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REVIEW

Neuropsychiatric symptoms in untreated Parkinson's disease

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Szabolcs Szatmari[1–3]
Ben Min-Woo Illigens[4]
Timo Siepmann[5,6]
Alexandra Pinter[5,7]
Annamaria Takats[8]
Daniel Bereczki[8]

[1]Department of Neurology, Sibiu County Emergency Hospital, Sibiu, [2]2nd Department of Neurology, Targu Mures Emergency Clinical County Hospital, Targu Mures, Romania; [3]János Szentágothai Doctoral School of Neurosciences, Semmelweis University, Budapest, Hungary; [4]Department of Neurology, Beth Israel Deaconess Medical Center, Harvard Medical School, Boston, MA, USA; [5]Center for Clinical Research and Management Education, Division of Health Care Sciences, Dresden International University, [6]Department of Neurology, University Hospital Carl Gustav Carus, Technical University of Dresden, Dresden, Germany; [7]Department of Family Medicine, [8]Department of Neurology, Semmelweis University, Budapest, Hungary

Correspondence: Timo Siepmann
Department of Neurology, University Hospital Carl Gustav Carus, Technical University of Dresden, 74 Fetscher Street, 01307 Dresden, Germany
Tel +49 351 458 3565
Fax +49 351 458 4365
Email timo.siepmann@uniklinikum-dresden.de

Abstract: Neuropsychiatric and cognitive symptoms are common in Parkinson's disease (PD) and may precede and exceed motor symptoms as major factors impacting disease course and quality of life. Neuropsychiatric symptoms (NPS) in PD are various and are attributed to pathologic changes within multiple brain regions, to psychological stress, and to adverse effects of dopamine replacement therapy. Sleep disorders and mood symptoms such as apathy, depression, and anxiety may antedate the development of motor symptoms by years, while other NPS such as impulse control disorders, psychosis, and cognitive impairment are more common in later stages of the disease. Few studies report on NPS in the early, untreated phase of PD. We reviewed the current literature on NPS in PD with a focus on the early, drug-naive stages of PD. Among these early disease stages, premotor and early motor phases were separately addressed in our review, highlighting the underlying pathophysiological mechanisms as well as epidemiological characteristics, clinical features, risk factors, and available techniques of clinical assessment.

Keywords: neuropsychiatric symptoms, Parkinson's disease, untreated

Introduction

In Parkinson's disease (PD), in addition to the typical motor symptoms, nonmotor symptoms (NMS) may occur, neuropsychiatric manifestations often being the most common.[1] The premotor phase in PD is dominated by different NMS that are known to have a major impact throughout the course of the disease. A number of clinical subtypes with differing NMS patterns have been established, which feature the early, untreated phase of the disease. This framework ensures that NMS are more readily identified and treated optimally. The phenotypic variants are as follows: park cognitive (predominantly presents with cognitive impairment at an early stage), park apathy (high scores on apathy scales), park depression/anxiety (early manifestation of these symptoms), park sleep (characterized by excessive daytime sleepiness or rapid eye movement behavior disorder), park pain (different pain syndromes dominate the clinical picture), park fatigue (exhibited as an independent and severe symptom), and park autonomic (gastrointestinal, genitourinary symptom dominant, and adrenergic dysfunction dominant) subtypes.[2] A recent study found that the prevalence of neuropsychiatric symptoms (NPS) in early, untreated PD patients was up to 56%.[3] Several prior studies have shown these symptoms to have an adverse impact on patient's everyday activities, quality of life, as well as the burden of their caregivers and the health services.[4–12] Previous research has also suggested that these symptoms are frequently unrecognized and untreated due to several factors such as the incomplete understanding of mental health problems, illness-specific concerns among patients,

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access-to-care issues, and inadequate detection of psychiatric complications by clinicians.[13–15]

NPS are identified to be integral to PD throughout the course of the disease, often developing in the early, untreated stages, before the onset of classical motor symptoms of PD, suggesting that neurophysiological impairments that cause NPS may already develop in the initial phases of PD.[3,16–19] In contrast, dopamine replacement therapy (DRT), particularly dopamine agonists that cause hyperdopaminergic states, has been associated with psychosis, impulse control disorders (ICDs), excessive daytime sleepiness, and hallucinations.[20,21] Hence, the occurrence of NPS in PD patients may frequently be related to potentially additive mechanisms, including psychological reactions to disability, psychiatric symptoms caused by structural brain damage, and adverse effects of DRT. This pathophysiological heterogeneity poses a challenge to the clinician. Moreover, knowledge is still limited about structural brain areas and the neuropathological and pathophysiological changes that may associate with NPS in PD. The main limitation of investigating these symptoms is that NPS are influenced by DRT and often are hardly differentiated from each other because of symptom overlaps.

For this reason, we have excluded studies investigating NPS in PD patients receiving pharmacological treatment. Our present review focuses on NPS in the untreated stages of the disease and separately addresses the premotor phase of the disease and the stage where motor signs are already present.

Search methodology

This is a narrative review. Literature research was undertaken using the database Medline via the PubMed interface. The keywords "neuropsychiatric symptoms", "Parkinson's disease", and "untreated" with the use of the Boolean operators "AND" or "OR" were used to identify relevant studies and reports that examined the association between NPS and PD. In the initial literature search, we exclusively chose these three keywords. In addition, we performed a second literature search using the same electronic database with more specific terms to ensure coverage of all aspects that our review focused on. For this purpose, we established a search strategy using the following terms and their combinations: "apathy", "depression", "anxiety", "impulse control disorder", "psychosis", "sleep disturbance", "cognitive deficit" AND untreated OR "drug naive" AND Parkinson's disease. We included randomized controlled studies, observational studies, meta-analyses, systematic reviews, and case reports published between 1990 and 2016. We reviewed the existing information on NPS that can be attributed to the following syndromes in patients with pharmacologically untreated PD: apathy, depression, anxiety, ICDs, psychosis, sleep disturbances, and cognitive deficits. For these syndromes, information on pathophysiology, epidemiology, clinical features, risk factors, and assessment instruments was extracted and formed the basis for this review.

Apathy in untreated PD

Apathy can be defined as a behavioral disturbance of primary loss of motivation that is not attributable to reduced intellectual impairment, emotional distress, or level of consciousness.[22] The underlying mechanism of apathy in PD patients is unclear. Positive correlation was found between apathy scores and cerebral metabolism in the inferior/middle frontal gyrus, cuneus, and the insula,[23] and there is evidence that apathy in PD is associated with reduced gray matter density in several brain regions such as the precentral gyrus, the inferior parietal gyrus, the inferior frontal gyrus, and the insula.[24] It has also been described that apathy is associated with reduced striatal dopamine transporter levels, independent of depression, suggesting that disruption of dopaminergic innervation in the right caudate nucleus and striatum may contribute to the development of apathy even in early, untreated PD with motor disability already present.[25] Moreover, recent findings suggest that combined dopaminergic and serotonergic degeneration, especially within the caudate nucleus, could be a key mechanism underlying apathy in newly diagnosed, untreated PD patients with motor symptoms.[26] Therefore, such results underline the fact that the pathogenesis of this symptom is complex and is not exclusively linked to dopaminergic dysfunction.

The prevalence of apathy in patients with PD ranges from 17% to 50%[3,27–30] overall. The wide range of the reported prevalence values may be attributable to differences between study design, disease severity, and the methods used to detect apathy. Apathy has been identified in untreated, newly diagnosed PD patients with motor symptoms, where the prevalence ranged between 12% and 33%;[28,31,32] however, such cohorts have not been extensively studied in this regard. Studies show that after excluding patients with depression or dementia, the prevalence of apathy in PD drops to 3%–11%,[33–36] suggesting that symptom overlaps are important to consider.

A case–control, multicenter study – the ONSET PD study – has shown that apathy can precede the onset of motor symptoms in drug-naive PD subjects at early stages, the prevalence being 50%.[37] In addition, a retrospective study that used interviews performed by telephone found

the frequency of apathy to be 23.7% in the prodromal untreated phase of PD.[38]

The assessment of apathy is difficult because of overlaps with depressive symptoms and cognitive impairment;[39,40] nevertheless, there is evidence confirming that apathy in PD also commonly occurs as an independent symptom.[41] A recent study validated the apathy evaluation scale (AES) as a reliable questionnaire for detecting apathy in PD.[32]

Apathy should be taken into consideration already in the early phases of PD because it has been associated with reduced quality of life in patients,[42] increased caregiver burden,[43,44] altered social relationships,[45] low cognitive status,[46] increased motor symptoms, and more severe disability;[47–50] furthermore, it can easily remain undetected, unless specifically screened for. Therefore, early and accurate identification, especially in untreated, newly diagnosed PD patients, can contribute to optimal clinical management.

