing worms on the floor, whereas actually there is a design in the flooring, which is misinterpreted because the pattern seems to move. Spectral illusions generally of a benign if not pleasant character are experienced. There may be hallucinations of people or animals roaming around the house … Complex scenes with a group of people wandering around, having a party … seem to go about their business without disturbing the patient. Patients may experience these visions for long periods of time but are afraid to mention them to anyone for fear of being thought 'crazy'. Finally, however the patient reacts, angrily ordering the strangers out of the house, accusing them of stealing…" [37].

Visual Illusions and Hallucinations

Establishing the time of the first true visual hallucinations may be difficult as they may begin insidiously, out of seemingly normal heightened perceptions, misperceptions (illusions), and very fleeting impressions with preserved insight that cause no

concern to the patients. Even after patients recognize the hallucinations as a false perception, many remain hesitant to admit them to family members [38]. The awareness of the presence of another person ("sensation de presence" or "Anwesenheit") and the sensation of movement in the peripheral visual field ("sensation de passage") were first described in PD in 1982 [39]. Fénelon et al. systematically investigated them as presumably prehallucinatory symptoms [18]. Isolated occurrence was noted in 14 % and combined occurrence with formed hallucinations in another 9 % of the patients. PD patients also frequently misinterpret nonliving objects, especially moving ones as living beings.

These illusions may be facilitated by dim light and/or reduced vigilance and attentiveness during drowsiness. Their frequency has been rarely investigated separately, because in systematic interviews it is often difficult for the PD patient to differentiate illusions from visual hallucinations [40, 41]. Most studies therefore combine illusions with visual hallucinations as a single phenomenon.

The content and contextual framework of the prototypic or core hallucinatory syndrome has been investigated by different research groups, and similar descriptive core features have been reported [29, 41, 42]. Patients with hallucinations typically report visual hallucinations that represent human beings, animals, or both, often mobile, appearing in scenes of short duration, lasting often only seconds. They are usually moving, doing otherwise appropriate activities without disturbing the patient. By their repetitive and stereotyped character, the visual hallucination figures become familiar to the patient, who, as a bystander, observes them with amused interest (the "marketplace effect") [43]. The patients never involve themselves in the activities of the hallucinations. Favored by dim light or reduced vigilance, visual hallucinations appear suddenly, without any known trigger or voluntary effort. They also vanish suddenly, sometimes when the patient tries to check their reality by approaching or touching them. It is notable that simple visual hallucinations, consisting in elementary geometrical patterns, are uncommon in PD [34]. Visual hallucinations are not regularly bound to the same motoric state ("on" or "off") and have no direct temporal relation to antiparkinsonian medication ingestion. Often a given visual hallucination occurs when the PD patient is in a specific environmental setting. Real objects may contribute to the scene by being mistaken in an illusionary way. Visual hallucinations often have blurred borders but have neither color predominance nor a specific localization to a field of vision (lateral vs. central) [43].

Affectively, patients usually express little concern about the visual hallucinations, although in two studies some patients found themselves anxious or depressed when a few felt terrified [18, 44]. Full-blown psychotic decompensation with secondary frightening paranoid delusion, without any insight, was a rare phenomenon in these studies [43]. Comparative prevalence and phenomenology at day- or nighttime have not been extensively studied, although one report found that diurnal visual hallucinations were more common than nocturnal visual hallucinations, with 46 % of patients indicating only diurnal visual hallucinations, 13 % only nocturnal visual hallucinations, and 41 % both types [41]. Another study with continuous polysomnographic recording found that in 20 hallucinating patients, 14 patients experienced

visual hallucinations during daytime, 8 during a "wakeful state," 5 during a twilight state, and 1 on awaking from napping in the afternoon. In contrast, four patients developed visual hallucinations upon awakening at night [45].

Hallucinations in Other Sensory Modalities

Auditory hallucinations may be elementary (ringing, knocks, etc.) or, more often, complex. The voice content is neutral or incomprehensible, but it can also be threatening [46, 47] and nonetheless differs from the pejorative or threatening auditory hallucinations of schizophrenia [18, 46]. Auditory hallucinations may constitute the "soundtrack" of visual hallucinations, with the patient hearing the conversation of unreal persons. Auditory hallucinations variably occur together with visual hallucinations and are less likely to be seen in isolation [46, 48]. Tactile hallucinations [49] involve contact with small animals, although they do not usually generate the belief of infestation. They may also manifest as the feeling of being touched by someone. Olfactory and gustatory hallucinations have only been reported in series and case reports [42]. Both olfactory and tactile hallucinations can be experienced as very unpleasant and long-lasting [49–51].

Multimodal Hallucinations

Patients experiencing visual hallucinations may also experience nonvisual hallucinations, although they often do not report them. When focusing on new-onset hallucinations, it has been shown that elderly patients were more likely to have multimodal hallucinations than pure visual hallucinations, suggesting that age and ageing processes may influence the phenomenology of hallucinations [52]. Nonvisual hallucinations are mostly accompanied by visual hallucinations [53]. Most patients have retained insight of their hallucinations although when severe and in the context of cognitive impairment insight may fluctuate or be lost [18, 42].

