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Psychiatric Issues in Cognitive Impairment

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Abstract

Neuropsychiatric symptoms (NPS) such as depression, hallucinations and apathy commonly occur in Parkinson's disease (PD) and have major clinical consequences including a negative impact on quality of life. This review discusses the epidemiology, clinical features, diagnostic procedures and treatment issues of NPS in PD and related disorders in the perspective of cognitive impairment, focusing on depression, anxiety, visual hallucinations, apathy, sleep disturbances, impulse control disorder and non-motor fluctuations. The majority of NPS are more common in PD patients with dementia, possibly related to shared underlying pathologies. Recent studies also suggest that NPS are associated with mild cognitive impairment in PD, in particular with the amnesic type. Accurate diagnosis of NPS is important but can be difficult, due to overlapping symptoms and similar appearance of symptoms of motor symptoms of parkinsonism, cognitive impairment, mood disorders and apathy. There are few systematic studies focusing on the management of NPS in PD with cognitive impairment.

Keywords

Neuropsychiatric symptoms; Parkinson's disease; cognitive impairment; depression; psychosis; anxiety; apathy

A variety of neuropsychiatric symptoms (NPS), including depression, anxiety, hallucinations, apathy, and impulse control disorders, occur in up to 60% of PD patients.¹ NPS have a significant impact on patients and their caregivers, as well as on the health care system.² However, they are underrecognized and undertreated overall,³ due to patient-related factors (e.g., incomplete understanding of mental health problems), access-to-care issues, and lack of interest and knowledge among clinicians.^{3,4}

Although little is known regarding causal factors, phenotypic variation suggests that a variety of factors contribute to NPS in PD. Some symptoms, such as depression and anxiety, are common in the elderly in general as well as in other brain diseases, whereas other symptoms are more characteristic for PD and related disorders, such as visual hallucinations, misidentification syndrome, REM-sleep behavioral disturbance (RBD), and impulse control disorders. The neuropsychiatric profile of PD thus differs from that of patients with Alzheimer's disease (AD)⁵ and even other diseases of the basal ganglia.⁶ Thus, PD-specific factors (e.g., involvement of specific brain regions and dopamine replacement therapy (DRT)), nonspecific psychological and social reactions, and genetic factors^{7,8} all seem to play a role for the development of NPS in PD.

Neuropsychiatric Symptoms and Their Association With Cognition in PD

There is evidence that the profile, frequency and severity of NPS are associated with dementia in PD (PDD). In one study, 89% of PDD patients had at least one NPS, and 60% had NPS of clinical significance.⁹ Hallucinations and comorbid symptoms were characteristic for PDD, whereas a syndrome with exclusively sleep or mood symptoms was more common in PD without dementia.¹⁰ More recently, in the large German GEPAD study with more than 1400 patients, of which 70% had at least one NPS (including dementia as a NPS), the increased frequency of psychotic symptoms in PDD compared to nondemented PD was confirmed, whereas anxiety symptoms, depression and insomnia did not differ.¹¹ In another study of 127 PDD patients, 89% had at least one NPI item with a non-zero score, the most common being anxiety, sleep problems, and apathy, all occurring in more than 50%. A slightly different combination of symptoms was found compared to the above studies, the three components identified by a principal component analysis were "depression and psychosis", "vegetative" and "frontal" symptoms.¹²

There are many possible explanations for the co-occurrence of dementia and NPS. Dementia-associated neocortical pathologies (e.g., tau, amyloid and synuclein inclusions) and neurotransmitter changes (cholinergic and monoaminergic changes in addition to dopaminergic deficits) all have been found to be associated with PDD and likely contribute to NPS as well. In addition, subjective cognitive decline may lead to anxiety and depression, and cognitive decline may influence the interpretation of various sensory stimuli, which may more easily be interpreted in a psychotic context.