Depression in untreated PD

Depression is defined as a low mood state as indicated by feelings of sadness, despair, anxiety, emptiness, discouragement or hopelessness, and aversion to activity that can affect a person's thoughts or feelings, behavior, and sense of well-being.[51]

Neurobiological factors associated with the underlying neurodegenerative processes in PD play an important role in the appearance of depressive symptoms and may not represent a reaction to disability only.[52] Several studies have analyzed the neuroanatomical background of depression in PD, mainly with neuroimaging techniques. These publications report that depressive symptoms in PD are related to decreased hippocampus and amygdala volume[53,54] and increased brain metabolism in the amygdala.[55] Bilateral decreases in regional cerebral blood flow of the medial prefrontal cortex is also a common finding in PD patients with depression.[56] Abnormal functional connectivity of the amygdala, the prefrontal-limbic system, the prefrontal cortex, and the lingual gyrus was associated with depressive symptoms in PD patients;[57,58] however, a study found intact limbic-prefrontal connections[54] in a similar group of patients. Furthermore, depression in PD is also related to gray and white matter volume deterioration in the orbitofrontal and temporal regions as well as in the cortical-limbic system.[59–61] Changes in neuronal systems that are associated with the regulation of mood disturbances, such as dopaminergic, noradrenergic, and serotonergic systems, in limbic and cortical structures might also be involved,[62] but the exact pathomechanism is yet unknown. Furthermore, depression can manifest as a mood reaction to PD itself and to the progressive disability. In summary, depressive symptoms in PD can have various etiologies. Interestingly, depression can appear several years before the onset of motor manifestations and use of DRT.[37] The strong link between depression and PD is underlined by the increased likelihood of developing PD in a cohort of patients with depression than in controls; therefore, it may also be an independent risk factor for PD.[17,18,63–66]

Depression is one of the most frequently reported NPS in PD generally;[67] prevalence varies depending on the diagnostic approach (major or minor depressive disorder and dysthymia), the evaluation of patients, and the study population used. A meta-analysis calculated the prevalence of depression in PD overall, taking into account the different settings and different approaches to diagnosis. The weighted prevalence of clinically significant depression in PD was 35%, more precisely of major depressive disorder was 17%, that of minor depression was 22%, and that of dysthymia was 13%.[67]

A study which assessed the impact of depression in the early, untreated stages of PD with motor symptoms already present found a prevalence rate of 27.6%.[68] Studies involving untreated PD patients showed that, of the NMS, depressed mood was more frequent 2 years and even 10 years before motor onset, the prevalence being 23.7%–68%.[37,38]

General risk factors for depression in PD include motor disability,[69] longer duration of the disease,[70] predominance of right-sided motor symptoms,[71] akinetic-rigid variant of PD,[72] presence of other NPS,[73,74] restless legs syndrome (RLS),[75] presence of sleep disorders,[76,77] higher daily doses of levodopa,[78] younger age,[78] and female gender.[79]

Since depression in PD has been associated with poorer quality of life and increased caregiver concern,[68,80,81] it is essential to adequately screen for and correctly treat depression already at the onset of PD. Depressive symptoms are frequently masked by other NPS and motor disturbances, and it can develop at any phase in the course of PD;[9] therefore, it is difficult to recognize it. For screening, the fourth edition of the DSM-IV diagnostic criteria for major depression, minor depression, and dysthymia in PD has been validated.[82] Still, one of the greatest challenges in PD remains diagnosing and treating depressive symptoms to the point of remission.

Anxiety in untreated PD

Generalized anxiety disorder (GAD) is characterized by excessive worry and anxiety that are difficult to control, cause significant impairment and distress, and occur on >50% of the days within at least 6 months.[51] GAD in PD is characterized by excessive worry about disease progression, muscle

tension, or everyday worries such as financial concerns. Social phobia in PD is described as fear of social consequences resulting from PD symptoms manifesting in public.[83]

The exact pathomechanism of anxiety is still unclear; however, dysfunction in the dopaminergic system might be implicated, even in newly diagnosed, never treated PD patients.[84–86] Tissue reduction in the amygdala and bilateral decreased metabolism in the caudate nucleus may also contribute to the development of anxiety.[55,87] These symptoms could precede the onset of motor symptoms by as much as 20 years and may be early manifestations during the prodromal phase of PD.[18,66] In addition, the risk of developing PD was found to be greater in a population with anxiety and correlated with the severity of anxiety according to a recent study.[88] Moreover, the psychological reaction to the development of motor disturbances should not be neglected.

Anxiety is a common NMS among patients with PD overall, with a prevalence interval between 34% and 65%, GAD being the most frequently diagnosed condition.[89–91] Other common anxiety disorders described in PD are panic attacks and social phobias.[92]

In two PD cohorts of drug-naive subjects with motor symptoms, the prevalence of anxiety (16.4% and 24.6%) was also higher than in non-PD controls.[3,93] A study examined anxiety in the premotor phase of untreated PD and found a prevalence of 13.3%.[38]

To assess the severity of anxiety symptoms, several scales are used (eg, State-Trait Anxiety Inventory); however, none of these meet the criteria to be recommended and are classified only as suggested.[94]

Risk factors and predictors reported for anxiety symptoms in patients with PD in general include young-onset PD, higher rates of motor fluctuations, morning dystonia,[92] severity of PD, postural instability, gait dysfunction, symptom clustering and experience of dyskinesia,[95] nontremor-dominant motor subtype, depressive symptoms, worst sleep quality, being nonwhite, female gender, and younger age.[93,96,97]

Similar to other NPS, anxiety symptoms in PD also have a negative impact on the quality of life;[98] therefore, its timely recognition and adequate treatment are of paramount importance.

ICDs in untreated PD

ICDs are a class of psychiatric disorders characterized by impulsivity, failure to resist a temptation, urge, or impulse that may harm oneself or others.[51] The clinical spectrum of ICDs is extensive; the primary disorders in PD include pathological gambling, compulsive shopping, hyperphagia, hypersexuality, and punding, as well as compulsive use of dopaminergic medication with consequent dopamine dysregulation syndrome (DDS).[20,99,100] The occurrence of ICD has been associated with overstimulation of the mesolimbic system by dopamine treatment.[101–103] Decreases in the binding potential of a dopaminergic tracer in the ventral striatum have been reported in PD patients with pathological gambling phenomena undergoing DRT.[104] In addition, another study of PD gamblers showed a disconnection between the anterior cingulate cortex and the striatum.[105] Furthermore, the development of ICD is somewhat related to a significant loss of gray matter volume in the frontal lobe.[106] In drug-naive PD patients with motor symptoms, who later on develop ICD, lower baseline dopamine transporter availability in the right ventral striatum, anterior-dorsal striatum, and posterior putamen has been shown.[107] As an adjunct, early dysfunction of the mesocorticolimbic circuits has also been hypothesized to play a role in ICD before dopamine treatment in PD patients.[108]

The association between high doses of dopaminergic medications, particularly dopamine agonists and increased risk to develop ICDs, seems evident;[20,109,110] however, currently available literature deals with PD patients undergoing DRT only. The prevalence of ICDs and related behaviors in treated PD was found to be ranging from 8.1% to 43%.[20,111,112] With motor symptoms already present, recent data suggest that the frequency of ICD symptoms is as common in patients with early-stage, drug-naive PD as in healthy controls,[113,114] the prevalence ranging between 17.5% and 18.5%. As far as we know, the prevalence of ICD in newly diagnosed, untreated PD in the premotor stage has not been studied so far.

The development of these behaviors in general is significantly associated with younger onset of PD, male gender, smoking,[111,115,116] comorbid psychiatric symptoms and greater functional impairment in PD,[117] personal or family history of gambling, and solitary marital status;[20] however, the main risk factor for developing impulsive behaviors remains the DRT.

For early detection and screening of ICD, the Questionnaire for Impulsive-Compulsive Disorders in Parkinson's Disease (QUIP) has been recently developed and validated, which appears to be a very sensitive instrument for this particular behavioral disorder assessment.[118,119]

Taken together, findings so far suggest that ICDs are frequent in PD even before the initiation of dopaminergic medication and they are as common as in healthy controls. Therefore, factors other than PD itself lead to the occurrence of ICDs. Careful identification and active screening of

predictive factors and symptoms are needed; moreover, close follow-up on the behavioral alterations to DRT of patients is needed, as these are not automatically reported to physicians. Besides, treatment is challenging and complex as patients may experience dopamine agonist withdrawal syndrome,[120,121] hence minimizing this complication is very advisable.