Delusions

Delusions are false beliefs that are maintained despite evidence of the contrary. Delusions affect about 8 % of treated patients with PD [54, 55]. They are usually paranoid in nature and commonly involve suspicions of spousal infidelity. Other paranoid themes include people stealing money, intruders living in the house, or nurses planning harmful plots. In contrast to this, thought broadcasting, ideas of reference, loosened associations, and "negative symptoms," which are all commonly found in schizophrenics, are not a feature of PD-associated psychosis [55].

Paranoid thoughts such as spousal infidelity are a common theme, although grandiose, somatic, persecutory, and religious delusions have also been documented [56]. Recent research suggests that the occurrence of delusions, as opposed to hallucinations, may be related to younger age at onset of PD and psychotic symptoms [57].

Delirium

Delirium with concomitant hallucinations can be found in PD patients, especially with advanced age [55]. When being part of a toxic delirium, hallucinations occur in the context of a clouded sensorium. Sometimes it starts as nocturnal confusion or "sundowning," which when left untreated can also affect the patient's behavior during the day. An associated problem is that the sleep cycle is often inverted [55].

In this syndrome, patients usually show signs of distractibility, agitation, myoclonus, paratonia. It may occur with systemic disease, in the context of fever, infection, or renal failure, and with medications including anticholinergic treatment or amantadine [58]. In the perioperative state, especially when PD patients receive pain medications, there is also a significantly increased risk of a confusional state with hallucinations [59]. In cases of anticholinergic toxic effects, visual hallucinations are accompanied by dry skin, urinary retention, and mydriasis [60]. In general, the hallucinations clear when the underlying medical condition is treated.

Epidemiology

Establishing the prevalence of neuropsychiatric disorders in PD is complicated by the symptomatic overlap between the somatic features of the neuropsychiatric and underlying movement disorder, differences in the phenomenology of these disorders in PD and the general population, frequently coexisting cognitive problems, psychiatric side effects of dopaminergic medication, the presence of motor and non-motor fluctuations, and the different diagnostic frameworks available. Thus, estimates of prevalence of neuropsychiatric disorders in PD vary considerably in published studies [61].

With regard to reports about hallucinations and psychosis in PD, one of the limitations of the published studies is their difference in study design, data collection, and study population. In addition, most studies utilized non-validated scales or arbitrary definitions of symptoms [35, 62, 63]. Furthermore, PD patients may not report visual hallucinations when completing self-report screening questionnaires.

For example, in a community-based sample, there was a 25 % lifetime prevalence [64] of psychotic phenomena compared with nearly 50 % in some clinic-based samples [18, 65]. Some studies have focused only on hallucinations and did not assess illusions or delusions [46, 66]. In spite of the limitations presented, several studies have reported a cross-sectional prevalence of psychosis in the range of 25–30 % [68, 69, 71–75]. The estimated prevalence of formed visual hallucinations has been recorded as 22–38 %, of minor psychotic symptoms (illusions of presence, passage, and visual illusions) as 17–72 %, of auditory hallucinations as 0–22 %, and of delusions as 1–7 %. Tactile, somatic, and olfactory hallucinations are relatively rare and usually not systematically sought. Lifetime prevalence of reported visual hallucinations was 50 % in a large retrospective autopsy study in pathologically proven PD (445 patients) [61]. Longitudinal studies have reported that the proportion of hallucinating PD patients increases with disease duration. In a 4-year prospective

longitudinal study, 33 % of the patients had visual hallucinations at baseline, 44 % at 18 months, and 63 % at 48 months [66]. Having hallucinations at baseline or at any given assessment was a strong predictor of continued hallucinations at all follow-up evaluations, demonstrating the chronicity of the hallucinatory syndrome. The evolution of the so-called "benign" hallucinations, defined as hallucinations with retained insight, has also been investigated. Unlike the name suggested, after 3 years, 81 % of the patients had hallucinations with loss of insight, if no specific treatment was initiated [65].

Pathophysiology

There has been considerable interest in identifying risk factors for developing psychotic symptoms in Parkinson's disease. Not all patients will develop them, and it appears that a variety of factors, both intrinsic and extrinsic, contribute to their occurrence [56]. In this section, we are reviewing the role of neurotransmitters that research has identified as facilitating the emergence of psychotic symptoms in PD.

Role of Dopamine

As early as in 1978, Moskowitz postulated a pharmacological kindling model to suggest enhanced sensitivity of dopaminergic receptors after chronic treatment with levodopa. Thus, excess dopamine from medications could overflow onto supersensitive receptors, inducing psychotic signs [77]. Since then extensive research has taken place in order to examine the relationship between dopamine and altered perceptions [78].

It is well recognized that dopaminergic agonists (such as amphetamines) can induce psychotic states [79] and that dopamine D2 receptor antagonists (such as haloperidol) are effective antipsychotics [78]. All PD medications (not just levodopa) have been implicated in the appearance of psychotic features, and these features often remit after drug therapy has been reduced or eliminated [80].