Recently, NPS were also found to be more common in those with mild cognitive impairment (MCI) compared with cognitively normal PD patients, particularly for amnesic MCI (aMCI).¹³ Specifically, hallucinations and irritability were found to be more common in MCI when adjusting for motor and functional impairment, but only irritability when

adjusting for PD medications. In addition, an association between early cognitive impairment and NPS, in particular mood symptoms, was observed already in de novo PD.¹⁴ Table 1 lists three studies showing the percentage of patients with positive Neuropsychiatric Inventory (NPI) item scores across the spectrum of cognitive impairment in PD. Although direct comparison across different cohorts is subject to selection bias, the tendency towards more frequent NPS with worsening cognition is evident. The frequency and pattern of NPS is even more pronounced in patients with DLB.¹⁵

Depression

Depressive symptoms are among the most common non-motor symptoms in PD, with approximately 35% of PD patients having clinically-relevant depressive symptoms. Although depressive symptoms may occur prediagnosis or at the time of diagnosis, the frequency tends to be higher in more advanced PD and in patients with cognitive impairment. Rates of depression based on the NPI were 70% in amnesic MCI, 60% in non-amnesic MCI, and 55% in normal cognition.¹³ In a large study, the frequency of depression (defined as a score ≥ 14 on the Montgomery and Åsberg depression rating scale) increased with disease stage, and was higher in PDD (44%) than nondemented (18%) patients. A recent meta-analysis confirmed the association between depression and cognitive impairment in PD with a moderately large effect size (0.52).¹⁷

Is Depression a Risk Factor for Cognitive Decline?

There is evidence that a history of depression is a risk factor for or a premotor clinical manifestation of PD.¹⁸ In addition, there is mixed evidence that depression is a risk factor for subsequent PDD. In two prospective studies, a high depression score¹⁹ or a diagnosis of major depression²⁰ predicted more rapid long-term cognitive decline. However, several other large studies failed to find that depression is associated with rate of subsequent cognitive decline²¹ or incident dementia.^{22,23} The underlying mechanisms for this possible association are unknown, but may involve the vulnerability of hippocampal neurons to the increased stress-response associated with depression.

Most longitudinal studies have enrolled prevalence samples at baseline, and fewer studies have explored whether depression at the time of diagnosis is associated with subsequent cognitive decline. In the CAM-PAIGN study, which enrolled a community-based, incident PD cohort, depression was not associated with subsequent cognitive decline.²⁴ In another study, 66 de novo PD patients were followed for one year. Of these, nearly 50% had depressive symptoms, but neither depressive nor anxiety symptoms were associated with the rate of cognitive decline over this short time period.²⁵ Similarly, in the Norwegian Park West study depression score at baseline did not predict conversion to dementia.²⁶

Diagnosis of Depression in PDD

There are overlapping symptoms of PD, depression, apathy, and dementia. In addition, cognitive impairment and apathy can reduce awareness and influence the capacity to communicate symptoms of depression. Thus there is a risk both for under- and over-diagnosis of depression in PDD. The provisional criteria for depression in PD recommend

an inclusive approach has been recommended, i.e., symptoms should be counted as representing depression.²⁷ In addition, to account for the effect of apathy, it was recommended to omit decreased interest as a core symptom of depression, and to interview a nonpatient informant in cognitively impaired patients. In a recent detailed study of psychological factors associated with a diagnosis of depression in non-demented PD patients, three independent factors (apathy, negative affect, and anhedonia) were identified and found to be significantly associated with a diagnosis of depression.²⁸ Negative affect was most strongly associated with a depression diagnosis, whereas apathy was associated with overall psychological disturbance. Although commonly used depression scales, such as Geriatric Depression Scale, Hamilton Depression Scale; Montgomery Åsberg Depression Rating Scale, and Hospital Anxiety and Depression Scale, have not been specifically assessed in PDD, they may still be used for patients with mild and even moderate dementia. Examples of informant-based scales are the Neuropsychiatric Inventory, and, the Cornell Scale for Depression in Dementia, which has been reported to have adequate psychometric properties also in PD.²⁹

Treatment

Antidepressants

Recent randomized trials have reported that antidepressants can improve depression in people with PD, including nortriptyline,³⁰ venlafaxine, and paroxetine.³¹ However, antidepressant trials in PD usually exclude people with dementia or substantial cognitive impairment, so the positive findings from these studies may not generalize to PDD. No studies have specifically explored whether antidepressants are efficacious in depressed PDD patients, but in one study³¹ the antidepressant effect did not differ between those with better versus worse (MMSE score < 27) cognitive performance. Of note, recent evidence suggests that antidepressants are not effective in people with AD,³² so antidepressant trials in PDD specifically are warranted.

