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The Prevalence and Determinants of Neuropsychiatric Symptoms in Late-Stage Parkinsonism

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ABSTRACT: Background: Late-stage parkinsonism and Parkinson's disease (PD) are insufficiently studied population. Although neuropsychiatric symptoms (eg, psychosis, depression, anxiety, behavioral problems) are frequently present, their prevalence and clinical predictors remain unknown.
Objective: To determine the prevalence and predictors of neuropsychiatric symptoms in late-stage PD.
Methods: We conducted a multinational study of patients with PD with ≥7 years disease duration and either a Hoehn and Yahr stage ≥4 or a Schwab and England score ≤ 50% in the *on* stage. Neuropsychiatric symptoms were assessed through interviews with carers using the Neuropsychiatric Inventory, with a frequency × severity score ≥ 4, indicating clinically relevant symptoms. The determinants analyzed were demographic characteristics, medication, and motor and nonmotor symptoms. Univariate and multivariate logistic analyses were performed on predictors of clinically relevant neuropsychiatric symptoms.
Results: A total of 625 patients were recruited in whom the Neuropsychiatric Inventory could be completed. In 92.2% (576/625) of the patients, at least 1 neuropsychiatric symptom was present, and 75.5% (472/625) had ≥1 clinically relevant symptom. The most common clinically relevant symptoms were apathy (n = 242; 38.9%), depression (n = 213; 34.5%), and anxiety (n = 148; 23.8%). The multivariate analysis revealed unique sets of predictors for each symptom, particularly the presence of other neuropsychiatric features, cognitive impairment, daytime sleepiness.
Conclusion: Neuropsychiatric symptoms are common in late-stage PD. The strongest predictors are the presence of other neuropsychiatric symptoms. Clinicians involved in the care for patients with late-stage PD should be aware of these symptoms in this specific disease group and proactively explore other psychiatric comorbidities once a neuropsychiatric symptom is recognized.

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Late-stage parkinsonism and Parkinson's disease (PD) is defined as a phase when patients have become dependent on caregivers for activities of daily living.[1] Patients with late-stage PD experience multiple motor symptoms and nonmotor symptoms,[1–3] including neuropsychiatric symptoms (NPSs) such as psychosis, depression, anxiety, apathy, and behavioral problems. The presence of NPSs is associated with a decreased quality of life, increased caregiver burden, and an increased risk of institutionalization.[4–7] Two small cohort studies suggest NPSs to be highly prevalent in late-stage PD.[2,3] In the first study with a cohort of 73 nursing home residents, the most frequent symptoms were depression (52.9%), irritability (42.0%), apathy (30.0%), and anxiety (28.6%).[3] In the second study with an outpatient cohort of 50 late-stage PD patients, depression was also the most commonly encountered symptom (62%), with anxiety (50%) and visual hallucinations (44%) also often being present.[2] However, information on the prevalence and correlates of NPSs in this population is limited. Depression in PD overall is associated with earlier age at onset and younger age, presence of cognitive impairment, freezing of gait, levodopa-induced dyskinesia (LID), motor-defined *off* state, pain, and problems with sleep.[8–13] Psychotic symptoms, including hallucinations and delusions, are more prevalent in patients with longer disease duration, advanced disease stage, and presence of dementia.[14,15] Also, treatment with dopaminergic medication can trigger psychotic symptoms.[14,16] However, studies on the determinants of NPSs were conducted either in cohorts of patients with short disease duration,[10,12,13,17–19] excluded patients with cognitive impairment,[11,20] focused solely on demented patients,[4,21] or did not include patient-related factors in the multivariate analyses. The aim of this study was to assess the prevalence and clinical predictors of NPSs in the overall group of patients with late-stage PD.

Methods

Study Design

We examined the prevalence and correlates of NPSs in patients in the Care of Late-Stage Parkinsonism study cohort, which is a longitudinal cohort study aimed to evaluate the needs of patients in late-stage PD. This article presents a detailed analysis of the extensive baseline measurements. Further details of the study have been described in full detail elsewhere.[22] In brief, the Care of Late-Stage Parkinsonism study included centers in London (United Kingdom), Lund (Sweden), Munich (Germany), Marburg (Germany), Nijmegen (The Netherlands), Bordeaux (France), and Lisbon (Portugal) and included patients with (1) a clinical diagnosis of Parkinsonism, (2) a disease duration of at least 7 years, and (3) a Hoehn and Yahr stage 4 or 5 in the *on* stage[23] or a score on the Schwab and England scale of 50% or less in *on* stage.[24] Patients with slowly progressive atypical parkinsonism were not excluded as differentiating distinct Parkinson syndromes is typically difficult in late-stage disease, and health care needs and provision are likely very similar. Exclusion criteria were (1) a clear history of dementia prior to the onset of Parkinsonism and (2) a diagnosis of "symptomatic parkinsonism," such as normal pressure hydrocephalus and drug-induced parkinsonism. Trained assessors collected the data during home visits or outpatient appointments. All clinical data were entered in a certified data management system. The study was conducted in compliance with the Helsinki Declaration and approved by the ethical committees of all participating study sites (London, Camden, and Islington NRES Committees 14/LO/0612; Bordeaux, South West, and Overseas Protection Committee III [South West and Overseas Protection Committee], 2014-A01501–46; Lisbon, Centro Hospitalar Lisboa Norte, DIRCLN-19SET2014–275; Lund, EPN regional ethics name Lund, JPND NC 559–002; Marburg, Ethics Commission at the State Medical Association Hesse, MC 309/2014; Munich, ethics committee at the LMU Munchen, 193–14; Nijmegen, Radboud University Medical Center, Group Staff Quality and Safety Human Research Committee, Arnhem-Nijmegen region, DJ/CMO300). To obtain consent, detailed oral and written information were given to the patients and their informant to ensure that the patient fully understood the potential risks and benefits of the study. If patients were unable to provide consent, consent was obtained with the legal representative, in accordance with national law. We confirm that we have read the Journal's position on issues involved in ethical publication and affirm that this work is consistent with those guidelines.