Psychosis in untreated PD

Psychosis is a condition of the mind broadly defined as a loss of contact with reality. Psychotic symptoms in PD include delusions and hallucinations, which are risk factors for dementia and predictors of poor prognosis, mortality, and nursing home placement.[122–124] In addition, it has been identified as a significant determinant of caregiver burden.[90]

Based on previous studies, hallucinations are mainly associated with dopaminergic agent use (especially dopamine agonists, amantadine, and monoamine oxidase B inhibitors).[125,126] In addition, in PD, persistent visual hallucinations have been linked to high densities of Lewy bodies in the amygdala and parahippocampus[127] and have been shown to be associated with dysfunction of the temporal lobe, frontal lobe cingulate cortex, hippocampus, primary and secondary visual cortex, thalamus, precuneus, and cerebellum.[128–134] Concerning the neural pathways, there is evidence, which indicates that serotonin may also contribute to the pathogenesis of complex visual hallucinations besides dopamine in PD, via involvement of the serotonin 2 receptor.[135] Historical descriptions of PD from the prelevodopa era suggest that hallucinations may be part of PD itself, especially in the context of depression or dementia.[136]

Visual hallucinations are present in about one-quarter to one-third of PD patients overall, auditory being as much as 20%. Sense of presence and visual illusions affect 17%–72% of the patients, and delusions affect ~5%. Nevertheless, in the early stages of PD with motor symptoms, minor hallucinatory phenomena (presence hallucinations, passage hallucinations, and visual hallucinations) have been described in up to 30% of patients.[122,137,138] In other studies, psychotic symptoms were very rare in patients with early-stage, untreated PD.[3,29,93] A very recent study analyzing incident PD patients, already in the premotor untreated phase, also confirmed the hypothesis that the use of dopaminergic drugs is not mandatory for hallucinations to appear in PD,[139] and 33.3% of patients with minor hallucinations manifested these as a premotor symptom; however, the confirmation of these results is necessary.

The main nonmodifiable risk factor of psychosis is cognitive impairment. Other associated factors include older age/longer duration of PD, disease severity, presence of daytime somnolence or rapid eye movement (REM) sleep behavior disorders (RBDs), depression, and dysautonomia.[122,140,141]

Since psychotic symptoms are not always reported voluntarily by patients, clinicians should always ask for such experiences. There are some rating scales in use, but none of them are widely accepted. The Neuropsychiatric Inventory and item 2 of the Movement Disorder Society Unified Parkinson's Disease Rating Scale (MDS-UPDRS) subscale 1 can be used for screening. More detailed assessments can be made using specific scales such as Parkinson Psychosis Rating Scale. An MDS Task Force recently reviewed psychosis rating scales used in PD and listed the "recommended" ones for use in PD.[142]

Despite the association between medication exposure and psychosis in PD, the duration and dosage of DRT do not clearly correlate with psychosis;[143] furthermore, based on the previous debating results mentioned, the etiology of psychosis in PD is complex and needs further investigation. In the early, untreated stages in PD, although psychosis is less frequent than in more advanced disease, better understanding of these phenomena is needed, which will lead to better care and improved quality of life.

Sleep disorders in untreated PD

The most frequent sleep disorders in PD are insomnia, excessive daytime sleepiness, RLS, and RBD.[144]

The causes of sleep disturbances are multifactorial, but damage to several brainstem nuclei that are directly involved in the regulation of sleeping mechanisms, which are affected in very early premotor stages of PD,[145,146] is probably significant. Nigrostriatal dopaminergic degeneration could also play a role in the pathogenesis of RBD but not essential for its development.[147] Abnormalities in primary sleep-regulating centers, some NMS have secondary effect on the quality of sleep, such as nocturia, RLS, and narcoleptic pattern of rapid onset of sleep, which are also important causes of sleep-related morbidity in PD.[148,149] As causative factors, besides the neurodegenerative processes within sleep regulatory brain circuitries, DRT and concomitant medications (eg, antidepressants) as well as comorbidities or other NMS (such as depression) are proposed.[144] Sleep-related problems are also reported to increase the risk of development of PD in the later life similarly to anxiety disorders and depression[146,150,151] or RLS,[152] and because they usually precede the classic motor abnormalities of PD by many years, they should be clinically evaluated as a potential marker for PD before its onset.[153,154] Similarly, sleep dysfunctions occur in untreated

PD as well.[155,156] These facts suggest that the condition is likely to be related to the underlying dopaminergic deficit rather than the effect of dopaminergic treatment, which seems to be only an aggravating component.

In general, sleep disorders affect up to 75% of patients with PD.[153] Other studies that have evaluated the prevalence of the various sleep disorders in PD patients reported a wide range of prevalence because of different methods used and different PD stage examinations.[157–163] A recent study exploring the distribution of sleep quality in untreated PD patients with motor symptoms found that 59.2% of the patients had sleep disturbances and the percentage was even higher in patients treated with DRT.[164] In premotor untreated PD, according to studies, the prevalence of sleep disturbances was 17%–52%.[37,38]

The presence of sleep problems in PD predicts more NMS, fatigue, depression, and cognitive decline,[159] and as other NPS, they have a significant negative impact on patients' quality of life.[165]

For the diagnosis of sleep disturbances, the recommended and validated regular screening questionnaires are as follows: the Pittsburgh Sleep Quality Index (PSQI) and the Medical Outcomes Study (MOS) Sleep Scale; for evaluating daytime sleepiness, the recommended and validated regular screening questionnaires are as follows: the Epworth Sleepiness Scale (ESS), the Inappropriate Sleep Composite Score (ISCS), and the Stanford Sleepiness Scale (SSS).[144] The Parkinson's Disease Sleep Scale (PDSS) has also been validated[166,167] as a simple screening tool for identifying the various types of nocturnal disabilities that disrupt sleep in PD.

Summing up, sleep disorders often precede the development of motor symptoms in PD. Close follow-up of patients with idiopathic sleep disorders could enable early detection of PD.

Cognitive impairment in untreated PD

Findings from prior studies suggest that initial cognitive decline in PD is triggered by comorbid pathology that occurs with aging, widespread PD pathology, or early diffuse brainstem pathology.[168–172]

The rate of cognitive decline in the premotor phase of PD compared to controls is similar based on two population-based studies,[173,174] suggesting that global cognitive dysfunction may not occur in premotor PD. Generally, in PD, ~25% of nondemented patients have mild cognitive impairment (MCI)[175] and up to 80% of all PD patients will eventually develop dementia.[176] Prior studies have shown that a representative rate (10%–40%) of new, untreated PD patients with motor symptoms have cognitive deficits.[93,177–179] This wide range might be attributed to many factors including study design, methodology, and definition for MCI in PD. The prevalences of cognitive deficits in the two studies with patients in the premotor untreated phase of PD were as follows: memory complaints 54%, inattention 60%, problems to recall words 32.4%, bradyphrenia 25.8%, and forgetfulness 41.9%.[37,38]

Patients with PD and cognitive decline have more severe dysfunction in the domains of executive and visuospatial functioning and attention, with lesser involvement of memory and language.[180]

Based on preliminary studies, cognitive decline is predicted by older age, male gender, being nonwhite, lower educational level, worse olfaction, more severe motor symptoms, presence of RBD symptoms, and other NPS at baseline.[93,181–184] Cognition in PD is assessed using the Parkinson's Disease-Cognitive Rating Scale and the Mattis Dementia Rating Scale-2, but there are several other scales, which can be used with the same purpose.[185,186]

Treatment of PD and its correlation with NPS

Although the mechanisms whereby primary NPS related to PD and NPS related to antiparkinsonian medication affect each other are not fully understood, clinical observations underscore the importance of an optimal personalized clinical management in these patients. In general, patients with dopaminergic therapy are more likely to be bad sleepers, depressed, and with cognitive impairment compared to untreated patients.[164,187,188] In addition, initiation of DRT is associated with an increase in ICD symptoms, psychosis, and excessive daytime sleepiness. However, a summary of several clinical trials on the effects of DRT in PD suggested therapeutic benefit regarding NPS, mainly depression and anxiety.[15] Practically, the introduction of DRT does not significantly improve most of these symptoms because the majority of NPS does not worsen extensively in the first years of PD regardless of treatment. This may suggest that the neuropsychiatric burden and cognitive deficits in newly diagnosed, untreated PD patients are not high overall compared to more advanced, treatment-influenced disease stages.