Effect of Antidepressants on Cognition in PD

It is well known that antidepressants can impact on cognition. In most instances, effective treatment of depression will lead to improvement of depression-associated cognitive impairment. On the other hand, antidepressants with a substantial anticholinergic effect (e.g., tricyclics) may have a negative effect on cognition,³³ and SSRIs may be associated with increased apathy.³⁴ In the most detailed analysis,³⁵ cognition did not change in neither the antidepressant (nortriptyline and paroxetine) nor the placebo groups over a period up to 24 weeks. Being a depression-responder at the end of the 8-week study period did not improve cognitive performance compared to nonresponders. Better baseline performance on tests of verbal memory, speed of processing, and executive functioning predicted a positive outcome on depression, independent of treatment group. In contrast, atomoxetine (a selective noradrenergic agent) was associated with improved global cognition, although the effect on depression did not reach statistical significance.³⁶

Other Treatment Modalities

Recent evidence suggests that cognitive behavioral therapy (CBT) is also effective for depression in PD,³⁷ with better executive functioning being a significant and independent predictor of response to treatment effect.³⁸ Adequate cognition is required for CBT, so dementia is usually an exclusion criterion.^{38,39}

Case reporting suggests that electroconvulsive therapy (ECT) has antidepressant effects in PD.^{40,41} There is little evidence of the effects and risk of ECT in patients with PD and cognitive impairment, although in general cognitively impaired patients are at increased risk for adverse cognitive effects after ECT. However, case reporting suggests that ECT is relatively safe and effective in non-PD patients with dementia in general.⁴²

Anxiety

Compared to depression, much less is known about anxiety in PD. In one large cohort, 34% met a diagnosis of one anxiety disorder, generalized anxiety disorder (GAD) being the most common diagnosed condition, followed by panic attacks and phobias.⁴³ GAD is characterized by excessive and uncontrollable worry accompanied by physiological arousal, e.g., muscle tension. Typically PD patients report worry about disease progression and everyday worries such as finances. Panic attacks are also common, with symptoms such as increased heart rate, chest pain, dizziness, difficulty breathing, sweating, and concern over “losing control” or “going mad”, and may lead to fear over their consequences and avoidance behavior. Patients with social phobia fear the perceived social consequences resulting from PD symptoms manifesting themselves in public.

Anxiety is strongly linked with symptoms of depression, which has been demonstrated in two large series^{44,45} but unlike many other NPS, anxiety was found to be less common in PDD compared to PD in a large German study.¹¹ Of note, anxiety symptoms are also related to motor symptoms. They are more common in patients with motor fluctuations (see below for a more detailed discussion on motor and nonmotor fluctuations), and seem to occur more commonly in the off condition, although in the majority of cases anxiety symptoms seem to occur without any temporal relationship with specific motor states.⁴⁶

Management

There have been no controlled anxiety treatment studies in PD, but antidepressant treatment studies have reported secondary benefit for anxiety symptoms. In one study, there was a significant benefit of nortriptyline over placebo on an anxiety scale, a secondary outcome measure, and a trend towards significant benefit of paroxetine.³⁰ As with many other NPS, there is no evidence regarding treatment of anxiety in PDD.

For patients who experience anxiety as part of an “off” state, PD medication adjustments can be made in an attempt to decrease the duration and severity of these episodes. However, many patients require treatment with benzodiazepines, although this medication class must be used cautiously in PD patients because of their propensity to increase sedation, gait imbalance, and further worsen cognitive impairment.

CBT (discussed previously) may relieve anxiety in people with and without PD,⁴⁷ but is less relevant for patients with dementia.

Psychosis

Background

Psychosis symptoms in PD include hallucinations and delusions, and the occurrence of these symptoms in PD patients are predictors of nursing home placement⁴⁸ and mortality.⁴⁹

Complex visual hallucinations, often of animals and people are the most typical manifestation,⁵⁰ but other visuoperceptual disturbances can occur, including illusionary experiences, sensations of movement in the periphery (passage hallucination) and sensations of presence (extracampine or “social”⁵¹ hallucination). Hallucinations in other modalities (auditory, tactile, and olfactory) occur but are less common.^{48,52}