Excessive dopaminergic activity, probably in mesocortical and mesolimbic systems, appears to play a role in the generation of hallucinations. This action may be mediated by dopamine's influence on glutamatergic systems [81]. There are experimental suggestions that chronic stimulation may cause persistent sensitization of dopamine receptors, leading to dysfunction of limbic structures responsible for assigning emotional and hedonic significance to sensory input. This dysfunction may result in misattributions of internal stimuli having originated from the external sensory world [82] causing thus psychotic phenomena [83, 84].

However, several observations have challenged the hypothesis that psychotic symptoms represent a medication-induced toxic syndrome [43]. Not only there are reports of hallucinations in PD patients before dopaminergic drugs became

available [85], but also studies of hallucinating PD patients have demonstrated that psychosis severity and medication doses are poorly correlated [42]. Moreover, Goetz showed that in predisposed patients, high-dose intravenous levodopa does not provoke visual hallucinations in a predefined clinical setting [86].

Role of Serotonin

Serotonin (5-HT) is another monoamine neurotransmitter, and it is also thought to play a role in producing psychotic symptoms. The body of evidence for serotonin's involvement parallels that for dopamine. Therefore, agonists at the 5-HT2 receptor can induce hallucinations, and 5-HT receptors antagonists (like novel antipsychotics) can ameliorate psychosis [87]. The efficacy of atypical antipsychotic, such as clozapine and quetiapine, without worsening motor function, has been partly attributed to their affinity to 5-HT receptors. However, the exact relationship between serotonergic systems and PD-related psychosis remains unclear [78].

Role of Acetylcholine

Although the role of acetylcholine is still under investigation, neuropathological studies of patients with DLB indicate that levels of choline acetyltransferase were lower and the ratio of 5-hydroxyindoleacetic acid to choline acetyltransferase was higher in hallucinating patients than in patients without hallucinations [88]. Moreover, marked degeneration of cholinergic neurons is evident in the brains of PD patients which is possibly even greater compared to what is seen in patients with Alzheimer's dementia [89, 90].

The possible role of acetylcholine in psychotic features is also supported by research that showed that after effectively treating hallucinations by reducing anticholinergic and/or dopaminergic agents, acetylcholine blockade may induce PD-related hallucinations. It was hypothesized that the responsible mechanism involves acetylcholine's reciprocal relationship with dopamine in limbic cortex [80]. Finally, another hypothesis is that as PD causes degeneration of cholinergic pedunculopontine neurons, which control rapid eye movement (REM) sleep, hallucinations may be fragments of dreams that are released from the usual cholinergic inhibition [88]. However, sleep dysregulation is discussed separately below.

Risk Factors

Apart from the role of dopaminergic treatment as a risk factor for developing psychotic features in PD, which has been reviewed above, other risk factors may contribute to the development of psychotic features in PD as discussed in this section.

Age and Disease Duration

Older age has been shown to be a risk factor of developing psychosis in PD [67], and psychotic symptoms in PD typically occur later in the course of the disease. On average, symptoms are reported 10 or more years after the initial diagnosis [91]. Moreover, psychotic symptoms tend to recur and worsen over time [92] as disease progresses and have been correlated to PD severity [61].

Cognitive Impairment

Dementia is an important risk factor for psychosis in PD, and severity of dementia and severity of psychosis are correlated [76, 93]. Psychosis may be an early indicator of beginning cognitive decline. Recently, it was suggested that the hippocampus is a neural substrate underlying the occurrence of psychosis, sleep disturbance, and cognitive impairment in PD patients [93]. However, if psychosis occurs in the early stages of PD, it is particularly important to consider other diagnoses, specifically dementia with Lewy bodies (DLB). In one study, all patients identified as having early-onset (within 3 months of initiating levodopa therapy) hallucinations were later found to carry a diagnosis other than or in addition to Parkinson's disease that could account for their psychotic symptoms [31].

Lewy Body Distribution

Lewy body deposition has long been known to be associated with dementia in Parkinson's disease, which has been identified as risk factor for PD psychosis. One study found a strong correlation between the distribution of Lewy bodies in the temporal lobe, specifically in the amygdale and parahippocampus, and well-formed visual hallucinations in Lewy body diseases such as DLB and Parkinson's disease dementia [94]. These temporal lobe Lewy bodies were also associated with an earlier onset of hallucinations. A large-scale autopsy study of 788 cases of parkinsonism showed a high specificity of visual hallucinations for Lewy body diseases (92.9 %) [95]. A recent clinicopathological comparison of 10 PD patients with a history of visual hallucinations and 10 PD controls revealed a significantly greater Lewy body burden in the amygdala and cortical areas in the hallucinating patients [96].

