Review

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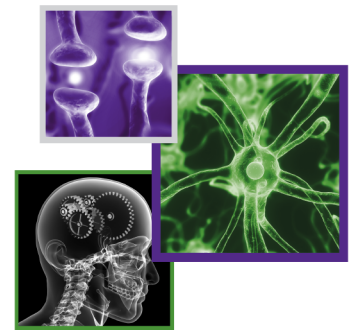
Neurodegenerative Disease Management



Parkinson's disease psychosis: presentation, diagnosis and management

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Practice points

Presentation & diagnosis

- Visual hallucinations are the most common presentation, however, nonvisual hallucinations and delusions also occur.
- Clinicians should screen explicitly for minor phenomena (illusions, presence hallucinations, passage hallucinations), hallucinations and delusions.
- Always consider alternative diagnoses, including delirium, dementia with Lewy bodies and primary psychiatric disorders.

Risk factors

- Disease-related risk factors include cognitive impairment, more advanced disease, longer disease duration, rapid eye movement sleep behavior disorder and depression.
- Dopaminergic medications play a role but are neither necessary nor sufficient to cause psychosis.

Treatment

- Evaluate for contributory medical issues.
- Eliminate unnecessary potentially contributory non-Parkinson's disease and Parkinson's disease medications.
- Start an acetylcholinesterase inhibitor in the setting of dementia.
- Consider an antipsychotic when symptoms are bothersome and fail to respond to other measures.

Parkinson'sdisease is a neurodegenerative disorder characterized by motor and nonmotor symptoms. Psychosis is a common feature of Parkinson's disease. Parkinson's disease psychosis (PDP) encompasses minor phenomena (illusions, passage hallucinations and presence hallucinations), visual and nonvisual hallucinations and delusions. PDP is associated with reduced function and quality of life. The initial management approach should focus on identification and treatment of any contributory medical factors, reduction or discontinuation of medications with potential to induce or worsen psychosis, nonpharmacological strategies and consideration of acetylcholinesterase inhibitor treatment in the setting of dementia. Pimavanserin, quetiapine and clozapine may all be considered for use in PDP. In this review, we discuss the presentation, diagnosis and management of PDP.

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Parkinson's disease (PD) is a neurodegenerative disorder characterized by motor and nonmotor features, including psychiatric symptoms such as depression, anxiety and psychosis. The prevalence of PD increases with age [1] and the lifetime risk of PD is 2.0% for men and 1.3% for women [2]. The prevalence of psychosis in cross-sectional studies of PD is 13–60% [3–12], depending on the selected diagnostic criteria and specific population, and the lifetime prevalence is 47–60% [13,14]. Parkinson's disease psychosis (PDP) negatively impacts quality of life [9], contributes to disability [9,14–15] and is associated with increased caregiver burden and distress [16–18]. We review the presentation, diagnosis and management of PDP.

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Table 1. Hallucinations by modality.

	n	Visual (%)	Auditory (%)	Tactile (%)	Olfactory (%)	Gustatory (%)	Somatic/visceral (%)	Ref.
Goetz	37	76 (28/37)	38 (14/37)	19 (7/37)	11 (4/37)	NR	NR	[23]
Inzelberg	45	100 (45/45)	22 (10/45)	NR	NR	NR	NR	[28]
Marsh	23	91 (21/23)†	65 (15/23)	13 (3/23)	13 (3/23)	NR	4 (1/23)	[30]
Amar	37	68 (25/37)	49 (18/37)	24 (9/37)	3 (1/37)	NR	NR	[21]
Papapetropoulos	31	77 (24/31)	39 (12/31)	NR	16 (5/31)	3 (1/31)	6 (2/31)	[22]

†Includes minor phenomena.
NR: Not reported.

Presentation

While visually hallucinations have been considered the most characteristic feature of PDP, the spectrum encompasses minor phenomena, visual and nonvisual hallucinations and delusions. Minor phenomena include presence hallucinations (the feeling of another person or an animal being present), passage hallucinations (fleeting imagery in one's peripheral vision) and visual illusions (the misperception of external stimuli). The prevalence of minor phenomena among individuals with PD is 20–45% [9,12,19–20], co-occurring with hallucinations in 13–27% [12,20].