Delusions manifest when insight is compromised, so are associated with degree of cognitive impairment. Delusions in PD tend to be paranoid in nature. Other phenomena, including delusional misidentification (e.g., Capgras and Fregoli syndromes) can occur in a minority of PDD patients,⁵³ and are also a feature of dementia with Lewy bodies (DLB).^{15,54}

Epidemiology

Psychotic symptoms affect up to 60% of PD patients long-term,^{11,49,52} although the precise point prevalence is not clear. Recent development of rigorous criteria will prove helpful in defining and investigating the epidemiology and aetiology of these symptoms (Table 2).⁵⁵

Complex visual hallucinations are present in 7–25% of PD patients, but rise to 41%–87% in PDD patients.^{48,56} Regarding delusions, determination of their true prevalence in PD is difficult as their occurrence is often conflated with visual hallucinations. However it appears that isolated delusions without hallucinations (prevalence of 4%–5%) probably occur less commonly than hallucinations.^{49,52,57}

Risk Factors and Association With Cognitive Impairment

It is clear that psychosis can manifest across the disease spectrum in PD, even in the earliest stages of the disease,⁵⁸ although typically it occurs later in the disease course.⁴⁹ Risk factors for visual hallucinations include disease duration (e.g.,^{59,60}), severity,¹⁵ ocular disorders,⁶¹ higher age of PD onset,⁴⁹ depression,⁶² and REM-sleep behavior disorder.⁶³

The role of cognitive impairment is more complex. The occurrence of visual hallucinations in PD may be a harbinger of subsequent cognitive decline, or in the presence of preexisting dementia lead to more rapid decline.^{64,65} On the other hand, declines in cognitive performance in PD may be an important risk factor for visual hallucinations⁵⁸ and it is notable that even nondemented PD hallucinators tend to have more executive dysfunction, poorer sustained attention, and worse visuoperceptual function compared with non-hallucinators.^{62,66–70}

Impairments in attention^{69,71} and visuo perceptual function⁷² are central to a number of aetiological models of visual hallucinations,^{73,74} so it may be that there are common neuropathologic processes leading to the occurrence of both hallucinations and cognitive decline. More broadly, cognitive function may be important in how a PD patient interprets visual hallucinations. Early in the disease, insight may be retained, which has led to the use of the term “benign hallucinations”. However, this term is probably a misnomer as it is notable that over 80% of patients with ‘benign hallucinations’ will lose insight and develop more severe psychotic symptoms.⁷⁵

The role of dopamine and DRT in the etiology of psychosis in PD remains controversial. While dopamine agonists seem to be associated with an increased risk of visual hallucinations,⁶⁰ it is notable that DLB patients can experience similar visual hallucinations without exposure to DRT, and there are historical reports of late-stage PD patients in the pre-levodopa era experiencing hallucinations. Similarly, intravenous levodopa in hallucinating PD patients does not precipitate hallucinations.⁷⁶ This, along with the observations that anticholinergics can exacerbate visual hallucinations⁷⁷ and cholinesterase inhibitors can improve them, suggests that a pure dopamine-based explanation for PD psychosis is unlikely, and that dysregulation in other neurotransmitter systems (e.g., cholinergic and serotonergic systems) also play a role.⁷⁸

Treatment

PD psychosis can be difficult to treat, and there are no systematic studies evaluating non-pharmacological interventions, although a small study has suggested benefit for ECT in patients refractory to antipsychotics.⁷⁹ Practically, removal of antiparkinsonian medications may help ameliorate psychotic symptoms, particularly in the earlier stages of the disease, and a specific order of withdrawal has been suggested beginning with anticholinergic agents through to dopamine agonists/COMT inhibitors and then finally, if required levodopa.⁸⁰ However reductions in dopamine therapies can be challenging given the need to adequately treat motor symptoms.

Specific pharmacological interventions include the use of antipsychotics. Nevertheless, while there have been numerous randomized control trials (RCTs) of antipsychotics for PD psychosis, there is a paucity of data looking at the benefits of these agents in PD patients with cognitive impairment specifically. The exception is clozapine, where one major study with a positive outcome⁸¹ included some PD patients with possible dementia (mean baseline MMSE placebo group: 21.7; clozapine group: 23.8). However, subgroup data for PDD patients were not provided, and the widespread use of clozapine is limited due to its potential to induce agranulocytosis and the necessity for regular blood monitoring.