Discussion/conclusion

Current data suggest that PD should not be considered as a motor disorder only. In addition to the motor symptoms, the prevalence of NPS in PD is high even in the early, untreated

phases of the disease and is associated with reduced quality of life of patients, increased disability, greater caregiver burden, and higher treatment costs. The most frequent NPS in the untreated phase of PD are those of depression, cognitive impairment, and sleep disturbances. The high heterogeneity of PD and the current descriptions of specific NMS-dominant phenotypes in the early, untreated phase of the disease support the idea of nonmotor subtyping. This may be challenging as PD subtypes are unlikely to be apparent, and there is considerable possibility that these subtypes will overlap throughout the course of the disease and are likely to be present only in a proportion of patients. Identification of such subtypes may ensure that NMS are not missed and may have important implications on the development of subtype-specific therapies. It is still unclear to what extent the etiology of NPS is a result of psychosocial stress factors, the neurodegenerative process of PD itself, or complications of DRT. It seems evident that NPS in PD are most likely multifactorial in origin, the contribution of these factors may differ across disease stages and it is highly influenced by DRT. Several but not all NPS are more common in untreated, newly diagnosed patients with PD compared to the general population, but they also remain relatively stable in the early stages of the disease. In contrast, initiation of DRT and disease progression is associated with increasing frequency of several NPS (Table 1). The prevalence and onset of NPS relative to the manifestation of first PD motor symptoms are not well characterized. Assessing the onset of NPS and NMS in general in the premotor phase is difficult because few patients can report them with sufficient precision. It is usually difficult for subjects to remember whether they had some specific symptoms. Therefore, data cannot be assumed to be entirely exact in this regard. It is uncertain to what extent NPS and cognitive impairment are the result of the widely distributed neurodegenerative process itself, psychological and clinical factors, or the complication of DRT. Undeniably, the contribution of each factor is probable resulting from a number of simultaneous processes throughout the course of the disease. The early and routine screening for a range of prevalent NPS and their related factors is important to initiate optimal treatment. Therefore, close collaboration and a multidisciplinary, personalized care are needed for the effective treatment of patients with PD. Relatively little is known about the clinical course and prognostic significance of NPS and cognitive impairment in PD; therefore, further studies are needed to better understand NPS and cognition in PD soon after the diagnosis and before DRT introduction.

Table 1 Reported prevalence of NPS in various phases of PD

NPS	Overall in PD (%)	Untreated premotor phase of PD (%)	Untreated motor phase of PD (%)
Apathy	17–50	24–50	12–30
Depression	35	24–68	28
Anxiety	34–65	13	16–25
ICD	8–43	No data	17–18
Psychosis	17–72	33	30
Sleep disturbances	75	17–52	59
Cognitive impairment	25–80	26–60	10–40

Abbreviations: ICD, impulse control disorder; NPS, neuropsychiatric symptoms; PD, Parkinson's disease.

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References

1. Aarsland D, Larsen JP, Lim NG, et al. Range of neuropsychiatric disturbances in patients with Parkinson's disease. *J Neurol Neurosurg Psychiatry*. 1999;67(4):492–496.
2. Sauerbier A, Jenner P, Todorova A, Chaudhuri KR. Non motor subtypes and Parkinson's disease. *Parkinsonism Relat Disord*. 2016; 22(suppl 1):S41–S46.
3. Aarsland D, Bronnick K, Alves G, et al. The spectrum of neuropsychiatric symptoms in patients with early untreated Parkinson's disease. *J Neurol Neurosurg Psychiatry*. 2009;80(8):928–930.
4. Taylor AE, Saint-Cyr JA. Depression in Parkinson's disease: reconciling physiological and psychological perspectives. *J Neuropsychiatry Clin Neurosci*. 1990;2(1):92–98.
5. Weintraub D. Neuropsychiatric symptoms in Parkinson disease and dementia with Lewy bodies: what geriatric psychiatry can learn. *Am J Geriatr Psychiatry*. 2013;21(6):497–500.
6. Weintraub D, Stern MB. Psychiatric complications in Parkinson disease. *Am J Geriatr Psychiatry*. 2005;13(10):844–851.
7. Weintraub D, Moberg PJ, Duda JE, Katz IR, Stern MB. Effect of psychiatric and other nonmotor symptoms on disability in Parkinson's disease. *J Am Geriatr Soc*. 2004;52(5):784–788.
8. Marsh L, Berk A. Neuropsychiatric aspects of Parkinson's disease: recent advances. *Curr Psychiatry Rep*. 2003;5(1):68–76.
9. Global Parkinson's Disease Survey Steering Committee. Factors impacting on quality of life in Parkinson's disease: results from an international survey. *Mov Disord*. 2002;17(1):60–67.
10. Schrag A, Jahanshahi M, Quinn N. What contributes to quality of life in patients with Parkinson's disease? *J Neurol Neurosurg Psychiatry*. 2000; 69(3):308–312.