Sleep Disorders

Psychosis in PD has also been linked to sleep disturbances such as insomnia [97] and daytime sleepiness [98], which are common in PD. The "continuum hypothesis" of psychosis in PD asserts that sleep disturbances in PD lead to altered dream

phenomena, which later lead to frank daytime hallucinations and delusions. Indeed, these early phenomena occur frequently in PD. A study found that 48 % of PD patients experienced some sort of altered dream phenomena such as vivid dreams, nightmares, and reports suggestive of REM disorder or night terrors [99]. 30.7 % of patients in an early retrospective study were reported to experience vivid dreams [77]. One study designed to test the continuum hypothesis found that sleep fragmentation, altered dream phenomena, and hallucinations/illusions were not independent; however, no interaction was found between sleep fragmentation and hallucinations/illusions, which the authors explained by suggesting that the three phenomena are distinct but often overlapping [99].

A prominent view of the relationship between sleep disturbances and PD psychosis involves a disruption in rapid eye movement (REM) sleep. Polysomnographic studies of Parkinson's patients have found a relationship between visual hallucinations and short, fragmented REM sleep. Specifically, patients experiencing hallucinations evidenced lower sleep efficiency and reduced total REM sleep time and percentage, as compared to patients not experiencing hallucinations [100]. Visual hallucinations in PD have been purported by some to represent narcolepsy-like phenomena involving the intrusion of REM dream imagery into the waking state [101]. This intrusion may be related to a reduction in acetylcholine, which leads to the disinhibition of the dream images and their release into the waking state [88].

Visual Processing Deficits

Research has suggested that PD patients who experience visual hallucinations may also suffer from deficits in visual processing. These patients have been found to have lower visual acuity [42], deficits in color and contrast recognition [102], and greater ocular pathology [18], including cataracts, retinal disease, and glaucoma, as compared to non-hallucinating PD patients. Dopamine deficiency at the level of the retina is also found in PD [103] and has been linked to the occurrence of visual hallucinations in both dementia with DLB [104] and PD [105]. These deficits may serve to facilitate the onset of visual hallucinations in PD.

While structural MRI studies of hallucinating PD patients have yielded little insight into specific occipital lobe or deep white matter lesions [106], more recent studies have used fMRI to identify functional abnormalities in the processing of visual stimuli among hallucinating patients. Specifically, Stebbins et al. found that hallucinating PD patients indexed more frontal (Brodmann areas 44, 6) and subcortical (caudate nucleus) activation and less visual cortical activation than non-hallucinating PD patients [107]. The authors postulated that PD patients with hallucinations suffer from a weakening of retinal–striatal–cortical signals, which may lead to the disinhibition of "top-down" processing and the subsequent release of internally generated images into areas that normally represent externally generated percepts. Another fMRI study documented a similar pattern of increased activation of visual association cortex (Brodmann area 19) coupled with decreased activation of

primary visual cortex (Brodmann area 17) in PD patients experiencing visual hallucinations [108]. Barnes et al. report deficient reality monitoring in PD patients with hallucinations in that these patients were more likely than non-hallucinating PD patients and elderly controls to believe that mental images were real external stimuli [109]. Currently, studies are underway to determine the effects of pharmacological treatments for hallucinations on functional visual networks. Gallagher et al. report that higher overall cortical Lewy body counts, particularly in areas implicated in visual perception and executive function, such as the middle frontal and middle temporal gyri, transentorhinal, and anterior cingulate cortices, were associated with visual hallucinations [110]. These data were in support of a unifying hypothesis proposed by Goetz that included impaired visual input and central visual processing, impaired brain stem regulation of sleep–wake cycle with fluctuating vigilance, intrusion of rapid eye movement dream imagery into wakefulness and emergence of internally generated imagery, cognitive dysfunction, and influence of pharmacological treatments [43].

Genetics

Recent research has increasingly attended to genetic contributions to Parkinson's disease and its associated neuropsychiatric symptoms. Family history of dementia appears to be a significant risk factor for the development of hallucinations in patients with PD [70]. Furthermore, preliminary evidence suggests that certain genetic profiles may be associated with the development of psychosis in PD. For example, studies have identified the APOE epsilon4 allele as a significant risk factor for drug-induced visual hallucinations in PD [111] and an earlier appearance of psychosis in PD [112]. However, other studies have failed to document an association between APOE4 and PD psychosis [113, 114]. More recently, a postmortem analysis reported an association between PD-related hallucinations and the tau H1H1 genotype [115]. Further research is necessary to elucidate the role of genetics in the expression of psychotic symptoms in PD.

Deep Brain Stimulation (DBS) Surgery

Many researchers have noted that DBS surgery may improve psychotic symptoms in Parkinson's disease, which is presumed to be due to the resultant reduction in dopaminergic medications [116]. However, there have also been reports of stimulation-induced psychotic symptoms as well as transient manic psychosis following DBS surgery, which may be more common in older patients [117–119].

Others

Other risk factors reported for Parkinson's disease psychosis include family history of depression, severe olfactory impairment [120], and autonomic dysfunction [121]. A recent study suggested that PD patients who show a blunted circadian blood pressure rhythm are more likely to develop psychosis than those whose BP decreases normally at night [23]. A recent case crossover study reported that elevation of plasma CRP is also another independent risk factor for psychosis in PD [122]. Finally, it is always important to consider that hallucinations can occur in the context of other conditions, e.g., confusion due to systemic infection or mood congruent hallucinations in the context of severe depression.

