NEUROPSYCHIATRIC FEATURES OF PARKINSON’S DISEASE WITH COGNITIVE IMPAIRMENT: AN OVERVIEW

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ABSTRACT

Parkinson’s disease (PD) is known to cause neuropsychiatric symptoms (NPS). It has been established that the more advanced the motor stage of PD is, the more frequent and severe the NPS may be. However, the relationship between NPS and stage of cognitive decline is less well understood. This is important because the majority of people with PD will experience some degree of cognitive decline during the course of their disease, and there is a high risk of developing dementia (PDD). In non-PD populations there is a strong association between NPS and cognitive impairment and the same association may apply in PD. Consequently, the aim of this article is to provide a brief overview of NPS in PD from the perspective of stage of cognitive decline. We highlight studies that have demonstrated the increasing prevalence and severity of NPS with increasing cognitive impairment in PD. We point out the importance of apathy as a possible precursor to PDD. We also describe the negative impact of NPS and cognitive impairment on caregiver distress and quality of life. Finally, we have summarised findings from key studies of cognitive enhancers in PDD which have examined the effect of these treatments on NPS.

Keywords: Parkinson’s disease, cognitive impairment, neuropsychiatric, mild cognitive impairment in PD (PD-MCI), dementia in PD (PDD), caregiver burden, quality of life.

INTRODUCTION

Idiopathic Parkinson’s Disease (PD) has been known predominantly as a motor disorder; however, over recent years there has been an increasing focus on non-motor symptoms (NMS) of PD.1 NMS occur in >90% of people across various stages of PD, and some of the most common manifestations of NMS include psychiatric symptoms, cognitive changes, autonomic instability, and sleep disturbance.1 While psychiatric syndromes, including depression, anxiety, psychosis, and apathy, have been well characterised in PD in general, the specific relationship of these syndromes to the cognitive changes in PD has not been as extensively described. In this paper, our aim is to provide a general overview of the neuropsychiatric symptoms (NPS) of PD with regards to the stage of cognitive impairment and to highlight the negative impact of these symptoms on quality of life (QoL) and caregiver burden. Since this is not intended to be a systematic review but rather a synopsis to highlight a new perspective on NPS in PD in order to aid the clinician, we will conclude our discussion with a summary of the efficacy of cognitive enhancers on NPS derived from therapeutic trials in PD dementia (PDD).

NPS

Non-PD Cognitive Impairment

The spectrum of NPS is frequently encountered in a range of primary mental health disorders such as psychosis, anxiety, and mood disorders, as well as conditions affecting brain function such as neurodegenerative disorders, delirium, traumatic brain injury, and systemic conditions. Additionally,
NPS commonly exist in people with mild cognitive impairment (MCI) and dementia outside of the context of PD, and have been described in care home residents, clinical dementia populations, and community-based epidemiological samples. The Cache County Study, one of the very few epidemiological studies examining NPS in dementia, found that >60% of a community sample of people over the age of 65 with dementia had at least one NPS. Of these, >50% had ‘clinically significant’ NPS, rated as ‘moderate-to-severe’ on the Neuropsychiatric Inventory (NPI). The most prominent NPS observed included apathy, depression, and aggression. As for MCI in non-PD populations, another community-based study, the longitudinal Cardiovascular Health Study (CHS), which examined 824 people, found that the prevalence of these symptoms was as high as 43%, with 29% having ‘clinically significant’ symptoms, which exceeds the prevalence of NPS in older people with intact cognition. Data also demonstrated that 270 of the 362 participants (75%) with dementia had at least one NPS, with >60% having a NPI score ≥4, demonstrating a severity of clinical significance. This suggests that NPS may be a precursor to subsequent cognitive decline, rather than being within a constellation of symptoms that exist in memory impairment, and may therefore have a predictive role. Consequently, examining the profile of NPS in relation to cognitive stage in PD has merit, and probes whether a similar continuum of severity of NPS exists in PD populations.