Hallucinations are abnormal perceptions that occur in the absence of external stimuli. They can be associated with retained insight or loss of insight. While hallucinations in PD can sometimes become threatening, the majority are not [21]. They may, however, still be distressing [22]. Visual hallucinations (VH) are the most common [4,21,23–25] and may occur more frequently at night time in dim lighting [7,25–26]. They are typically brief (seconds) and recur at least once per week [22,26]. Formed VH most commonly involve people [7,22] but can involve animals or objects [5,22]. The content may be familiar or unfamiliar [5,27], black and white or color [26] and of normal or distorted size [5,22].

As a group, nonvisual hallucinations (auditory, tactile, olfactory and gustatory) are not uncommon, as depicted in Table 1. Nonvisual hallucinations are more frequently seen in older individuals [23] and frequently co-occur with VH [21,28]. Auditory hallucinations most commonly involve human voices but can include animal noises or other sounds [21,28]. Tactile hallucinations are generally stereotyped and most commonly involve insects or small animals [21]. While there are overlapping features between the hallucinations of primary psychiatric conditions and those in PD, there are some differences. In comparison to those in PDP, hallucinations in schizophrenia are most commonly auditory (although frequently multimodal), more frequent, more likely to be ego-syntonic and to have an associated emotional valence, and result in a more negative impact on individuals [29].

Delusions, which are fixed false beliefs, are less frequent than hallucinations. Prevalence estimates range from 3 to 14% [9,18,25,30–33] and are higher in PD dementia (PDD; 19–51%) [15–17]. Delusions are most commonly paranoid and the most common theme is infidelity [30]. In a large cross-sectional study of individuals with non-treatment naive PD, 2.5% exhibited delusional jealousy [34]. Delusional misidentification syndromes, including Capgras syndrome (the belief that familiar people have been replaced by imposters), Fregoli syndrome (the belief that familiar people are disguised as strangers) and reduplicative paramnesia (the belief that a person, place, object or event has been duplicated) have also been described in PD [35,36] and in one cohort of individuals with PDD, were identified in 17% [37].

Diagnosis

The DSM criteria for "*psychotic disorder due to medical condition – Parkinson disease*" were historically considered to be the gold standard for the diagnosis of PDP [38]. In 2007, a NINDS-NIMH work group proposed new diagnostic criteria for PDP; the diagnosis requires the presence of a characteristic symptom or symptoms that develop following the onset of PD, persist either continuously or recurrently for at least 1 month, and are not more likely to be secondary to an alternative diagnosis as detailed in Table 2 [39]. Unlike the DSM-IV criteria, the NINDS-NIMH criteria do not require symptoms sufficient to cause impaired reality testing or significant distress and result in higher prevalence estimates [12,40–41].

A 2006 American Academy of Neurology review was unable to recommend any psychosis rating scale for use in PD [42] and a 2008 Movement Disorder Society task force recommended several scales for consideration but cautioned that no scale adequately captured the full spectrum of PDP [43]. Newer scales, including the Schedule for Assessment of Positive Symptoms Parkinson's disease (SAPS-PD), which is a shortened and more clinically relevant version of the SAPS, may perform better [44]. We suggest probing specifically for minor hallucinations, which might

Table 2. NINDS-NIMH Criteria for the diagnosis of Parkinson's disease psychosis.

Criteria	Details
Characteristic symptom or symptoms that are recurrent or persistent for ≥1 month	– Illusions – Presence hallucinations – Hallucinations – Delusions
Diagnosis of PD	UK brain bank criteria
Onset of characteristic symptoms follows the diagnosis of PD	
Exclusion of other more probable diagnoses	– Dementia with Lewy bodies – Psychiatric disorder – Delirium

PD: Parkinson's disease.
Data taken from [39].

otherwise be missed, and applying the NINDS-NIMH diagnostic criteria. Caregivers should be involved whenever possible.