Quetiapine is the antipsychotic used most frequently for PD psychosis, but there is no evidence from controlled studies for its efficacy in PDD.⁸² Additionally, prolonged use of antipsychotics may have deleterious effects on cognition,⁸³ and they significantly increase cerebrovascular events and mortality in older people with dementia in general⁸⁴ so these agents should be used cautiously in PD patients with cognitive impairment until demonstrated not to increase morbidity and mortality in this population.

Cholinesterase inhibitors, in particular rivastigmine,⁸⁵ may be an alternative first-line treatment option, as these agents can improve cognition, function and NPS. However, while these drugs may improve visual hallucinations in DLB, the EXPRESS trial found no significant reduction in visual hallucinations in PDD patients with the use of rivastigmine, although the more frequent emergence of visual hallucinations as an adverse event in the placebo group suggested a potential protective effect against visual hallucination occurrence with rivastigmine.

Other drugs such as memantine (NMDA antagonist) and ondansetron (5-HT₃ antagonist) have also been considered for the treatment of PD psychosis. Overall the therapeutic benefit of memantine remains inconclusive, and from a psychosis perspective improvements in the neuropsychiatric inventory (NPI) in patients with PDD have not been observed, although there may be some benefit in DLB patients.^{86,87}

A promising new drug for PD psychosis is pimavanserin (selective 5-HT_{2A} inverse agonist). A recent controlled trial found a significant benefit of pimavanserin on all endpoints, including the Scale for Assessment of Positive Symptoms in Parkinson's Disease (SAPS-PD) score, with additional improvement in night-time sleep and daytime somnolence.⁸⁸ Overall pimavanserin was well tolerated and did not worsen motor symptoms.

Sleep Disturbances

Sleep disturbances in PD fall into two main categories: excessive daytime sleepiness (EDS) and disturbances to nocturnal sleep. EDS and nocturnal sleep disturbances in PD are very common nonmotor symptoms in PD, affecting up to 80% and 90% of patients respectively.^{89–91}

Nocturnal sleep disturbances in PD include a gamut of symptoms such as insomnia, sleep fragmentation, restless legs syndrome (RLS), periodic limb movements of sleep, circadian dysrhythmia, obstructive Sleep Apnoea (OSA), sleep disordered breathing, and REM sleep behavior disorder (RBD). The latter sleep disturbance, RBD, has received a lot of attention given its specific clinicopathological/cognitive implications and is dealt within a separate section.

Excessive Daytime Sleepiness

Although EDS is another possible prodromal symptom of PD,⁹² the incidence of EDS increases with disease duration. In PD, more severe expressions of EDS have been referred to as “sleep attacks”.⁹³ Both EDS and sleep attacks can have significant consequences by interfering with activities of daily living, particularly driving.^{93,94}

There is an association between the severity of cognitive impairment and EDS in PD,^{95–98} and the presence of EDS is one of the associated clinic-behavioral features that supports a diagnosis of PDD.⁵⁶

The etiology of EDS is not well understood, although neuropathological changes to sleep-wake centres in the brainstem and hypothalamus (particularly hypocretin secreting neurons)

have been implicated.⁹⁹ Widespread cortical grey matter atrophy as well as atrophy of nucleus basalis of Meynert appear more frequent in PD patients with EDS, even in the absence of cognitive impairment and hallucinations.¹⁰⁰

Related to EDS is the symptom of cognitive fluctuations, which are defined as spontaneous alterations in cognition, attention and arousal. While more commonly known as a core feature of DLB,¹⁰¹ fluctuations also occur in PDD¹⁰² and may relate to cholinergic deficits.¹⁰³ However, cognitive fluctuations as a symptom construct remains unclear,¹⁰⁴ due to conflation of arousal and cognitive elements, and cognitive fluctuations and daytime alertness in the Lewy body dementias may occur independently of each other.¹⁰⁵

With regard to treatment of EDS, there is mixed evidence for use of modafinil and psychostimulants.^{106–109} The efficacy of such agents for EDS in the presence of cognitive impairment or their direct effect on cognitive performance in PD remains to be established, although there are preliminary data suggesting benefit on attention with modafinil or armodafinil treatment.¹¹⁰