11. Findley L, Aujla M, Bain PG, et al. Direct economic impact of Parkinson's disease: a research survey in the United Kingdom. *Mov Disord*. 2003; 18(10):1139–1145.
12. Pressley JC, Louis ED, Tang MX, et al. The impact of comorbid disease and injuries on resource use and expenditures in parkinsonism. *Neurology*. 2003;60(1):87–93.
13. Dobkin RD, Rubino JT, Friedman J, Allen LA, Gara MA, Menza M. Barriers to mental health care utilization in Parkinson's disease. *J Geriatr Psychiatry Neurol*. 2013;26(2):105–116.
14. Weintraub D, Moberg PJ, Duda JE, Katz IR, Stern MB. Recognition and treatment of depression in Parkinson's disease. *J Geriatr Psychiatry Neurol*. 2003;16(3):178–183.
15. Chaudhuri KR, Schapira AH. Non-motor symptoms of Parkinson's disease: dopaminergic pathophysiology and treatment. *Lancet Neurol*. 2009;8(5):464–474.
16. Sauerbier A, Ray Chaudhuri K. Non-motor symptoms: the core of multi-morbid Parkinson's disease. *Br J Hosp Med (Lond)*. 2014;75(1): 18–24.
17. Ishihara L, Brayne C. A systematic review of depression and mental illness preceding Parkinson's disease. *Acta Neurol Scand*. 2006;113(4): 211–220.
18. Shiba M, Bower JH, Maraganore DM, et al. Anxiety disorders and depressive disorders preceding Parkinson's disease: a case-control study. *Mov Disord*. 2000;15(4):669–677.
19. Bower JH, Grossardt BR, Maraganore DM, et al. Anxious personality predicts an increased risk of Parkinson's disease. *Mov Disord*. 2010; 25(13):2105–2113.
20. Weintraub D, Koester J, Potenza MN, et al. Impulse control disorders in Parkinson disease: a cross-sectional study of 3090 patients. *Arch Neurol*. 2010;67(5):589–595.
21. Burn DJ, Troster AI. Neuropsychiatric complications of medical and surgical therapies for Parkinson's disease. *J Geriatr Psychiatry Neurol*. 2004;17(3):172–180.
22. Marin RS. Apathy: a neuropsychiatric syndrome. *J Neuropsychiatry Clin Neurosci*. 1991;3(3):243–254.
23. Robert G, Le Jeune F, Lozachmeur C, et al. Apathy in patients with Parkinson disease without dementia or depression: a PET study. *Neurology*. 2012;79(11):1155–1160.
24. Reijnders JS, Scholtissen B, Weber WE, Aalten P, Verhey FR, Leentjens AF. Neuroanatomical correlates of apathy in Parkinson's disease: a magnetic resonance imaging study using voxel-based morphometry. *Mov Disord*. 2010;25(14):2318–2325.
25. Santangelo G, Vitale C, Picillo M, et al. Apathy and striatal dopamine transporter levels in de-novo, untreated Parkinson's disease patients. *Parkinsonism Relat Disord*. 2015;21(5):489–493.
26. Thobois S, Maillet A, Metereau E, Krack LP. Motor and nonmotor symptoms in drug-naive de novo parkinsonian patients and their relationship to dopaminergic and serotonergic lesions. *Mov Disord*. 2015; 30(suppl 1):58.
27. Aarsland D, Marsh L, Schrag A. Neuropsychiatric symptoms in Parkinson's disease. *Mov Disord*. 2009;24(15):2175–2186.
28. Pedersen KF, Alves G, Bronnick K, Aarsland D, Tysnes OB, Larsen JP. Apathy in drug-naive patients with incident Parkinson's disease: the Norwegian ParkWest study. *J Neurol*. 2010;257(2):217–223.
29. Erro R, Picillo M, Vitale C, et al. Non-motor symptoms in early Parkinson's disease: a 2-year follow-up study on previously untreated patients. *J Neurol Neurosurg Psychiatry*. 2013;84(1):14–17.
30. Dujardin K, Langlois C, Plomhause L, et al. Apathy in untreated early-stage Parkinson disease: relationship with other non-motor symptoms. *Mov Disord*. 2014;29(14):1796–1801.
31. Santangelo G, Vitale C, Trojano L, et al. Relationship between apathy and cognitive dysfunctions in de novo untreated Parkinson's disease: a prospective longitudinal study. *Eur J Neurol*. 2015;22(2):253–260.
32. Santangelo G, Barone P, Cuoco S, et al. Apathy in untreated, de novo patients with Parkinson's disease: validation study of Apathy Evaluation Scale. *J Neurol*. 2014;261(12):2319–2328.
33. Starkstein SE, Merello M, Jorge R, Brockman S, Bruce D, Power B. The syndromal validity and nosological position of apathy in Parkinson's disease. *Mov Disord*. 2009;24(8):1211–1216.
34. Dujardin K, Sockeel P, Devos D, et al. Characteristics of apathy in Parkinson's disease. *Mov Disord*. 2007;22(6):778–784.
35. Drijgers RL, Dujardin K, Reijnders JS, Defebvre L, Leentjens AF. Validation of diagnostic criteria for apathy in Parkinson's disease. *Parkinsonism Relat Disord*. 2010;16(10):656–660.
36. Pedersen KF, Larsen JP, Alves G, Aarsland D. Prevalence and clinical correlates of apathy in Parkinson's disease: a community-based study. *Parkinsonism Relat Disord*. 2009;15(4):295–299.
37. Pont-Sunyer C, Hotter A, Gaig C, et al. The onset of nonmotor symptoms in Parkinson's disease (the ONSET PD study). *Mov Disord*. 2015;30(2):229–237.
38. Gaenslen A, Swid I, Liepelt-Scarfone I, Godau J, Berg D. The patients' perception of prodromal symptoms before the initial diagnosis of Parkinson's disease. *Mov Disord*. 2011;26(4):653–658.
39. Santangelo G, Trojano L, Barone P, Errico D, Grossi D, Vitale C. Apathy in Parkinson's disease: diagnosis, neuropsychological correlates, pathophysiology and treatment. *Behav Neurol*. 2013;27(4):501–513.
40. Starkstein SE. Apathy in Parkinson's disease: diagnostic and etiological dilemmas. *Mov Disord*. 2012;27(2):174–178.
41. den Brok MG, van Dalen JW, van Gool WA, Moll van Charante EP, de Bie RM, Richard E. Apathy in Parkinson's disease: a systematic review and meta-analysis. *Mov Disord*. 2015;30(6):759–769.
42. Gerritsen DL, Jongenelis K, Steverink N, Ooms ME, Ribbe MW. Down and drowsy? Do apathetic nursing home residents experience low quality of life? *Aging Ment Health*. 2005;9(2):135–141.
43. Aarsland D, Bronnick K, Ehrt U, et al. Neuropsychiatric symptoms in patients with Parkinson's disease and dementia: frequency, profile and associated care giver stress. *J Neurol Neurosurg Psychiatry*. 2007; 78(1):36–42.
44. Leroi I, Harbishettar V, Andrews M, McDonald K, Byrne EJ, Burns A. Carer burden in apathy and impulse control disorders in Parkinson's disease. *Int J Geriatr Psychiatry*. 2012;27(2):160–166.
45. Pluck GC, Brown RG. Apathy in Parkinson's disease. *J Neurol Neurosurg Psychiatry*. 2002;73(6):636–642.
46. Varanese S, Perfetti B, Ghilardi MF, Di Rocco A. Apathy, but not depression, reflects inefficient cognitive strategies in Parkinson's disease. *PLoS One*. 2011;6(3):e17846.
47. Skorvanek M, Rosenberger J, Gdovinova Z, et al. Apathy in elderly nondemented patients with Parkinson's disease: clinical determinants and relationship to quality of life. *J Geriatr Psychiatry Neurol*. 2013; 26(4):237–243.
48. Oguru M, Tachibana H, Toda K, Okuda B, Oka N. Apathy and depression in Parkinson disease. *J Geriatr Psychiatry Neurol*. 2010; 23(1):35–41.
49. Rodriguez-Violante M, Gonzalez-Latapi P, Cervantes-Arriaga A, Martinez-Ramirez D, Velazquez-Osuna S, Camacho-Ordonez A. Apathy and associated factors in Mexican patients with Parkinson's disease. *Neurol Sci*. 2014;35(5):729–734.
50. Pedersen KF, Alves G, Aarsland D, Larsen JP. Occurrence and risk factors for apathy in Parkinson disease: a 4-year prospective longitudinal study. *J Neurol Neurosurg Psychiatry*. 2009;80(11):1279–1282.
51. APA. *Diagnostic and Statistical Manual of Mental Disorders, Fifth Edition (DSM-5)*. Arlington, VA: APA; 2013.
52. Ehmann TS, Beninger RJ, Gawel MJ, Riopelle RJ. Depressive symptoms in Parkinson's disease: a comparison with disabled control subjects. *J Geriatr Psychiatry Neurol*. 1990;3(1):3–9.
53. van Mierlo TJ, Chung C, Foncke EM, Berendse HW, van den Heuvel OA. Depressive symptoms in Parkinson's disease are related to decreased hippocampus and amygdala volume. *Mov Disord*. 2015;30(2):245–252.
54. Surdhar I, Gee M, Bouchard T, Coupland N, Malykhin N, Camicioli R. Intact limbic-prefrontal connections and reduced amygdala volumes in Parkinson's disease with mild depressive symptoms. *Parkinsonism Relat Disord*. 2012;18(7):809–813.