Prognosis

Course

Psychotic symptoms in PD typically occur later in the disease. On average, symptoms are reported 10 or more years after the initial diagnosis [91, 92]. In its early stages, psychosis in PD occurs within a context of a clear sensorium and retained insight [123]. Psychotic symptoms tend to recur and worsen over time, and insight may be lost [92]. Psychosis in PD has often been conceptualized as occurring along a continuum in that experiences such as vivid dreaming and illusions herald more frank hallucinations and delusions, which ultimately lead to florid psychosis and dementia [77]. However, recent evidence suggests that this conceptualization may not be accurate [99]. While the specific course of PD psychosis remains to be adequately described, it seems clear that psychotic symptoms, once present, are persistent and distressing.

Thus, the existence of hallucinations at baseline is also a strong predictor of their presence at follow-up evaluations [64]. Some studies documented no differences in hallucinations between patients who received treatment compared to those who did not, and many treated patients were still experiencing hallucinations at long-term follow-up [21, 64]. Other reports suggest that many patients receiving antipsychotic treatment experience continued efficacy, especially those who responded to their medication early on [124]. However, there is little data to suggest that antipsychotic treatment improves long-term functional outcome.

Once patients initiate antipsychotic therapy, continued treatment may be necessary to maintain symptom control and avoid exacerbation of psychosis. One study that attempted to wean psychosis-free PD patients off of their antipsychotic medications

was aborted after enrolling only six patients (with an average antipsychotic exposure of 20 months) because five out of the six subjects experienced "rebound psychosis" [125]. Furthermore, three out of these five patients experienced a worsening of psychotic episodes (compared to their original psychotic episode that prompted antipsychotic use) in the form of paranoid delusions or threatening auditory hallucinations. This experience, which is also congruent with anecdotal evidence and the authors' experiences, also provides support for the efficacy of antipsychotic medications at least in some patients. Additional research is needed to confirm the efficacy and necessary treatment duration with antipsychotic treatment.

Prognostic Indicators

The prognostic value of psychosis and hallucinations in PD varies depending upon when symptoms are seen during the disease course. If symptoms are evident at time of diagnosis or very early on in the disease, then a preexisting psychiatric disorder or another parkinsonian syndrome such as DLB is likely to be present, and additional symptoms of such disorders may manifest [31].

When psychotic features arise later in the disease course, they may suggest additional complications such as cognitive impairment [126] and weight loss [127] or may be a manifestation of concomitant depression with mood congruent hallucinations. They are also associated with negative outcome variables such as caregiver distress [19], nursing home placement [20], and mortality [128]. Kempster and colleagues surveyed 129 case records from donors with pathologically proven PD. These cases were separated into five groups according to age at death, thus comparing patients who reached the advanced stage of the disease at different ages. Four milestones of advanced disease (frequent falls, visual hallucinations, dementia, and need for residential care) occurred at a similar time, approximately 5 years from death in each group. There were no significant differences in disease duration across these age groupings, nor were there differences in the severity and distribution of Lewy body and other pathologies. Once this advanced disease stage was reached, survival was similar in all groups [129].

Psychotic symptomatology has been considered by some to represent a "harbinger to cognitive decline" [13] as PD patients who present with visual hallucinations are more likely to develop cognitive impairments later on [21, 56, 126]. Psychosis and cognitive decline often co-occur, and both have been related to the development of the other.

A case control study identified hallucinations as the primary factor differentiating PD patients who were placed in a nursing home from those who were not, whereas motor and cognitive impairment did not differ between the groups [128]. In a 2-year follow-up study, the authors found that 100 % of nursing home PD patients had died [130]. Recent reports have documented more conservative nursing home mortality rates, which have been attributed in part to the increasingly common use of atypical antipsychotic agents for the treatment of psychosis [21, 124]. However, the finding

that hallucinations and other psychotic phenomena are predictive of negative outcome has been well replicated and underscores the importance of both treating PD psychosis as well as its utility as a prognostic indicator. When psychosis and dementia coexist in PD, it is perhaps the greatest limiting factor for the optimal treatment of motor symptoms.

Management

The management of psychosis is dependent upon an understanding of the pathophysiology, which is due to a complex mixture of intrinsic and extrinsic factors. Intrinsic factors (such as the neurochemical changes in dopaminergic, serotonergic, and cholinergic systems) increase the likelihood of misinterpretation of visual images and the development of delusions [131]. In the presence of extrinsic factors (such as PD medications), the development of psychosis also becomes more likely [131].

1st Step: Identify and Treat Other Potential Conditions

Before treating psychosis in PD, it is important to rule out underlying medical illnesses as the cause of the symptoms in the context of delirium. For example, urinary and pulmonary infections, metabolic and endocrine imbalances, cerebral hypoperfusion states, and psychosocial stressors can lead to delirium and psychotic symptoms, especially in geriatric patients [78]. In addition, severe depression may lead to mood-congruent, distressing hallucinations, which can improve with antidepressant treatment alone.