Pathophysiology

The pathophysiology of PDP is complex and not fully elucidated. Most dopaminergic PD medications exhibit high propensities for eliciting psychotic symptoms [45], and conversely, dopamine receptor antagonists are used to treat psychosis. Chronic dopaminergic treatment has been postulated to result in hypersensitivity of mesolimbic dopamine receptors, which may play a role in the development of psychosis [46,47]. Dopaminergic treatment is also associated with the development of impulse control disorders, punding and dopamine dysregulation syndrome, perhaps secondary to dopamine receptor desensitization, downregulation and hypersensitivity [48]. However, not all individuals with PD on dopaminergic medications develop psychosis, high-dose levodopa infusions do not provoke hallucinations [49], and nondopaminergic medications such as anticholinergics and NMDA-receptor antagonists (perhaps through dopamine–acetylcholine imbalance), are associated with the development of psychosis. Furthermore, hallucinations can occur in untreated PD [50] and the prevalence of psychosis in *de novo*, untreated PD is 3% [51,52]. Minor phenomena, however, occur in up to 42% and may precede the development of motor symptoms [19]. Of course, it is possible that some cases of dementia with Lewy bodies (DLB) may have been erroneously included in these studies. Most studies have failed to identify an association between PDP and dopaminergic treatment [4–5,7,25,53–55], although, some studies have shown an association with higher levodopa dose [14,56] or dopamine agonist treatment [6,57–59]. Dopaminergic medications appear to be neither necessary nor sufficient to cause PDP [60].

Rather, the development of PDP likely reflects a combination of exogenous (treatment-related) and endogenous (disease-specific, patient-specific) factors. PDP has consistently been shown to be associated with cognitive impairment [3,5,7–8,10,15,25,28,30,33–34,54–55,58,61–64], disease severity [5,23,25,34,55–56,58,61,64] and disease duration [7,10,25,34,55,58,61,64–65] and less consistently with older age [7,10,15,25,34,64] and older age at PD onset [14,54,66]. Associations may differ depending on the type of psychosis. For example, while delusional content may include jealousy in patients of all ages and at any stage of disease, delusional jealousy has been associated with younger age, less advanced PD and dopamine agonist treatment and may develop together with hypersexuality in individuals treated with dopamine agonists raising the possibility of a shared underlying mechanism [34,67].

Cognitive impairment is the clinical feature most consistently associated with psychosis in PD and psychosis is a risk factor for dementia, suggesting a common neurobiological substrate [47]. PD dementia (PDD) is characterized by a higher burden of cortical LB pathology than PD without dementia [68]. In PD, VH are associated with greater cortical and amygdalar LB pathology as well as more amyloid plaque and neurofibrillary tangles [69]. Ffytche *et al.* have suggested that the progression of psychosis in PD parallels the progression of LB pathology from brainstem to basal forebrain to cortex [70]. PDD and DLB have overlapping clinical features and VH are highly specific for LB parkinsonism (DLB and PD) versus non-LB parkinsonism [71]. Both conditions are characterized by cholinergic dysfunction [72] and this system may play a role in PDP [46]. Indeed, neuronal loss in the cholinergic nucleus basalis of Meynert is greater in PD than in Alzheimer's dementia, and even more extensive in PDD [73]. Anticholingeric medications can cause or contribute to cognitive impairment. Conversely, the cholinesterase inhibitor rivastigmine is beneficial in the treatment of DLB and hallucinations in PDD [74].

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Serotonergic dysfunction has also been implicated in PDP. Degeneration of serotonergic neurons in the raphe nucleus is associated with the development of nonmotor symptoms [75,76]. PDP is associated with two such symptoms, depression [4–5,7–8,10,18,33,58] and anxiety [4,18,58]. Progressive serotonergic degeneration results in compensatory 5HT2A upregulation, which is seen preferentially in the prefrontal and visual cortices of patients with PDP [75]. Hallucinations can be provoked by stimulation of 5HT2A receptors [77] and inhibited by 5HT2A receptor blockade. Dopamine binds to a multitude of 5HT receptors [78], suggesting another mechanism by which dopaminergic agents may exacerbate psychosis. Compared with levodopa, the risk of psychosis may be higher with dopamine agonists, which may reflect stimulation of serotonin receptors [46]. Atypical antipsychotics generally possess more potent 5HT2A blockade relative to D2 blockade (distinguishing them from typical antipsychotics) [79] and the only two agents for which there is robust clinical trial evidence of efficacy in PDP are the atypical antipsychotics clozapine and pimavanserin, which are relatively potent 5HT2A antagonists. However, clinical trials of olanzapine, have demonstrated lack of efficacy, despite its similar receptor profile [80,81].