Disturbances to Nocturnal Sleep

Rates of sleep disturbance¹¹¹ are reported to be similar in PD patients with and without MCI, and there is a lack of evidence to suggest they are associated with severity of global cognitive impairment or with domain-specific cognitive deficits,⁹⁵ although it has been suggested that circadian dysrhythmias may be more common in PD patients with hallucinations and cognitive impairment.¹¹²

Nocturnal motor symptoms may be improved by manipulation of antiparkinson medications and use of long-acting levodopa preparations. Melatonin may improve subjective sleep disturbances^{113,114} and a recent trial of the Z-drug eszopiclone for insomnia in PD was partially positive.¹¹⁵ From a cognitive perspective, good sleep in PD appears to be associated with enhanced working memory function, thus improving sleep disturbances may be an important therapeutic approach for improving cognition.¹¹⁶ Use of anticholinergics for nocturia is probably best avoided in those with cognitive impairment, although nocturia itself can markedly worsen night-time sleep.

REM Sleep Behavior Disorder

REM sleep behavior disorder (RBD) is common in PD, with frequencies ranging from 46%–58%,^{117,118} and can antedate the onset of PD by up to several decades.^{119–121}

Rates of MCI are about six to seven times higher in PD patients with RBD compared to PD patients without RBD,¹²² and RBD in PD is a marker for earlier onset of dementia compared with PD patients without RBD.^{123,124} PD patients with RBD typically have a pattern of cognitive deficits similar to PDD, characterized by impaired attention, visuoconstructional and visuo-perceptual abilities, but with relative preservation of memory and naming.¹²³

The mechanism of RBD is presumed to involve damage to the brainstem, in particular to the descending reticular formation, although reduced striatal dopaminergic activity has also been implicated.¹²⁵

Clonazepam and melatonin¹²⁶ have been used to treat RBD. However there are possible negative effects of sedative-hypnotic use in PD patients with cognitive impairment (e.g., worsening cognition, sedation, and gait impairment), although the severity of these remain to be formally evaluated.¹²⁷

Apathy—Apathy, succinctly defined as a decrease in goal-directed behavior, verbalization, and mood, is common in a range of neurodegenerative diseases, including frontotemporal dementia (FTD), progressive supranuclear palsy (PSP), DLB, AD, and PD.^{128,129} Apathy usually is accompanied by diminished self-awareness, so changes typically are noticed and brought to the attention of clinicians by caregivers. A common assumption is that the patient is depressed, though a lack of endorsement of sad mood and the typical cognitive changes seen in depression (e.g., guilt, helplessness, suicide ideation, and hopelessness) suggest a diagnosis of apathy instead.

Apathy can occur independently of cognitive impairment in PD, but overlap is common.^{56,129} Studies estimate the prevalence of apathy in PDD to be up to 50%.⁹ In a study comparing PD patients with a similarly-disabled group (i.e., osteoarthritis patients),¹³⁰ apathy was significantly more common in the PD group, was associated with cognitive impairment, but not associated with either depression or anxiety. Another study reported similar findings,^{131,132} with apathy being more common in PDD patients than in PD patients without dementia. All PD patients showed a decrease in action initiation compared with healthy controls, but PDD patients were significantly more impaired in this regard. Additionally, they exhibited lower emotional responses and decreased self-awareness compared with PD patients without dementia. Regarding specific cognitive domains, apathy in PD is associated with executive deficits (e.g., impairments in verbal fluency, Trails making test B, and Stroop Test), memory impairment, and bradyphrenia.^{129,130,133}

Goal-directed behavior is associated with dopaminergic and noradrenergic function, and with activation of the frontal cortex and basal ganglia.¹³⁴ There is an emerging understanding of the neural substrate of apathy in PD, based primarily on the results of structural imaging studies. This research has found an association between apathy and decreased cingulate, inferior frontal, and orbitofrontal gyri volumes.^{135,136}

Regarding treatment, there has been one controlled study for apathy in PD. This was a 12-week placebo-controlled trial in 37 patients presenting with apathy following deep brain stimulation of the subthalamic nucleus and discontinuation of dopamine agonist treatment. In this study, patients randomized to reintroduction of a dopamine agonist (piribedil) experienced greater improvement in apathy than placebo-treated patients.¹³⁷

Additionally, anecdotally psychostimulants (e.g., methylphenidate, dextroamphetamine), stimulant-related compounds (e.g., modafinil), and cholinesterase inhibitors are used in clinical practice, but their effectiveness for apathy is not known.¹³⁶ Based on the proposed neuropathophysiology of apathy, antidepressants and other medications that increase dopamine or norepinephrine activity (e.g., tricyclic antidepressants, dual reuptake inhibitor antidepressants, bupropion, and atomoxetine) may be beneficial,¹³⁸ although controlled research is needed.