2nd Step: Optimize the Environment

Similarly to the management of delirium, a team of healthcare professionals who are familiar to the patient suffering from PD psychosis should be involved. It is important to avoid moving people within and between wards or rooms unless absolutely necessary [132]. Optimizing the environment will reduce the likelihood of visual misinterpretations. Environmental interventions are designed to reduce or eliminate factors that exacerbate delirium. They include providing an optimal level of environmental stimulation (such as optimal lighting), reducing sensory impairments (such as loud noises), and providing environmental cues that facilitate orientation (such as a clock on the wall).

Contrary to schizophrenic patients, PD patients frequently use self-driven coping strategies for dealing with their psychotic symptoms such as visual techniques

(including better focusing on the hallucinatory object, focusing at another object, or looking away from the hallucination), cognitive techniques (related to the patient's self-initiated reactions that do not involve other people, consciously noting that the hallucinations are not real or purposefully reassuring oneself that they will resolve shortly), and interactive techniques, relying on discussions with family and other caregivers to gain comfort and reassurance as well as verification of the non-reality of the hallucinations [44]. Therefore, cognitive training in such techniques may improve the psychotic symptoms.

3rd Step: Changing PD Treatment

PD medications contribute to psychosis through effects on both the dopaminergic and cholinergic systems with the latter exacerbating an existing cholinergic dysfunction. Stopping all potentially offending antiparkinsonian drugs is usually not an option for most patients, although dose reduction can frequently be accomplished with amelioration of hallucinations and little loss of drug-related benefit. Antiparkinsonian drugs can be reduced or stopped in reverse order starting from the last medication introduced before occurrence of hallucinations and continuing based on the potential of the drug to cause hallucinations. A stepwise approach to the consideration of withdrawal of medication is recommended [131]. Anticholinergics and tricyclics (which have anticholinergic properties) should be withdrawn first [133], followed by careful reduction or gradual withdrawal of other monoamine oxidase-B inhibitors, amantadine, and dopamine agonists. In severe cases, the basis of management is maintaining the patient on the minimum amount of antiparkinsonian medication focusing on levodopa as the main treatment [131]. Figure 6.1 summarizes the suggested order for withdrawal of medications in psychosis in PD.

4th Step: Specific Management

Clozapine is a dibenzodiazepine that binds to D1 mesolimbic receptors with relative sparing of striatal dopamine receptors. It has prominent activity at D4 dopamine receptors and is an antagonist at adrenergic, cholinergic, histaminergic, and serotonergic receptors. Clozapine has been shown to be effective for psychosis in PD [134]. However, it can cause granulocytopenia in 1–2 % of patients, and weekly to biweekly blood counts are required on treatment. The risk of clozapine-induced leukopenia or agranulocytosis decreases exponentially over time, and the likelihood of developing fatal granulocytopenia beyond 6 months of clozapine treatment is low [135]. It is important to start at a low dose, either 6.25 or 12.5 mg once a day. Most patients will only require 25 mg and do not require doses beyond 50 mg. There are concerns about possible anticholinergic side effects in larger doses,

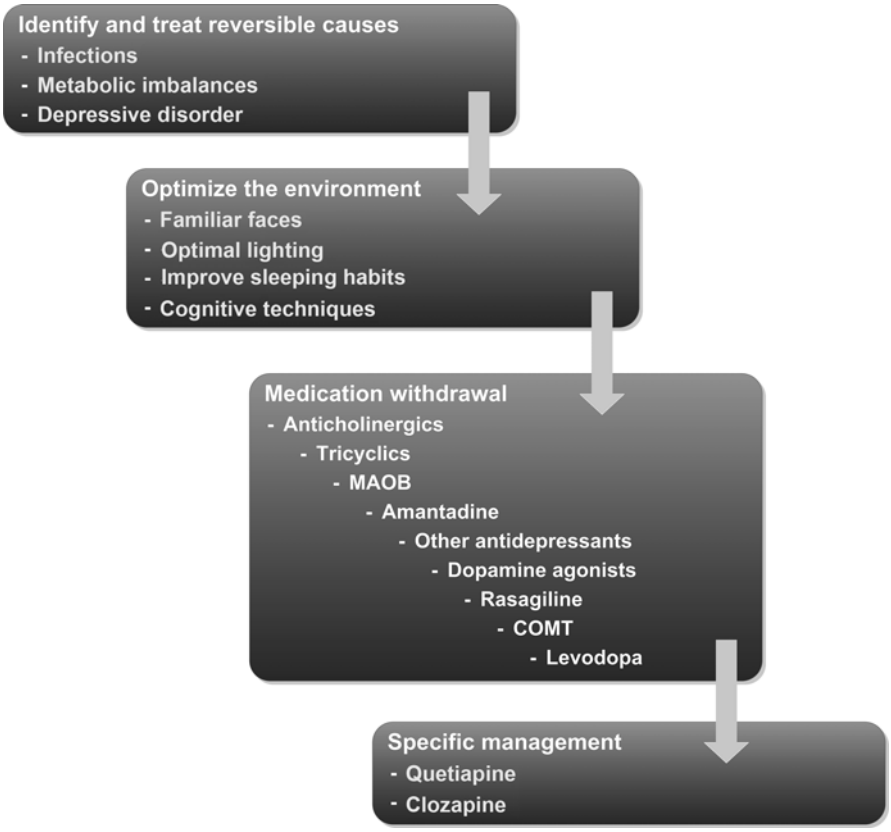

Fig. 6.1 Suggested management of psychosis in PD, including the order of withdrawal of medication

but in practice, these are avoided in the smaller doses in PD [136]. Clozapine is metabolized through the cytochrome system with inhibitors of metabolism clozapine levels [137, 138].