55. Huang C, Ravdin LD, Nirenberg MJ, et al. Neuroimaging markers of motor and nonmotor features of Parkinson's disease: an [18F]fluorodeoxyglucose positron emission computed tomography study. *Dement Geriatr Cogn Disord*. 2013;35(3–4):183–196.
56. Ring HA, Bench CJ, Trimble MR, Brooks DJ, Frackowiak RS, Dolan RJ. Depression in Parkinson's disease. A positron emission study. *Br J Psychiatry*. 1994;165(3):333–339.
57. Sheng K, Fang W, Su M, et al. Altered spontaneous brain activity in patients with Parkinson's disease accompanied by depressive symptoms, as revealed by regional homogeneity and functional connectivity in the prefrontal-limbic system. *PLoS One*. 2014;9(1):e84705.
58. Hu X, Song X, Yuan Y, et al. Abnormal functional connectivity of the amygdala is associated with depression in Parkinson's disease. *Mov Disord*. 2015;30(2):238–244.
59. Feldmann A, Illes Z, Kosztolanyi P, et al. Morphometric changes of gray matter in Parkinson's disease with depression: a voxel-based morphometry study. *Mov Disord*. 2008;23(1):42–46.
60. Kostić VS, Agosta F, Petrović I, et al. Regional patterns of brain tissue loss associated with depression in Parkinson disease. *Neurology*. 2010;75(10):857–863.
61. Matsui H, Nishinaka K, Oda M, et al. Depression in Parkinson's disease. Diffusion tensor imaging study. *J Neurol*. 2007;254(9):1170–1173.
62. Aarsland D, Pahlhagen S, Ballard CG, Ehrt U, Svenningsson P. Depression in Parkinson disease – epidemiology, mechanisms and management. *Nat Rev Neurol*. 2011;8(1):35–47.
63. Shen CC, Tsai SJ, Perng CL, Kuo BI, Yang AC. Risk of Parkinson disease after depression: a nationwide population-based study. *Neurology*. 2013;81(17):1538–1544.
64. Fang F, Xu Q, Park Y, et al. Depression and the subsequent risk of Parkinson's disease in the NIH-AARP Diet and Health Study. *Mov Disord*. 2010;25(9):1157–1162.
65. Schuurman AG, van den Akker M, Ensinck KT, et al. Increased risk of Parkinson's disease after depression: a retrospective cohort study. *Neurology*. 2002;58(10):1501–1504.
66. Jacob EL, Gatto NM, Thompson A, Bordelon Y, Ritz B. Occurrence of depression and anxiety prior to Parkinson's disease. *Parkinsonism Relat Disord*. 2010;16(9):576–581.
67. Reijnders JS, Ehrt U, Weber WE, Aarsland D, Leentjens AF. A systematic review of prevalence studies of depression in Parkinson's disease. *Mov Disord*. 2008;23(2):183–189. quiz 313.
68. Ravina B, Camicioli R, Como PG, et al. The impact of depressive symptoms in early Parkinson disease. *Neurology*. 2007;69(4):342–347.
69. Riedel O, Klotsche J, Spottke A, et al. Frequency of dementia, depression, and other neuropsychiatric symptoms in 1,449 outpatients with Parkinson's disease. *J Neurol*. 2010;257(7):1073–1082.
70. Wichowicz HM, Slawek J, Derejko M, Cubala WJ. Factors associated with depression in Parkinson's disease: a cross-sectional study in a Polish population. *Eur Psychiatry*. 2006;21(8):516–520.
71. Starkstein SE, Preziosi TJ, Bolduc PL, Robinson RG. Depression in Parkinson's disease. *J Nerv Ment Dis*. 1990;178(1):27–31.
72. Starkstein SE, Petracca G, Chemerinski E, et al. Depression in classic versus akinetic-rigid Parkinson's disease. *Mov Disord*. 1998;13(1):29–33.
73. Marsh L, Williams JR, Rocco M, Grill S, Munro C, Dawson TM. Psychiatric comorbidities in patients with Parkinson disease and psychosis. *Neurology*. 2004;63(2):293–300.
74. Chen JJ, Marsh L. Depression in Parkinson's disease: identification and management. *Pharmacotherapy*. 2013;33(9):972–983.
75. Krishnan PR, Bhatia M, Behari M. Restless legs syndrome in Parkinson's disease: a case-controlled study. *Mov Disord*. 2003;18(2):181–185.
76. Tandberg E, Larsen JP, Karlsen K. A community-based study of sleep disorders in patients with Parkinson's disease. *Mov Disord*. 1998;13(6):895–899.
77. Happe S, Berger K; FAQT Study Investigators. The association between caregiver burden and sleep disturbances in partners of patients with Parkinson's disease. *Age Ageing*. 2002;31(5):349–354.
78. Tandberg E, Larsen JP, Aarsland D, Laake K, Cummings JL. Risk factors for depression in Parkinson disease. *Arch Neurol*. 1997;54(5):625–630.
79. Rojo A, Aguilar M, Garolera MT, Cubo E, Navas I, Quintana S. Depression in Parkinson's disease: clinical correlates and outcome. *Parkinsonism Relat Disord*. 2003;10(1):23–28.
80. Muller B, Assmus J, Herlofson K, Larsen JP, Tysnes OB. Importance of motor vs. non-motor symptoms for health-related quality of life in early Parkinson's disease. *Parkinsonism Relat Disord*. 2013;19(11):1027–1032.
81. Starkstein SE, Mayberg HS, Leiguarda R, Preziosi TJ, Robinson RG. A prospective longitudinal study of depression, cognitive decline, and physical impairments in patients with Parkinson's disease. *J Neurol Neurosurg Psychiatry*. 1992;55(5):377–382.
82. Starkstein SE, Merello M, Jorge R, et al. A validation study of depressive syndromes in Parkinson's disease. *Mov Disord*. 2008;23(4):538–546.
83. Aarsland D, Taylor JP, Weintraub D. Psychiatric issues in cognitive impairment. *Mov Disord*. 2014;29(5):651–662.
84. Weintraub D, Newberg AB, Cary MS, et al. Striatal dopamine transporter imaging correlates with anxiety and depression symptoms in Parkinson's disease. *J Nucl Med*. 2005;46(2):227–232.
85. Moriyama TS, Felicio AC, Chagas MH, et al. Increased dopamine transporter density in Parkinson's disease patients with Social Anxiety Disorder. *J Neurol Sci*. 2011;310(1–2):53–57.
86. Erro R, Pappata S, Amboni M, et al. Anxiety is associated with striatal dopamine transporter availability in newly diagnosed untreated Parkinson's disease patients. *Parkinsonism Relat Disord*. 2012;18(9):1034–1038.
87. Vriend C, Boedhoe PS, Rutten S, Berendse HW, van der Werf YD, van den Heuvel OA. A smaller amygdala is associated with anxiety in Parkinson's disease: a combined FreeSurfer-VBM study. *J Neurol Neurosurg Psychiatry*. 2016;87(5):493–500.
88. Lin CH, Lin JW, Liu YC, Chang CH, Wu RM. Risk of Parkinson's disease following anxiety disorders: a nationwide population-based cohort study. *Eur J Neurol*. 2015;22(9):1280–1287.
89. Leentjens AF, Dujardin K, Marsh L, Martinez-Martin P, Richard IH, Starkstein SE. Symptomatology and markers of anxiety disorders in Parkinson's disease: a cross-sectional study. *Mov Disord*. 2011;26(3):484–492.
90. Martinez-Martin P, Rodriguez-Blazquez C, Forjaz MJ, et al. Neuropsychiatric symptoms and caregiver's burden in Parkinson's disease. *Parkinsonism Relat Disord*. 2015;21(6):629–634.
91. Rutten S, Ghielen I, Vriend C, et al. Anxiety in Parkinson's disease: symptom dimensions and overlap with depression and autonomic failure. *Parkinsonism Relat Disord*. 2015;21(3):189–193.
92. Pontone GM, Williams JR, Anderson KE, et al. Prevalence of anxiety disorders and anxiety subtypes in patients with Parkinson's disease. *Mov Disord*. 2009;24(9):1333–1338.
93. Weintraub D, Simuni T, Caspell-Garcia C, et al. Cognitive performance and neuropsychiatric symptoms in early, untreated Parkinson's disease. *Mov Disord*. 2015;30(7):919–927.
94. Leentjens AF, Dujardin K, Marsh L, et al. Anxiety rating scales in Parkinson's disease: critique and recommendations. *Mov Disord*. 2008;23(14):2015–2025.
95. Dissanayaka NN, Sellbach A, Matheson S, et al. Anxiety disorders in Parkinson's disease: prevalence and risk factors. *Mov Disord*. 2010;25(7):838–845.
96. Negre-Pages L, Grandjean H, Lapeyre-Mestre M, et al; DoPaMiP Study Group. Anxious and depressive symptoms in Parkinson's disease: the French cross-sectionnal DoPaMiP study. *Mov Disord*. 2010;25(2):157–166.
97. Brown RG, Landau S, Hindle JV, et al; PROMS-PD Study Group. Depression and anxiety related subtypes in Parkinson's disease. *J Neurol Neurosurg Psychiatry*. 2011;82(7):803–809.
98. Pontone GM, Williams JR, Anderson KE, et al. Anxiety and self-perceived health status in Parkinson's disease. *Parkinsonism Relat Disord*. 2011;17(4):249–254.