PD

NPS manifesting at some point in the clinical course of PD is already well recognised and the significant negative impact of these symptoms on the QoL of those affected has previously been documented. However, hitherto, there has been very little attempt to examine these symptoms in relation to the degree of PD-related motor and cognitive impairment. A ‘stage-based’ understanding of NPS and their impact in PD is important since the appearance of NPS may be a harbinger of cognitive decline or the onset of dementia, or vice versa. Specifically, once dementia has been diagnosed, the neuropsychiatric slippery slope may appear, heralding the onset of a more rapid global decline in health and QoL and a step-up in caregiver burden. Furthermore, the progression of underlying neurodegenerative pathophysiology through the Braak stages supports the notion that brain stem nuclei related to both the neuropsychiatric (e.g. raphe nuclei and locus coeruleus) and the cognitive symptoms of PD may appear simultaneously or in close proximity to each other.

One of the most fruitful ways to examine NPS in PD is using the NPI (Cummings et al.), which is the gold-standard rating scale for NPS in dementia. The NPI is a structured 12-item caregiver-rated screening tool designed to help assessment of behavioural disturbances in dementia by ascertaining the presence of a range of NPS ‘domains’ and rating them according to their frequency and severity. It is a valid instrument, with high inter-rater and test-retest reliability, but despite its strengths, NPI data are prone to recall bias as carers give their own account of observed behaviour. For example, one of the domains - apathy - is a loss of motivation; however, informants can struggle to differentiate between apathy and depression. This diagnostic challenge has been debated frequently and studies have demonstrated the ability to discriminate between the two using validated rating scales for both apathy and depression. Nevertheless, in PD, several studies have utilised the NPI, although unlike the larger epidemiological studies in dementia, these have generally been confined to clinic samples or PD-specific cohorts as outlined below.

NPS According to Cognitive Stage in PD

Intact cognition in PD

Aarsland et al. conducted a large cohort study in order to describe the neuropsychiatric profile in untreated people with PD without dementia. By using the NPI, this study found that >50% of 175 people with PD had positive scores in at least one domain compared to a much smaller proportion of non-PD participants (p<0.001). Of these, nearly 35% of participants’ carers endorsed two or more NPI items. The most prevalent NPS to emerge were apathy and depression. Ojagbemi et al. (2013) compared people with PD (n=50) with a non-PD control group (n=50). The NPI showed that delusions, hallucination, and apathy were significantly higher in the PD group, and the mean total NPI magnitude scores for the PD and control groups were 9.4 (SD 10.6) and 3.5 (SD 7.7), respectively (p=0.002).
MCI IN PD

Until recently, there were no clearly defined operationalised criteria for cognitive impairment in PD. To address this, the Movement Disorder Society (MDS) established a task force to define specific criteria for two different cognitive states in PD: PD-MCI and PDD. These clinical consensus criteria have been based on clinical, cognitive, and functional parameters to clearly define the phenotype of each syndrome. It has been argued that the presence of PD-MCI increases the likelihood of developing PDD, therefore, early recognition of cognitive decline in PD and its subsequent management is crucial. Since the criteria for PD-MCI have only recently been established, very few studies describing NPS in PD according to this cognitive classification exist in the literature.

One study using the new categorisation of PD-MCI and PDD is that of Leroi et al. In this cross-sectional study, 127 PD participants with intact cognition (PD-NC; n=54), PD-MCI (n=48), and PDD (n=25) were examined using the NPI. Nearly 78% of all participants, regardless of cognitive stage, reported at least one NPS on the NPI. Interestingly, there was no significant difference in the frequency or severity of NPS between PD-NC and PD-MCI, other than in the domain of apathy. Apathy in the PD-MCI group had a frequency of 48% and a mean magnitude (frequency x severity) of 3.79 (SD 4.91), nearly three times more than the PD-NC group. The rate of apathy in PD-MCI was similar to the rate found in the PDD group (52%). This correlation of apathy between both groups suggests the possibility that the emergence of apathy in PD-MCI could presage the conversion to PDD. This argues for a closer scrutiny for the presence of apathy in the PD-MCI population.