PDP has been frequently associated with rapid eye movement (REM) sleep behavior disorder (RBD) and sleep abnormalities [4,7,10–11,14,19,25,33,58,82]. RBD is a prodromal feature associated with the development of synucleinopathic diseases, including PD, DLB and multiple system atrophy [83]. The long-term risk of conversion to a synucleinopathic disease is 41–92% [83]. The presence of RBD in PD may signify a distinct phenotype characterized by more severe motor, cognitive and psychiatric impairments [83], including psychosis. Several structures involved in visual processing have also been implicated in the development of visual hallucinations. PD visual hallucinations have been associated with retinal pathology [60], poor visual acuity [5], impaired color and contrast discrimination and abnormalities in higher-level processing [46].

Continuum

Psychosis may exist on a continuum in which minor phenomena progress to hallucinations with retained insight to hallucinations with loss of insight and delusions [70]. Once psychosis develops, there is a high likelihood that it will persist [23,84]. In a longitudinal study, 81% of individuals with hallucinations with retained insight progressed to hallucinations with loss of insight or delusions within 3 years [85]. Retrospective analysis from a small nonrandomized trial suggest that while both reduction in PD medications and initiation of antipsychotic treatment results in initial benefit, only the latter significantly delays progression of hallucinations [86].

It is not clear whether minor phenomena exist on the same continuum or reflect a different underlying neurobiological process. In a longitudinal study of *de novo* PD, individuals with minor phenomena were followed for a mean of 4.4 ± 1.5 years [19]. Symptoms resolved in 10% of individuals, remained stable in 52% and worsened in 38%. As mean disease duration was only 19.5 ± 15 months at baseline, the duration of follow-up may not have been sufficient to demonstrate progression of psychosis. Another longitudinal study of *de novo*, untreated PD patients demonstrated that minor phenomena preceded formed hallucinations in about 50% of cases [53]. In addition, those with minor phenomena do not differ from those without minor phenomena with respect to cognitive impairment [19,41,53,87].

Similarly, delusions may reflect a different underlying neurobiological process, an idea supported by one cross-sectional study which found an association between cognitive impairment and hallucinations but not delusions [88]. Indeed, Factor *et al.* recently proposed a new classification system for PDP which recognizes different subtypes of PDP: class I symptomatic psychosis, class II dopaminergic drug-induced psychosis (predominantly delusions), class III psychosis associated with affective disorders and serotonergic dysfunction, and class IV psychosis associated with cognitive decline and cholinergic dysfunction [89]. Within this classification system, only class IV psychosis is recognized as progressive and associated with a poor outcome.

Treatment

PDP negatively impacts quality of life [9], contributes to disability [9,14–15] and contributes to increased caregiver burden and distress [16–18]. Thought to be progressive [85], PDP increases the risk of nursing home placement [90,91] and mortality [92,93]. All of these reasons suggest that treatment should be initiated early, but, there have not been any prospective studies examining whether treatment of psychosis impacts long-term outcomes (e.g., development of dementia, nursing home placement, mortality). Complicating the issue further is the possibility of increased morbidity and mortality risk among individuals with PD exposed to antipsychotics [94,95].

In the treatment of PDP, many factors must be taken into account and treatment should be individualized. Initial management should consist of:

- A search for causal or exacerbating medical factors (e.g., infection, electrolyte imbalances or subdural hematoma). An altered level of consciousness is not typically associated with PDP and its presence should prompt a search for medical causes of delirium or consideration of an alternative diagnosis such as DLB.
- Review of medications and attempts to discontinue any nonessential centrally acting medications. Whenever possible, medications less apt to worsen mental status should be chosen for a given indication. For example, melatonin would be favored over clonazepam for the treatment of RBD in PDP.
- Adjustments of PD medications as motor function will tolerate. If a medication change occurred prior to the development or worsening of psychosis, causality should be considered and adjustments made as indicated. Otherwise, we suggest discontinuation of adjunctive PD medications, carefully considering the relative potential benefits for motor function and risks for worsening psychosis, in determining the order in which to discontinue anticholinergics, monoamine oxidase-B inhibitors, amantadine, dopamine agonists and COMT inhibitors. Adjustment of carbidopa–levodopa dosage should be reserved for last.
- Patient and caregiver counseling regarding the diagnosis and recommendations for environmental modifications and behavioral interventions. Patients with VH may benefit from avoidance of low light situations, correction of any visual problems and may be amenable to reality testing, incorporating cognitive, interactive (engagement of caregivers) and/or visual strategies [96,97].