99. Voon V, Mehta AR, Hallett M. Impulse control disorders in Parkinson's disease: recent advances. *Curr Opin Neurol*. 2011;24(4):324–330.
100. Vilas D, Pont-Sunyer C, Tolosa E. Impulse control disorders in Parkinson's disease. *Parkinsonism Relat Disord*. 2012;18(suppl 1): S80–S84.
101. Morrish PK, Sawle GV, Brooks DJ. Regional changes in [18F]dopa metabolism in the striatum in Parkinson's disease. *Brain*. 1996;119(pt 6): 2097–2103.
102. Cools R, Barker RA, Sahakian BJ, Robbins TW. L-Dopa medication remediates cognitive inflexibility, but increases impulsivity in patients with Parkinson's disease. *Neuropsychologia*. 2003;41(11): 1431–1441.
103. Braak H, Ghebremedhin E, Rub U, Bratzke H, Del Tredici K. Stages in the development of Parkinson's disease-related pathology. *Cell Tissue Res*. 2004;318(1):121–134.
104. Steeves TD, Miyasaki J, Zurowski M, et al. Increased striatal dopamine release in Parkinsonian patients with pathological gambling: a [11C] raclopride PET study. *Brain*. 2009;132(pt 5):1376–1385.
105. Cilia R, Cho SS, van Eimeren T, et al. Pathological gambling in patients with Parkinson's disease is associated with fronto-striatal disconnection: a path modeling analysis. *Mov Disord*. 2011;26(2):225–233.
106. Biundo R, Formento-Dojot P, Facchini S, et al. Brain volume changes in Parkinson's disease and their relationship with cognitive and behavioural abnormalities. *J Neurol Sci*. 2011;310(1–2):64–69.
107. Vriend C, Nordbeck AH, Booij J, et al. Reduced dopamine transporter binding predates impulse control disorders in Parkinson's disease. *Mov Disord*. 2014;29(7):904–911.
108. Balarajah S, Cavanna AE. The pathophysiology of impulse control disorders in Parkinson disease. *Behav Neurol*. 2013;26(4):237–244.
109. Weintraub D, Siderowf AD, Potenza MN, et al. Association of dopamine agonist use with impulse control disorders in Parkinson disease. *Arch Neurol*. 2006;63(7):969–973.
110. Weintraub D, Sohr M, Potenza MN, et al. Amantadine use associated with impulse control disorders in Parkinson disease in cross-sectional study. *Ann Neurol*. 2010;68(6):963–968.
111. Poletti M, Logi C, Lucetti C, et al. A single-center, cross-sectional prevalence study of impulse control disorders in Parkinson disease: association with dopaminergic drugs. *J Clin Psychopharmacol*. 2013;33(5): 691–694.
112. Callesen MB, Weintraub D, Damholdt MF, Moller A. Impulsive and compulsive behaviors among Danish patients with Parkinson's disease: prevalence, depression, and personality. *Parkinsonism Relat Disord*. 2014;20(1):22–26.
113. Weintraub D, Papay K, Siderowf A; Parkinson's Progression Markers Initiative. Screening for impulse control symptoms in patients with de novo Parkinson disease: a case-control study. *Neurology*. 2013;80(2): 176–180.
114. Antonini A, Siri C, Santangelo G, et al. Impulsivity and compulsivity in drug-naive patients with Parkinson's disease. *Mov Disord*. 2011; 26(3):464–468.
115. Valenca GT, Glass PG, Negreiros NN, et al. Past smoking and current dopamine agonist use show an independent and dose-dependent association with impulse control disorders in Parkinson's disease. *Parkinsonism Relat Disord*. 2013;19(7):698–700.
116. Bastiaens J, Dorfman BJ, Christos PJ, Nirenberg MJ. Prospective cohort study of impulse control disorders in Parkinson's disease. *Mov Disord*. 2013;28(3):327–333.
117. Voon V, Sohr M, Lang AE, et al. Impulse control disorders in Parkinson disease: a multicenter case – control study. *Ann Neurol*. 2011;69(6): 986–996.
118. Weintraub D, Hoops S, Shea JA, et al. Validation of the questionnaire for impulsive-compulsive disorders in Parkinson's disease. *Mov Disord*. 2009;24(10):1461–1467.
119. Probst CC, Winter LM, Moller B, et al. Validation of the questionnaire for impulsive-compulsive disorders in Parkinson's disease (QUIP) and the QUIP-rating scale in a German speaking sample. *J Neurol*. 2014; 261(5):936–942.
120. Rabinak CA, Nirenberg MJ. Dopamine agonist withdrawal syndrome in Parkinson disease. *Arch Neurol*. 2010;67(1):58–63.
121. Cunnington AL, White L, Hood K. Identification of possible risk factors for the development of dopamine agonist withdrawal syndrome in Parkinson's disease. *Parkinsonism Relat Disord*. 2012;18(9): 1051–1052.
122. Fenelon G, Alves G. Epidemiology of psychosis in Parkinson's disease. *J Neurol Sci*. 2010;289(1–2):12–17.
123. Goetz CG, Fan W, Leurgans S, Bernard B, Stebbins GT. The malignant course of "benign hallucinations" in Parkinson disease. *Arch Neurol*. 2006;63(5):713–716.
124. Goetz CG, Stebbins GT. Mortality and hallucinations in nursing home patients with advanced Parkinson's disease. *Neurology*. 1995; 45(4):669–671.
125. Factor SA, Molho ES, Podskalny GD, Brown D. Parkinson's disease: drug-induced psychiatric states. *Adv Neurol*. 1995;65:115–138.
126. Williams DR, Lees AJ. Visual hallucinations in the diagnosis of idiopathic Parkinson's disease: a retrospective autopsy study. *Lancet Neurol*. 2005;4(10):605–610.
127. Harding AJ, Broe GA, Halliday GM. Visual hallucinations in Lewy body disease relate to Lewy bodies in the temporal lobe. *Brain*. 2002; 125(pt 2):391–403.
128. Shin S, Lee JE, Hong JY, Sunwoo MK, Sohn YH, Lee PH. Neuroanatomical substrates of visual hallucinations in patients with nondemented Parkinson's disease. *J Neurol Neurosurg Psychiatry*. 2012; 83(12):1155–1161.
129. Oishi N, Udaka F, Kameyama M, Sawamoto N, Hashikawa K, Fukuyama H. Regional cerebral blood flow in Parkinson disease with nonpsychotic visual hallucinations. *Neurology*. 2005;65(11): 1708–1715.
130. Gama RL, Bruin VM, Tavora DG, Duran FL, Bittencourt L, Tufik S. Structural brain abnormalities in patients with Parkinson's disease with visual hallucinations: a comparative voxel-based analysis. *Brain Cogn*. 2014;87:97–103.
131. Nagano-Saito A, Washimi Y, Arahata Y, et al. Visual hallucination in Parkinson's disease with FDG PET. *Mov Disord*. 2004;19(7): 801–806.
132. Ramirez-Ruiz B, Marti MJ, Tolosa E, et al. Brain response to complex visual stimuli in Parkinson's patients with hallucinations: a functional magnetic resonance imaging study. *Mov Disord*. 2008; 23(16):2335–2343.
133. Watanabe H, Senda J, Kato S, et al. Cortical and subcortical brain atrophy in Parkinson's disease with visual hallucination. *Mov Disord*. 2013;28(12):1732–1736.
134. Pagonabarraga J, Soriano-Mas C, Llebaria G, Lopez-Sola M, Pujol J, Kulisevsky J. Neural correlates of minor hallucinations in non-demented patients with Parkinson's disease. *Parkinsonism Relat Disord*. 2014; 20(3):290–296.
135. Ballanger B, Strafella AP, van Eimeren T, et al. Serotonin 2A receptors and visual hallucinations in Parkinson disease. *Arch Neurol*. 2010; 67(4):416–421.
136. Fenelon G, Goetz CG, Karenberg A. Hallucinations in Parkinson disease in the prelevodopa era. *Neurology*. 2006;66(1):93–98.
137. Fenelon G, Soulas T, Zenasni F, Cleret de Langavant L. The changing face of Parkinson's disease-associated psychosis: a cross-sectional study based on the new NINDS-NIMH criteria. *Mov Disord*. 2010; 25(6):763–766.
138. Fenelon G, Soulas T, Cleret de Langavant L, Trinkler I, Bachoud-Levi AC. Feeling of presence in Parkinson's disease. *J Neurol Neurosurg Psychiatry*. 2011;82(11):1219–1224.
139. Pagonabarraga J, Martinez-Horta S, Fernandez de Bobadilla R, et al. Minor hallucinations occur in drug-naive Parkinson's disease patients, even from the premotor phase. *Mov Disord*. 2016;31(1):45–52.
140. Morgante L, Colosimo C, Antonini A, et al; PRIAMO Study Group. Psychosis associated to Parkinson's disease in the early stages: relevance of cognitive decline and depression. *J Neurol Neurosurg Psychiatry*. 2012;83(1):76–82.