In another slightly larger study, those with PD-MCI (n=246) had higher rates of four NPS domains compared to those with intact cognition (n=164). Specifically, in those with PD-MCI, rates of depression (65.5%), sleep disturbance (63.3%), anxiety (58.2%), and apathy (50.7%) were all prominent in PD-MCI but not statistically different in frequency from the PD-NC group. Irritability was found to be significantly higher in the PD-MCI group compared to the PD-NC group. In this study, PD-MCI was defined more loosely than in the previous study and included gradual cognitive decline, Mini-Mental State Exam (MMSE) score ≤23.8, absence of or minimal impairment in activities of daily living, and absence of dementia. Those with PD-MCI were further subdivided into amnestic and non-amnestic subtypes (PD-aMCI and PD-naMCI, respectively) according to Petersen's criteria. This difference in the definition of PD-MCI may account for the differences observed in the two studies. Furthermore, this study also found that motor symptoms, demonstrated by the Unified Parkinson’s Disease Rating Scale (UPDRS) were significantly higher in PD-MCI than PD-NC suggesting a relationship between motor symptoms and NPS, either secondary to a psychological reaction to disability or to the neuropathological progression seen in PD.

PDD

The mean duration of subtle cognitive symptoms in PD developing into a full dementia syndrome is around 10 years, emphasising the importance of understanding different cognitive stages along this progression. Such an understanding will aid in the detection of associated complications and will enable further support and intervention. As the degree of cognition declines in PD, NPS become increasingly common. This is supported by a handful of studies examining NPS in PDD cohorts. For example, Lee et al. found that 113 out of a cohort of 127 (89%) participants with PDD had at least one NPS, with anxiety (57.5%), sleep problems (53.5%), and apathy (52%) being the most common. Amongst these participants, hallucinations were most strongly linked to extent of cognitive impairment as demonstrated by MMSE score. Aarsland et al. found that 64% of 527 participants with PDD endorsed at least one NPI item in the ‘clinically significant’ range (score ≥4). The rate of ‘any NPS’ regardless of severity was similar to that found by Lee et al. at nearly 90%. It is notable that the rate of NPS in PDD is significantly higher than the rate of NPS found in those with Alzheimer’s Disease (AD), suggesting that those with both physical and cognitive difficulties, such as is the case in PDD, have a greater neuropsychiatric load. This greater degree of impairment suggests more cognitive involvement in PDD than AD and may, therefore, lead to greater caregiver burden.

Few other studies have compared neuropsychiatric differences between PDD and AD. Starkstein et al. reported no significant differences between apathy, delusions, and irritability. However, major
Depression was significantly more prevalent in PDD whereas disinhibiton was significantly more prevalent in AD. Interestingly, Aarsland et al.\textsuperscript{28} reported hallucinations to be more commonly seen in PDD than AD, whereas other NPS of apathy, agitation, disinhibition, and irritability were more prominent in those with AD. These differences, yet not fully understood, suggest different regional and neurochemical pathways as mechanisms of cognitive impairment. A summary of NPS in PD-NC, PD-MCI, and PDD is summarised in Table 1, and the frequency of NPS is shown in Table 2.

Table 1: Summary of neuropsychiatric symptoms in Parkinson’s disease with different stages of cognitive impairment (mean frequency x severity scores on the NPI).

<table>
<thead>
<tr>
<th>Parkinson’s Disease without Cognitive Impairment</th>
<th>Parkinson’s Disease with Mild Cognitive Impairment</th>
<th>Parkinson’s Disease Dementia</th>
</tr>
</thead>
<tbody>
<tr>
<td>Ojagbemi\textsuperscript{18}</td>
<td>Aarsland\textsuperscript{17}</td>
<td>Leroi\textsuperscript{21}</td>
</tr>
<tr>
<td>PD-aMCI</td>
<td>PD-naMCI</td>
<td>PD-aMCI</td>
</tr>
<tr>
<td>n=50</td>
<td>n=175</td>
<td>n=54</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Item</th>
<th>Mean NPI Item Score (frequency x severity) (Standard Deviation)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Delusions</td>
<td>0.88 (2.02)</td>
</tr>
<tr>
<td>Hallucinations</td>
<td>0.36 (1.74)</td>
</tr>
<tr>
<td>Agitation</td>
<td>0.54 (1.91)</td>
</tr>
<tr>
<td>Depression</td>
<td>1.42 (2.24)</td>
</tr>
<tr>
<td>Anxiety</td>
<td>1.00 (2.12)</td>
</tr>
<tr>
<td>Euphoria</td>
<td>0.22 (0.98)</td>
</tr>
<tr>
<td>Apathy</td>
<td>1.64 (3.52)</td>
</tr>
<tr>
<td>Disinhibition</td>
<td>0.04 (0.28)</td>
</tr>
<tr>
<td>Irritability</td>
<td>0.76 (1.67)</td>
</tr>
<tr>
<td>Aberrant Motor Behaviour</td>
<td>0.28 (1.21)</td>
</tr>
<tr>
<td>Sleep Problems</td>
<td>1.02 (2.33)</td>
</tr>
<tr>
<td>Appetite Problem</td>
<td>1.08 (2.40)</td>
</tr>
<tr>
<td>Total NPI</td>
<td>9.36 (10.57)</td>
</tr>
</tbody>
</table>