Other

Impulse Control Disorders—Impulse control disorders (ICDs; e.g., compulsive gambling, buying, sexual behavior, and eating) are increasingly recognized as common and clinically significant disorders in PD. Given that research suggests that the strongest risk factors for ICD development in PD are dopamine agonist treatment and younger age,¹³⁹ and given that cognitively impaired patients are more likely to be older and less likely to be prescribed a dopamine agonist, it is not surprising that ICDs are not commonly reported in PDD patients. In one single center study of 805 PD patients, ICD symptoms were less common in PD patients with dementia (3.8%) compared with nondemented patients (9.6%), but this may have been an artifact of DA prescribing practice.¹⁴⁰

However, there is an emerging neuropsychological test and cognitive neuroscience literature that pertains to ICDs in PD. On standard neuropsychological tests, PD patients with ICDs demonstrated impairment on a range of cognitive domains, including executive abilities and spatial planning, compared with PD patients without an ICD.^{141,142} On tests of cognitive abilities thought to be of specific relevance to ICD behaviors, PD patients with an ICD (compared with PD controls) demonstrate the following differences: an increased rate of learning for gain (versus loss) outcomes,¹⁴³ a strong preference for immediate over future rewards,¹⁴⁴ increased risk taking,¹⁴⁵ altered reward-punishment learning,^{146,147} and increased novelty seeking.¹⁴⁸

Nonmotor Fluctuations—Most PDD patients are on chronic levodopa treatment, and many experience motor fluctuations (MFs), which involve “off” periods characterized by worsening parkinsonism. The majority of patients with MFs also experience nonmotor fluctuations (NMFs), typically a mix of psychiatric (e.g., anxiety, fatigue, and dysphoria) and cognitive (e.g., slowness of thinking, confusion, poor concentration, word finding problems, impaired memory) symptoms.^{149,150} Interestingly, there is not always a correlation between motor and nonmotor symptoms.^{151,152} It remains to be seen if treatments shown to reduce severity or time of MFs also lead to improvements in severity or duration of NMFs.¹⁵³

Progressive Supranuclear Palsy, Corticobasal Degeneration and Multiple System Atrophy

Often referred to as the “parkinson’s plus” disorders, progressive supranuclear palsy (PSP), corticobasal degeneration (CBD), and multiple system atrophy (MSA) have varying, but overlapping, degrees of motor parkinsonism, cognitive deficits¹⁵⁴ and NPS. Focus on the specific cognitive and NPS profiles of these disorders has been lacking although more research has been carried out on the latter (Table 3). In contrast to PD and PDD, delusions and hallucinations are rare in these conditions, even in the context of DRT.⁶

Previously underrecognized,¹⁵⁵ cognitive impairment is actually relatively common in PSP and MSA; the Neuroprotection and Natural History in Parkinson Plus Syndromes study reported that cognitive impairment occurred in 57% of the PSP group and 20% of the MSA group, with frontal deficits in 62% of PSP and 32% of MSA patients. In CBD dementia rates are estimated to be between 25%–100%,^{156,157} with cognitive deficits and NPS presenting in the prodromal phase or early in the disease course. Thus similar to PSP, CBD is

frequently misdiagnosed in the early stages and may be inappropriately treated with antipsychotic medications.¹⁵⁸

The etiological basis of cognitive deficits in MSA is not well understood, although it probably overlaps that of PD. In CBD and PSP, prominent deficits in basal ganglia networks, particularly those with orbito-frontal and medial frontal components, likely contribute to the constellation of cognitive, motor, and neuropsychiatric symptoms seen, including executive dysfunction, disinhibition and apathy.⁶

There is a paucity of research into the treatment of NPS in these disorders. SSRIs have been tried, without evidence for benefit, in PSP,¹⁵⁹ and data on the efficacy of noradrenergic drugs are limited and focussed on motor outcomes.¹⁶⁰