Underscoring the importance of these initial steps, among individuals with PDP referred for a quetiapine clinical trial, 65% (17/26) underwent PD medication adjustment and 20% (5/26) were treated for a systemic illness before entering the trial [98]. 62% (16/26) experienced sufficient improvement to no longer warrant antipsychotic treatment. It is important to exercise caution in prescribing dopaminergic medications in patients with a history of conditions that may worsen or re-emerge with such therapy (e.g., mania, mood disorder with psychotic features, impulse control disorder [ICD]).

We have found acetylcholinesterase inhibitors helpful for the management of PDP in the setting of PDD. Two studies support a possible role for rivastigmine, although neither were designed specifically to assess treatment of PDP. An open-label trial of rivastigmine for PDD, demonstrated an improvement in hallucinations (but not delusions) and caregiver burden [99]. In a randomized, double-blind, placebo-controlled trial of rivastigmine for PDD the rivastigmine group demonstrated significant improvement on cognitive and behavioral measures and the benefit was greater among those with VH [74]. The results of several small open-label studies suggest donepezil may improve psychosis [60,100]; however, no improvement in psychosis was seen in two randomized controlled trials of donepezil in PD [101,102].

In the absence of prospective data to support earlier initiation of antipsychotic therapy, we generally reserve antipsychotic treatment until symptoms become bothersome or pose a safety concern. Antipsychotics that may be considered include clozapine, pimavanserin and quetiapine as they are not associated with significant motor worsening. All three drugs can cause QTc prolongation and carry a black box warning for increased mortality among elderly with dementia-related psychosis. However, it should be noted that this is a class-wide warning and there are no data supporting increased mortality risk with pimavanserin [103]. Other atypical antipsychotics, including risperidone, olanzapine and aripiprazole, and typical antipsychotics (i.e., neuroleptics) should be avoided given the concern for motor worsening [80–81,104–109].

Clozapine is effective for the treatment of PDP and does not worsen motor function, as demonstrated by two double-blind, placebo-controlled, randomized trials [110,111]. Due to the risk of potentially fatal agranulocytosis, use of clozapine is overseen through a national registry and frequent laboratory monitoring is required. As such, its use has been limited [112]. Although, retrospective studies of PD patients on longer-term clozapine treatment have confirmed a low rate of leukopenia and identified no instances of agranulocytosis [112–115] regular monitoring remains an essential component of management. In addition, several studies have identified somnolence/sedation as a common or potentially treatment-limiting side effect [113–116]. Because of the cumbersome monitoring requirements, we use clozapine infrequently, reserving it for patients who do not respond to quetiapine or pimavanserin.

Quetiapine, a $5HT_{2A}$ blocker with low affinity for D2 dopamine receptors [117], is the most commonly used antipsychotic in PD [118]. Several open-label studies suggested that quetiapine may be effective for the treatment of PDP [119–121]. Two open-label, rater-blinded studies compared quetiapine and clozapine, noting that treatment with either medication resulted in significant improvement in psychosis [122,123]. However, numerous double-blind, randomized, placebo-controlled have failed to demonstrate efficacy [124–128]. The only such trial to demonstrate a statistically significant improvement in psychosis failed to demonstrate efficacy on the primary outcome (quantity

of REM sleep) [129]. Dementia may represent a risk factor for motor worsening [117,121,130] and nonresponse to quetiapine [130] suggesting that it, like other antipsychotics, should be used with appropriate caution in PDD. Despite the absence of supporting evidence, we routinely use quetiapine because we have generally had positive clinical experiences with it. A more extensive review of clozapine and quetiapine in PDP can be found elsewhere [131].