PD: Parkinson’s disease; MCI: mild cognitive impairment; NPI: neuropsychiatric inventory; PD-aMCI: PD-amnestic MCI; PD-naMCI: PD-nonamnestic MCI.

The majority of people with PD live in their own homes with family members who are integral in providing care for them. Caregivers assist with household chores and help with physical and personal needs. As PD progresses, caregivers take on more tasks, particularly related to changes in cognitive ability in the person with PD. Consequently, the burden of care increases significantly as cognition declines.\textsuperscript{29}
The ‘Parkinson’s UK Members’ Survey (2007; n=1,881) found that caregivers with an increasing number of tasks, financial strain, and with their own health problems have a greater burden of care.30 Moreover, there is now evidence that one of the most important predictors of institutionalisation for people with PD is the presence of visual hallucinations and dementia.31 Other NPS such as depression are also important predictors of caregiver distress, even outweighing the impact of other non-neuropsychiatric factors.32 This underscores the importance of NPS in the emotional wellbeing of caregivers, which ultimately reflects on the wellbeing and QoL of the person with PD.

Just as depression in PD impacts negatively on caregiver distress, the negative impact of depression on health-related quality of life (HR-QoL) is also significant.33 Leroi et al.29 examined the impact of cognitive stage in PD on QoL using the Parkinson’s Disease Questionnaire (PDQ-8), which focuses on eight dimensions. This study found more impaired QoL in the group with PDD (n=25) compared to PD participants with intact cognition (n=54) and those with PD-MCI (n=48), although no specific association with frequency and severity of NPS was examined. These findings support the negative influences that exist between disease severity, degree of cognitive impairment, and caregiver distress. The negative trajectory of change suggests that those with PD-MCI need more intense interventions to curb the likelihood of dementia, institutionalisation, costs of care, and caregiver burden.

### MANAGEMENT OF NPS WITH COGNITIVE IMPAIRMENT

In PD, the underlying neurodegenerative pathology is largely characterised by deterioration of dopaminergic pathways. However, cholinergic pathways may also be affected, which plays an important role in cognitive impairment, particularly PDD. Consequently, attempts at increasing the cholinergic load in PD to improve cognition is a reasonable therapeutic strategy. Several randomised controlled trials (RCTs) have demonstrated the efficacy of cholinesterase inhibitors (ChEI) in improving cognition in PDD. Most notably, the EXPRESS study (Emre et al.34) demonstrated a positive effect of rivastigmine over placebo. There have been very few RCTs of typical treatments of NPS, such as antipsychotics and antidepressants, which have specifically taken cognitive stage into account, therefore, we have not addressed them here. Instead, several of the studies investigating the effect of cognitive enhancers in PDD have included the NPI as a secondary outcome measure in order to evaluate the efficacy of these interventions

### Table 2: Most common NPS in Parkinson’s disease with different stages of cognitive impairment (percentage on the NPI with any score greater than zero).

<table>
<thead>
<tr>
<th>Parkinson’s Disease without Cognitive Impairment</th>
<th>Parkinson’s Disease with Mild Cognitive Impairment</th>
<th>Parkinson’s Disease Dementia</th>
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<tbody>
<tr>
<td>Ojagbemi18 Aarsland17 Leroi21 Monastero22</td>
<td>Monastero22 Leroi21</td>
<td>Lee25 Aarsland26 Leroi21</td>
</tr>
<tr>
<td>Ojagbemi18 Aarsland17 Leroi21 Monastero22</td>
<td>Monastero22 Leroi21</td>
<td>Lee25 Aarsland26 Leroi21</td>
</tr>
<tr>
<td>n=50 n=175 n=54 n=164</td>
<td>n=142 n=104 n=48</td>
<td>n=127 n=537 n=25</td>
</tr>
</tbody>
</table>