Quetiapine is an atypical dibenzothiazepine structurally similar to clozapine. As clozapine, quetiapine also does not appear to worsen parkinsonism to the same degree as other atypical neuroleptics such as risperidone and olanzapine or the typical neuroleptics such as haloperidol. The use of quetiapine in clinical practice is well established, and it is by far the most widely used antipsychotic for dopaminergic-induced psychosis. However, there are inconsistent study data regarding the effectiveness of quetiapine. Although several open label studies reported that quetiapine is effective for treatment of psychosis in patients with PD and two single-blind randomized trials [137] comparing quetiapine and clozapine reported they were equally effective, only one of five small randomized controlled

trials found benefit for quetiapine compared with placebo [139]. In community studies, quetiapine was reported to have a lower risk of cardiovascular death compared to other atypical agents, with an absence of a dose–response effect in relation to the risk of death [140]. Moreover, studies in nursing homes have shown a lower risk of cerebrovascular incidents or infections compared to other antipsychotics [141]. Small doses of quetiapine should be used in older people starting at 25 mg just once a day. It is important to remember that quetiapine is metabolized through the cytochrome system [142] with inhibitors of this system (such as diltiazem and clarithromycin) increasing quetiapine levels and inducers of metabolism (such as carbamazepine), reducing levels [138].

Other drugs that have been studied regarding their efficacy in managing psychotic features in PD include antipsychotics and cholinesterase inhibitors. Olanzapine was rated in the MDS 2011 report as not efficacious, with an unacceptable risk of exacerbating parkinsonism, and clinically not useful [143]. The efficacy of other antipsychotics (including risperidone, aripiprazole, ziprasidone, and melperone) and cholinesterase inhibitors (including rivastigmine, donepezil, and galantamine) has only been reported based in open label studies, case series, or single case reports [56, 144]. Subanalyses of a double-blind, placebo-controlled study in PD dementia [145] suggested that rivastigmine was more effective in some cognitive and behavioral measures in patients experiencing hallucinations compared to patients not experiencing hallucinations [146]. Thus, there is some support for the use of cholinesterase inhibitors for the treatment of psychosis in cognitively impaired PD patients, which are commonly used in this setting, but evidence for their use in treating psychosis in non-demented PD is lacking [144].

Recently, the experimental antipsychotic agent pimavanserin was found to be significantly better than placebo at reducing PD-related psychosis in a 6-week double-blind randomized placebo-controlled trial of 199 patients with Parkinson's disease psychosis. Antipsychotic treatments were not permitted during the study, but controlled antiparkinsonian medication or deep brain stimulation was allowed. Eligible participants entered a 2-week non-pharmacological lead-in phase to limit the placebo response, after which they were randomly allocated (1:1) to receive pimavanserin 40 mg per day or matched placebo. The primary outcome was antipsychotic benefit as assessed by central, independent raters with the Parkinson's disease-adapted scale for assessment of positive symptoms (SAPS-PD). Pimavanserin was associated with a −5.79 decrease in SAPS-PD scores. Pimavanserin was well tolerated and was not associated with worsening of motor symptoms or other adverse effects. The investigators concluded that pimavanserin, though not clinically available yet, may benefit patients with Parkinson's disease psychosis for whom few other treatment options exist. Further studies are needed to confirm the long-term safety and efficacy of pimavanserin [147].

Finally, it is important to consider that psychotic symptoms may be attributable to a preexisting psychiatric disorder such as major depression or another parkinsonian syndrome such as DLB.

Case Scenarios

Case Report 1 This report describes presence hallucinations in a patient with PD [39].

A 71-year-old woman had had tremor-predominant Parkinson's disease diagnosed 2 years previously, with no cognitive impairment. She received levodopa, mianserin, and lorazepam for an anxiety disorder. She had daily presence hallucinations for approximately 6 months before inclusion. The patient lived alone and had a sister living somewhere else. During the night or when awakening in the morning, she repeatedly had the vivid sensation that her sister was lying beside her in the bed. She knew that this was not possible and she did not see her, but she used to lift the top sheet to check that her sister was not there. Later in the morning, when passing near her bed, she often again had the feeling that her sister was there and she had to check again. Each episode lasted only a few seconds.

Case Report 2 This report describes passage hallucinations [39].

A 59-year-old man had received levodopa and bromocriptine for Parkinson's disease diagnosed 3 years previously. In the evening, while clearing away the tables and chairs, he often had the brief impression of a mouse passing on the right. He turned his head to the right but could not see anything.