141. Pacchetti C, Manni R, Zangaglia R, et al. Relationship between hallucinations, delusions, and rapid eye movement sleep behavior disorder in Parkinson's disease. *Mov Disord*. 2005;20(11):1439–1448.
142. Fernandez HH, Aarsland D, Fenelon G, et al. Scales to assess psychosis in Parkinson's disease: critique and recommendations. *Mov Disord*. 2008;23(4):484–500.
143. Aarsland D, Larsen JP, Cummins JL, Laake K. Prevalence and clinical correlates of psychotic symptoms in Parkinson disease: a community-based study. *Arch Neurol*. 1999;56(5):595–601.
144. Schrempf W, Brandt MD, Storch A, Reichmann H. Sleep disorders in Parkinson's disease. *J Parkinsons Dis*. 2014;4(2):211–221.
145. Grinberg LT, Rueb U, Alho AT, Heinsen H. Brainstem pathology and non-motor symptoms in PD. *J Neurol Sci*. 2010;289(1–2):81–88.
146. Iranzo A, Molinuevo JL, Santamaria J, et al. Rapid-eye-movement sleep behaviour disorder as an early marker for a neurodegenerative disorder: a descriptive study. *Lancet Neurol*. 2006;5(7):572–577.
147. Kim YK, Yoon IY, Kim JM, et al. The implication of nigrostriatal dopaminergic degeneration in the pathogenesis of REM sleep behavior disorder. *Eur J Neurol*. 2010;17(3):487–492.
148. Arnulf I, Konofal E, Merino-Andreu M, et al. Parkinson's disease and sleepiness: an integral part of PD. *Neurology*. 2002;58(7):1019–1024.
149. Rye DB, Jankovic J. Emerging views of dopamine in modulating sleep/wake state from an unlikely source: PD. *Neurology*. 2002;58(3):341–346.
150. Abbott RD, Ross GW, White LR, et al. Excessive daytime sleepiness and subsequent development of Parkinson disease. *Neurology*. 2005;65(9):1442–1446.
151. Postuma RB, Gagnon JF, Vendette M, Montplaisir JY. Idiopathic REM sleep behavior disorder in the transition to degenerative disease. *Mov Disord*. 2009;24(15):2225–2232.
152. Szatmari S Jr, Bereczki D, Fornadi K, Kalantar-Zadeh K, Kovesdy CP, Molnar MZ. Association of restless legs syndrome with incident Parkinson disease. *Sleep*. Epub 2016 Nov 28. Accepted for publication.
153. Garcia-Borreguero D, Larrosa O, Bravo M. Parkinson's disease and sleep. *Sleep Med Rev*. 2003;7(2):115–129.
154. dos Santos AB, Kohlmeier KA, Barreto GE. Are sleep disturbances preclinical markers of Parkinson's disease? *Neurochem Res*. 2015;40(3):421–427.
155. Buskova J, Klempir J, Majerova V, et al. Sleep disturbances in untreated Parkinson's disease. *J Neurol*. 2011;258(12):2254–2259.
156. Dhawan V, Dhoat S, Williams AJ, et al. The range and nature of sleep dysfunction in untreated Parkinson's disease (PD). A comparative controlled clinical study using the Parkinson's disease sleep scale and selective polysomnography. *J Neurol Sci*. 2006;248(1–2):158–162.
157. Gjerstad MD, Wentzel-Larsen T, Aarsland D, Larsen JP. Insomnia in Parkinson's disease: frequency and progression over time. *J Neurol Neurosurg Psychiatry*. 2007;78(5):476–479.
158. Happe S, Berger K; FAQT Study Investigators. The association of dopamine agonists with daytime sleepiness, sleep problems and quality of life in patients with Parkinson's disease – a prospective study. *J Neurol*. 2001;248(12):1062–1067.
159. Onofrj M, Thomas A, D'Andreamatteo G, et al. Incidence of RBD and hallucination in patients affected by Parkinson's disease: 8-year follow-up. *Neurol Sci*. 2002;23(suppl 2):S91–S94.
160. Goetz CG, Wuu J, Curgian LM, Leurgans S. Hallucinations and sleep disorders in PD: six-year prospective longitudinal study. *Neurology*. 2005;64(1):81–86.
161. Larsen JP, Tandberg E. Sleep disorders in patients with Parkinson's disease: epidemiology and management. *CNS Drugs*. 2001;15(4):267–275.
162. Prudon B, Duncan GW, Khoo TK, Yarnall AJ, Anderson KN. Primary sleep disorder prevalence in patients with newly diagnosed Parkinson's disease. *Mov Disord*. 2014;29(2):259–262.
163. Gjerstad MD, Boeve B, Wentzel-Larsen T, Aarsland D, Larsen JP. Occurrence and clinical correlates of REM sleep behaviour disorder in patients with Parkinson's disease over time. *J Neurol Neurosurg Psychiatry*. 2008;79(4):387–391.
164. Zhang H, Gu Z, An J, Wang C, Chan P. Non-motor symptoms in treated and untreated Chinese patients with early Parkinson's disease. *Tohoku J Exp Med*. 2014;232(2):129–136.
165. Martinez-Martin P. Nonmotor symptoms and health-related quality of life in early Parkinson's disease. *Mov Disord*. 2014;29(2):166–168.
166. Chaudhuri KR, Pal S, DiMarco A, et al. The Parkinson's disease sleep scale: a new instrument for assessing sleep and nocturnal disability in Parkinson's disease. *J Neurol Neurosurg Psychiatry*. 2002;73(6):629–635.
167. Martinez-Martin P, Salvador C, Menendez-Guisasola L, et al. Parkinson's Disease Sleep Scale: validation study of a Spanish version. *Mov Disord*. 2004;19(10):1226–1232.
168. Vendette M, Gagnon JF, Decary A, et al. REM sleep behavior disorder predicts cognitive impairment in Parkinson disease without dementia. *Neurology*. 2007;69(19):1843–1849.
169. Williams-Gray CH, Foltynie T, Brayne CE, Robbins TW, Barker RA. Evolution of cognitive dysfunction in an incident Parkinson's disease cohort. *Brain*. 2007;130(pt 7):1787–1798.
170. Boot BP, Boeve BF, Roberts RO, et al. Probable rapid eye movement sleep behavior disorder increases risk for mild cognitive impairment and Parkinson disease: a population-based study. *Ann Neurol*. 2012;71(1):49–56.
171. Baba T, Kikuchi A, Hirayama K, et al. Severe olfactory dysfunction is a prodromal symptom of dementia associated with Parkinson's disease: a 3 year longitudinal study. *Brain*. 2012;135(pt 1):161–169.
172. Alves G, Larsen JP, Emre M, Wentzel-Larsen T, Aarsland D. Changes in motor subtype and risk for incident dementia in Parkinson's disease. *Mov Disord*. 2006;21(8):1123–1130.
173. Sanchez-Ferro A, Benito-Leon J, Louis ED, et al. Rate of cognitive decline in premotor Parkinson's disease: a prospective study (NEDICES). *Mov Disord*. 2013;28(2):161–168.
174. Sanchez-Ferro A, Benito-Leon J, Mitchell AJ, et al. Premotor cognitive status in a cohort of incident Parkinson disease patients (NEDICES). *J Neurol Sci*. 2011;310(1–2):211–215.
175. Aarsland D, Bronnick K, Williams-Gray C, et al. Mild cognitive impairment in Parkinson disease: a multicenter pooled analysis. *Neurology*. 2010;75(12):1062–1069.
176. Aarsland D, Andersen K, Larsen JP, Lolk A, Kragh-Sorensen P. Prevalence and characteristics of dementia in Parkinson disease: an 8-year prospective study. *Arch Neurol*. 2003;60(3):387–392.
177. Aarsland D, Bronnick K, Larsen JP, Tysnes OB, Alves G; Norwegian ParkWest Study Group. Cognitive impairment in incident, untreated Parkinson disease: the Norwegian ParkWest study. *Neurology*. 2009;72(13):1121–1126.
178. Poletti M, Frosini D, Pagni C, et al. Mild cognitive impairment and cognitive-motor relationships in newly diagnosed drug-naive patients with Parkinson's disease. *J Neurol Neurosurg Psychiatry*. 2012;83(6):601–606.
179. Erro R, Santangelo G, Picillo M, et al. Link between non-motor symptoms and cognitive dysfunctions in de novo, drug-naive PD patients. *J Neurol*. 2012;259(9):1808–1813.
180. Biundo R, Weis L, Facchini S, et al. Cognitive profiling of Parkinson disease patients with mild cognitive impairment and dementia. *Parkinsonism Relat Disord*. 2014;20(4):394–399.
181. de la Riva P, Smith K, Xie SX, Weintraub D. Course of psychiatric symptoms and global cognition in early Parkinson disease. *Neurology*. 2014;83(12):1096–1103.
182. Muslimovic D, Post B, Speelman JD, Schmand B. Cognitive profile of patients with newly diagnosed Parkinson disease. *Neurology*. 2005;65(8):1239–1245.
183. Poletti M, Bonuccelli U. Impulse control disorders in Parkinson's disease: the role of personality and cognitive status. *J Neurol*. 2012;259(11):2269–2277.

184. Poletti M, De Rosa A, Bonuccelli U. Affective symptoms and cognitive functions in Parkinson's disease. *J Neurol Sci*. 2012;317(1–2):97–102.
185. Pagonabarraga J, Kulisevsky J, Llebaria G, Garcia-Sanchez C, Pascual-Sedano B, Gironell A. Parkinson's disease-cognitive rating scale: a new cognitive scale specific for Parkinson's disease. *Mov Disord*. 2008;23(7):998–1005.
186. Llebaria G, Pagonabarraga J, Kulisevsky J, et al. Cut-off score of the Mattis Dementia Rating Scale for screening dementia in Parkinson's disease. *Mov Disord*. 2008;23(11):1546–1550.
187. Barone P, Antonini A, Colosimo C, et al; PRIAMO study Group. The PRIAMO study: a multicenter assessment of nonmotor symptoms and their impact on quality of life in Parkinson's disease. *Mov Disord*. 2009;24(11):1641–1649.
188. Drijgers RL, Verhey FR, Tissingh G, van Domburg PH, Aalten P, Leentjens AF. The role of the dopaminergic system in mood, motivation and cognition in Parkinson's disease: a double blind randomized placebo-controlled experimental challenge with pramipexole and methylphenidate. *J Neurol Sci*. 2012;320(1–2):121–126.

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