| Depression (46) | Sleep (30) | Apathy (28) | Appetite (26) | Sleep (55.6) | Anxiety (42.6) | Depression (33.3) | Sleep (57.3) | Anxiety (54.9) | Depression (54.9) | Apathy (45.1) | Depression (70.4) | Sleep (66.9) | Depression (59.6) | Anxiety (55.8) | Apathy (60.6) | Depression (47.1) | Sleep (58) | Apathy (48) | Anxiety (36) | Depression (36) | Sleep (57.5) | Apathy (49) | Anxiety (52) | Depression (50.4) | Depression (56) | Apathy (52) | Irritability (52) | Anxiety (48) |
|-----------------|------------|------------|-------------|--------------|---------------|-------------------|---------------|---------------|-------------------|-------------|-------------------|---------------|-------------------|---------------|-------------------|-------------------|---------------|-------------------|---------------|-------------------|-------------------|-------------------|-------------------|-------------------|-------------------|-------------------|-------------------|-------------------|-------------------|-------------------|

PD: Parkinson’s disease; MCI: mild cognitive impairment; NPI: Neuropsychiatric Inventory; NPS: neuropsychiatric symptoms; PD-aMCI: PD-amnesic MCI; PD-naMCI: PD-nonamnesic MCI.
on NPS. We have therefore summarised some of these key findings below.

Donepezil was the first ChEI to be trialled in PDD. Recently, Ishikawa et al.\textsuperscript{35} reported that, in an open-label study with nine participants on donepezil, an improvement of 8.3 total NPI points was observed at week 12 (p<0.01). Aarsland et al.\textsuperscript{36} conducted a 10-week randomised double-blind crossover single centre study comparing donepezil to placebo in 14 participants with PDD. Although a significant effect of donepezil on MMSE score was demonstrated, no similar effect was noted on NPI scores. Leroi et al.\textsuperscript{37} also conducted a double-blind placebo-controlled RCT of donepezil in PDD and showed greater reduction in NPI scores in those on donepezil compared to those on

<table>
<thead>
<tr>
<th>Medication</th>
<th>Author</th>
<th>Study Design</th>
<th>Neuropsychiatric Symptoms</th>
</tr>
</thead>
<tbody>
<tr>
<td>Donepezil</td>
<td>Ishikawa et al.\textsuperscript{4}</td>
<td>Donepezil in PDD; prospective open-label exploratory study over 12 weeks; n=9</td>
<td>NPI (primary outcome) showed improvements in predominantly aberrant motor behaviour, anxiety and hallucinations by 1.7, 1.6, and 1.3 points, respectively</td>
</tr>
<tr>
<td></td>
<td>Aarsland et al.\textsuperscript{35}</td>
<td>Donepezil vs placebo in PD with cognitive impairment; randomised double-blind crossover study over 10 weeks; n=14</td>
<td>NPI (secondary outcome) highlighted depression being most common at baseline but no significant change was observed in the donepezil group</td>
</tr>
<tr>
<td></td>
<td>Leroi et al.\textsuperscript{36}</td>
<td>Donepezil vs placebo in PD with cognitive impairment; randomised double-blind study over 18 weeks in 2 centres; n=16</td>
<td>NPI (secondary outcome) total score dropped 40.9% in the donepezil group compared to 26.4% reduction in final visit in the placebo group</td>
</tr>
<tr>
<td>Galantamine</td>
<td>Aarsland et al.\textsuperscript{38}</td>
<td>Galantamine in PDD; multi-centre open-label study over 8 weeks; n=13</td>
<td>NPI (primary outcome) used to assess hallucination; 7 out of 9 (78%) improved from baseline</td>
</tr>
<tr>
<td></td>
<td>Grace et al.\textsuperscript{37}</td>
<td>Galantamine vs placebo in PD without dementia; randomised double-blind study over 16 weeks; n=69</td>
<td>NPI (secondary outcome) showed improvements by 1.14 points but no significant difference between groups</td>
</tr>
<tr>
<td>Rivastigmine</td>
<td>Emre et al.\textsuperscript{33}</td>
<td>Rivastigmine vs placebo in PD with cognitive impairment; randomised multi-centre double-blind study over 24 weeks; n=541</td>
<td>NPI (secondary outcome) showed significant improvement in treatment group (p=0.02), with over 40% having at least 30% improvement in NPI scores</td>
</tr>
<tr>
<td>Memantine</td>
<td>Leroi et al.\textsuperscript{41}</td>
<td>Memantine vs placebo in PDD; randomised double-blind study over 22 weeks; n=25</td>
<td>NPI (secondary outcome) showed no significant difference between groups (p=0.70)</td>
</tr>
<tr>
<td></td>
<td>Aarsland et al.\textsuperscript{42}</td>
<td>Memantine vs placebo in PDD; randomised multi-centre study over 24 weeks; n=72</td>
<td>NPI (secondary outcome) showed no significant difference between groups</td>
</tr>
<tr>
<td></td>
<td>Emre\textsuperscript{43}</td>
<td>Memantine vs placebo in PDD and DLB; randomised double-blind multicentre study; n=199</td>
<td>NPI (secondary outcome) showed no significant difference between groups at any point in PDD contrary to LBD: delusions (p=0.02), hallucinations (p=0.02), and sleep behaviour (p=0.04)</td>
</tr>
</tbody>
</table>