Pimavanserin, is a novel antipsychotic which exhibits selective 5-HT_{2A} inverse agonist activity with much lower affinity for 5-HT_{2C} receptors and negligible D_2 and histamine receptor activity [103,132]. It is effective for the treatment of PDP and does not worsen motor function [132,133]. In a Phase II trial, no difference was seen between groups in change in UPDRS II + III score or in the adverse event profile and a significant improvement was seen on select psychosis measures [132]. The failure of a subsequent Phase IIB/III trial to demonstrate significant improvement in psychosis was attributed to high placebo response [134] and the following Phase III study incorporated a novel psychosocial therapy run-in to exclude placebo responders. In this multicenter, randomized, double-blind, placebo-controlled 6-week trial there was significant improvement in the pimavanserin group compared with the placebo group on the primary outcome of change in SAPS-PD, multiple secondary psychosis outcomes, and sleep and caregiver burden outcomes [133]. The mean improvement on the SAPS-PD in the pimavanserin group was 37% compared with 14% in the placebo group. There were a significantly higher proportion of responders in the pimavanserin group compared with the placebo group (49 vs 26%). Side effects that occurred in more than 5% of those in the pimavanserin group included nausea, peripheral edema, urinary tract infections, falls, confusion and hallucinations. In the pimavanserin group, the rate of serious adverse events was higher and a greater number of individuals discontinued treatment due to an adverse event.

A meta-analysis of four randomized, placebo-controlled trials of pimavanserin found no significant differences in adverse event rate between groups with the exception of orthostatic hypotension (which was more frequent in the placebo group) [135]. Results from an open-label extension study of pimavanserin suggest that the mortality rate and serious adverse event rate may be significantly higher among those concurrently prescribed another antipsychotic, however, this was a *post hoc* analysis and the observed difference may reflect baseline differences rather than treatment [103,136]. Additional postmarketing data are needed to determine whether long-term use of pimavanserin is safe, tolerable and efficacious. In a small retrospective study of 15 patients with parkinsonism and psychosis treated with pimavanserin, 10/15 improved and 5/15 discontinued treatment due to lack of benefit [137]. Our preliminary clinical experience suggests that pimavanserin initiated at 34-mg daily is generally well tolerated and that it may take several weeks to obtain any benefit (which stands in contrast to clozapine which can take effect much more quickly within a matter of days) [111,138]. A recent white paper from the Parkinson's Foundation provides suggestions regarding how to switch antipsychotics [139].

Future perspective

Future research should focus on answering the following questions: do all PDP symptoms exist on the same progressive continuum or are there different subtypes of psychosis with different prognoses? Research should aim to better understand the natural history of psychosis progression (i.e., minor phenomena to VH with insight, to loss of insight and delusions) and to identify if there are clinical profiles associated with more likely progression. With a greater understanding of the natural history of PDP, clinicians would be better equipped to determine when to initiate antipsychotic treatment and to provide anticipatory guidance to patients and families. Which is the most effective antipsychotic for treatment of PDP? Head-to-head comparison trials of antipsychotics are warranted to determine the optimal treatment for PDP. Does antipsychotic treatment impact the long-term course of or outcomes associated with PDP? The short-term, symptomatic benefit of certain antipsychotics has been demonstrated but it is not known whether treatment impacts the progression of disease or long-term outcomes, such as nursing home placement and mortality. Do acetylcholinesterase inhibitors improve PDP? While employed in clinical practice, there have not been any studies specifically designed to evaluate the impact of acetylcholinesterase inhibitors on PDP.

Conclusion

PDP is common, contributes to worse quality of life and caregiver burden, and is a risk factor for nursing home placement and mortality. PDP can manifest as minor phenomena, visual or, less commonly, nonvisual hallucinations with or without insight or delusions. Exogenous and endogenous factors, including dopaminergic treatment, cholinergic dysfunction, serotonergic dysfunction, advanced disease and sleep dysfunction contribute to the development and perpetuation of PDP. Management should include attempts to address potentially contributing

medical conditions, minimization of medications likely to induce or worsen psychosis and nonpharmacological interventions. Treatment may consist of consideration of acetylcholinesterase inhibitors in the setting of dementia and when necessary, antipsychotic treatment.

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•• **Interesting longitudinal study that highlights the common occurrence of minor phenomena in early Parkinson's disease and their evolution over time.**

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