Case Report 3 This report describes formed visual hallucinations in the context of cognitive impairment in PD [39].

A 71-year-old man had had Parkinson's disease for 8 years and was taking levodopa. His motor symptoms and signs were mild to moderate, and he was independent in all daily activities. However, the patient also had developed cognitive impairment about 4 years after the onset of motor symptoms. Hallucinations had started during a therapeutic trial of a dopaminergic agonist but had not subsided after the agonist was withdrawn. They consisted of characters that commonly took the form of small ill-formed devils with a blurred face and a changing size. They moved rapidly in "a sort of haze." During an episode of lumbar pain, the patient described these characters as armed with blades and was "butchering" his back. However, in most instances, the hallucinations of devils were not frightening and were well tolerated. The patient said that he had become familiar with them, that their lives were now intermingled with his own, and that it was like "living in a fantasy novel" or a "parallel world." The patient repeatedly stated that he was aware of the unreality of the visions but admitted that he would occasionally speak to them because they "looked so real." Visual hallucinations occurred daily, predominantly at night, and the characters seemed to be "scared" and "scattered" by light, a noise, or a sudden wave of the hand. The patient also experienced presence hallucinations: "it's a presence behind me; I try to catch it by turning round but I never see its face."

Case Report 4 This report describes rare auditory hallucinations in PD psychosis [39].

A 68-year-old-woman had received a diagnosis of Parkinson's disease 18 years previously. She was taking levodopa, bromocriptine, piribedil, and amantadine. She had subtle cognitive impairment and has also felt depressed. She had experienced presence hallucinations (of an unidentified person) for the last 6 months. In one instance, she saw her deceased son with another person. Her son distinctly said to her: "take care of yourself."

Case Report 5 This report highlights the importance of monitoring and screening the psychotic symptoms in patients treated with oral dopamine agonists, especially in elderly patients [148].

The patient was an 89-year-old man with a 6-year history of PD. Two years previously, he had been started on amantadine and selegiline. Three months later, pramipexole (0.25 mg/day) had been added to his treatment regimen to combat his persistent tremor and bradykinesia, and the dosage was increased to 0.5 mg/day in 2 weeks. One month after the dosage was titrated to 0.5 mg/day, visual hallucinations (VH) developed. He could see faces of people and ghosts in different sizes and colors. The occurrence of VH was mostly limited to nighttime, when he was fully conscious and aware, but he did not inform the others about these symptoms. In terms of his prominent motor symptoms, pramipexole was titrated up to 2.25 mg/day 5 months before this admission. After 2 months on this regimen, he experienced an increased frequency of complex VH and also had olfactory hallucinations, delusions of being poisoned, delusions of persecution, and destructive behaviors. All these psychotic symptoms persisted under normal consciousness. Amantadine and selegiline were discontinued. Pramipexole was decreased to 1.5 mg/day, and quetiapine 25 mg/day was prescribed. However, all the psychotic symptoms remained the same for 1 week under the regimen. He was then admitted, and pramipexole was discontinued. Due to his vivid psychotic symptoms and agitation, quetiapine was increased gradually to 300 mg/day in 10 days. Three weeks after admission, his psychotic symptoms gradually resolved. After discharge, quetiapine dosage was reduced gradually without psychotic exacerbation. In addition, no antiparkinsonian drug was used for his tremor and bradykinesia, which were reported as tolerable.

Case Report 6 The following case illustrates the challenge of advanced Parkinson's disease in schizophrenic patient on neuroleptic treatment. Differentiating between drug-induced parkinsonism and idiopathic Parkinson's disease is recommended by presynaptic nuclear imaging (e.g. FP-CIT SPECT) [149].

A 74-year-old man with no dementia was previously diagnosed with paranoid schizophrenia and repeatedly treated with first- and second-generation antipsychotics. Ten years ago, parkinsonism was first noticed, and antipsychotic treatment was switched to clozapine (62.5 mg/day). As the patient refused to take clozapine in the course of the disease, it was replaced by olanzapine (5 mg/day). Additionally, he received L-DOPA (400 mg/day) and pramipexole (4 mg/day) to treat parkinsonism. He responded well to treatment but later developed on/off fluctuations and peak-dose dyskinesias, wherefore a treatment with amantadine (200 mg/day) was initiated.

He then rapidly developed severe delusions. On admission, he was floridly psychotic but also disabled by severe on/off fluctuation and peak-dose dyskinesias. As there was some doubt concerning the diagnosis of idiopathic Parkinson's disease, FP-CIT SPECT was performed, and it showed bilaterally marked reduction of striatal dopamine transporter binding in the putamen. Pramipexole and amantadine were stopped, and quetiapine (125 mg/day) was added to the drug regimen, which led to marked improvement of the mental state. However, motor symptoms became worse. The total dose of L-DOPA was increased to 500 mg in combination with entacapone, and the intervals between the doses were shortened (five times 100 mg, every 3–4 h) whereby good motor control was achieved.

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