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TABLE 1

Proportion (%) with a non-zero score on NPI items in PD by cognitive status

Study	Aarsland et al. ¹⁶	Monastero et al. ¹³	Monastero et al. ¹³	Monastero et al. ¹³	Aarsland et al. ⁹
NPI item	De novo (n = 175)	Normal cognition (n = 164)	MCI		Dementia (n = 537)
			PD-naMCI (n = 104)	PD-aMCI (n = 142)	
Delusions	1.1	1.2	2.9	7	24.6
Hallucinations	1.2	3	9.6	16.2	43.9
Agitation	5.7	9.1	12.5	16.2	32.6
Depression	34.3	54.9	60.6	70.4	57.5
Anxiety	16.4	54.9	55.8	60.6	49
Euphoria	0	1.8	0	3.8	7
Apathy	27.4	45.1	47.1	54.2	54.3
Disinhibition	4	0.6	1	2.1	3.7
Irritability	8.6	14.6	31.7	38.0	29.7
Abnormal motor activity	2.3	2.4	2.9	8.5	22
Sleep disturbance	17.8	57.3	59.6	66.9	–
Appetite disturbance	14.9	9.8	17.3	19	–
Total score ^a	Median: 1	13.3	11.1	5.8	12.9

Numbers represent % with score > 1.

^aMean score (if not otherwise indicated)

Abbreviations: aMCI, amnesic MCI; naMCI, non-amnesic MCI.

TABLE 2

Movement Disorders Society criteria for psychosis

TABLE 1. NINDS-NIMH diagnostic criteria for PD-associated psychosis
<i>Characteristic symptoms</i>
<i>Presence of at least one of the following symptoms:</i>
Illusions
False sense of presence
Hallucinations
Delusions
<i>Primary diagnosis</i>
UK Brain Bank criteria for PD
<i>Chronology of the onset of symptoms of psychosis</i>
The symptoms in Criterion A occur after the onset of PD
<i>Duration</i>
The symptom(s) in Criterion A are recurrent or continuous for 1 month
<i>Exclusion of other causes</i>
The symptoms in criterion A are not better accounted for by another cause of parkinsonism such as dementia with Lewy bodies, psychiatric disorders or a general medical condition including delirium

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TABLE 3

Motor, cognitive and neuropsychiatric/behavioural symptoms in progressive supranuclear palsy, corticobasal degeneration, and multiple system atrophy

	Motor symptoms	Cognitive deficits	Neuropsychiatric/behavioral symptoms
Progressive supranuclear palsy	Rigidity (axial), bradykinesia, occasional tremor, postural instability, ophthalmoparesis, swallowing difficulties (late stage)	Executive dysfunction ^{155,161,162} ; <ul style="list-style-type: none"> Fluency both semantic and phonemic) – often more severe than MSA/PD^{154,162} Initiation & perseveration, slowed cognitive speed and impaired flexibility/set shifting. Memory (although recognition relatively preserved)	Apathy, depression, sleep problems, irritability, disinhibition, bulbar affect, eating problems
Corticobasal degeneration	Unilateral parkinsonism including rigidity, bradykinesia, and occasional tremor. Postural instability Cortical “movement disorders”: <ul style="list-style-type: none"> apraxia myoclonus alien-limb phenomena cortical sensory loss 	Executive dysfunction: <ul style="list-style-type: none"> set shifting,¹⁶³ reduced word fluency¹⁶⁴ Constructional apraxia are also usual findings ¹⁶⁵ Episodic memory function deficits Speech difficulties ¹⁶⁶	Depression, apathy, agitation, irritability. Occasionally Kluver-Bucy syndrome.
Multiple system atrophy	Rigidity, bradykinesia, occasional tremor, postural instability	Executive dysfunction ^{155,162} ; <ul style="list-style-type: none"> language deficits (fluency), initiation & perseveration, cognitive speed/flexibility 	Depression and anxiety are common (perhaps less so than in PSP). ¹⁶⁷ Sleep disorders common as well (perhaps more than in PD for a similar disease duration) ¹⁶⁸

Abbreviations: MSA: multiple system atrophy; PSP: progressive supranuclear palsy.