Table 3: Response of neuropsychiatric symptoms to cognitive enhancers in key Parkinson’s disease dementia trials.

PD: Parkinson’s disease; PDD: Parkinson’s disease Dementia; NPI: Neuropsychiatric Inventory; LBD: Lewy Body Dementia.
placebo, suggesting that such interventions may have a promising role in managing NPS associated with PDD.

Galantamine, another ChEI but with a stronger affinity to nicotinic receptors than donepezil, has also been examined in a placebo-controlled trial in PDD. However, in this study of 69 participants with 38 on active treatment, no significant improvement in NPS was seen in the active treatment group as compared to those on placebo. In another study of galantamine in PDD using an open-label design, Aarsland et al. found that 8 out of 13 (62%) participants with PDD had improved cognition. Importantly, of the nine participants who had hallucinations at baseline, seven had improved by week 8 on active treatment.

The largest RCT of a ChEI in PDD is the EXPRESS study (Emre et al.), which compared rivastigmine, the third ChEI, to placebo in 541 participants with PDD. The NPI demonstrated significant improvement in NPS in those who received rivastigmine compared to those on placebo (p=0.02). A minimum of 30% improvement in NPI scores was found in a significantly greater proportion of those on rivastigmine than those on placebo (45.5% versus 34.6%, respectively). These findings were supported by another study which also demonstrated a greater efficacy of rivastigmine on apathy and anxiety, and a significant improvement in aspects of cognition compared to placebo in people with dementia with Lewy bodies (DLB) (McKeith et al.). Rivastigmine now has a specific UK license for use in PDD to improve cognition and may also be used as first-line therapy to manage hallucinations and delusion associated with PDD. This strategy may obviate the need for poorly tolerated antipsychotic medication if used as first-line therapy.

Finally, a cognitive enhancer of a different class that has also been trialled in PDD is memantine, an N-methyl-D-aspartate (NMDA) receptor antagonist. Memantine has been shown to have a role in improving NPS in non-PD dementias; therefore, it was hypothesised to have a similar effect in PDD-related NPS. In the first reported RCT of memantine in PDD, no significant difference in NPI scores between memantine and placebo was noted (Leroi et al.). Another randomised study (Aarsland et al.), this time looking at both PDD and DLB, also found no significant difference in NPS outcomes between memantine and placebo over a 24-week period. A subsequent larger study, which also included participants with PDD and DLB, showed no improvement in NPI scores (p=0.52) in PDD at 24 weeks but a significant improvement in delusions, hallucinations, and sleep behaviour in DLB was seen. A summary of the findings on NPS from the key studies on cognitive enhancers in PDD is outlined in Table 3.

CONCLUSION

In conclusion, we have provided a brief outline of studies which demonstrate the increasing prevalence of NPS with worsening cognitive function in PD. Examining NPS, particularly apathy and psychosis, in the context of the clinical entities, PD-MCI and PDD can be important in order to anticipate further cognitive deterioration and to guide clinical decision-making, particularly regarding the use of cognitive enhancers. The high prevalence of NPS in PD with cognitive impairment emphasises the need to more fully explore the underlying pathophysiology, impact, and management of these symptoms. Further work is needed to examine the relationship of NPS and cognitive decline with disease duration of PD.

REFERENCES