Assessments

NPSs were assessed with the Neuropsychiatric Inventory (NPI) nursing home version.[25] The NPI was originally developed for use in research with dementia patients and was suggested for use in PD patients to assess NPSs by the Movement Disorder Society.[26] The NPI scores 10 NPSs (delusion, hallucination, agitation, depression, anxiety, euphoria, apathy, disinhibition, irritability, aberrant motor behavior) and 2 items associated with NPSs (sleep disturbances and appetite/eating changes). Each item is scored in an interview with a carer for frequency and severity on a Likert scale ranging from 0 to 4 and from 0 to 3, respectively, with higher scores indicating higher frequency or higher severity. Multiplying frequency with severity scores produces a composite score ranging from 0 to 12. NPSs with a composite score ≥ 4 are considered clinically relevant.[27,28]

Demographic, disease-related, or treatment-related variables that were considered as potential predictors of NPSs in PD included age, gender, years of education, disease duration, disease severity, comorbidity, and a range of motor and nonmotor features (see Table 1). Disease severity was assessed using Hoehn and Yahr stages.[23] Motor function was measured with the Unified Parkinson Disease Rating Scale, Part III (UPDRS-III).[24] The UPDRS-III consist of 14 items, from which subscores were derived for speech (item 18), facial expression (item 19), tremor (items 20 and 21), rigidity (item 22), bradykinesia (items 23–26), postural instability and gait impairment (items 27–29), and body hypokinesia (item 30).[29] The Mini-Mental State Examination (MMSE),[30] clock drawing test, and verbal fluency were used for the assessment of cognitive performance. Activities of daily living were assessed with the UPDRS, Part II (UPDRS-II).[24] Treatment complications were measured with the UPDRS, Part IV (UPDRS-IV), which were

TABLE 1 *Demographic, disease-related, and treatment-related variables included in the multivariate analysis*

Demographics	*Nonmotor symptoms*	*Neuropsychiatric features (continued)*
Age	Light-headedness	Apathy/indifference
Gender	Fainting	Disinhibition
Years of education	Daytime sleepiness	Irritability/lability
	Fatigue	Aberrant motor behavior
Disease-related characteristics	Difficulties falling asleep	Sleep and night-time behavior disorders
Disease duration	Restless legs	Appetite and eating changes
Hoehn and Yahr score	Hypersalivation	
	Difficulty swallowing	*Activities of daily living (UPDRS-II)*
Cognitive performance	Constipation	Speech
MMSE total score	Urgency	Salivation
	Frequency	Swallowing
Motor function (UPDRS-III)	Nocturia	Handwriting
Speech	Losing interest in sex	Cutting food and handling utensils
Facial expression	Sexual dysfunction	Dressing
Tremor	Pain	Personal hygiene
Rigidity	Anosmia	Turning in bed
Bradykinesia	Weight loss	Falling (unrelated to freezing)
Postural instability and gait impairment	Excessive sweating	Freezing when walking
Body hypokinesia		Walking
	Neuropsychiatric symptoms	Tremor
Motor complications (UPDRS-IV)	Delusions	Sensory complaints related to Parkinson's disease
Dyskinesia	Hallucinations	
Off periods	Agitation/aggression	Treatment
	Depression	Levodopa equivalent daily dose
	Anxiety	
	Elation/euphoria	

The following variables were not included because of missing data: Charlson Comorbidity Index, verbal fluency, clock drawing test.
Abbreviations: MMSE, Mini Mental State Examination; UPDRS-III, Unified Parkinson Disease Rating Scale, Part III; UPDRS-IV, Unified Parkinson Disease Rating Scale, Part IV; UPDRS-II, Unified Parkinson Disease Rating Scale, Part II.

summarized for LID (items 32–34) and *off* periods (items 36–39).[24] NPI items other than the dependent variables were used as independent variables. Other nonmotor features were measured with the Non-Motor Symptoms Scale (NMSS) in the following domains: cardiovascular, sleep/fatigue, gastrointestinal tract, urinary, sexual function, and miscellaneous.[31] The NMSS measures a composite of severity (0–3) × frequency (0–4) for each item. Comorbid diseases were assessed using the Charlson Comorbidity Index.[32] The dopaminergic medications were recalculated to levodopa equivalent daily doses.[33] Psychotropic drug use was collected for antidepressants, antipsychotics, antidementia drugs, anxiolytics, and hypnotics.

Statistical Analysis

The results were first examined for missing data. Variables were excluded from further analysis when >20% of the data were missing. To reduce missing data, imputation techniques were used for the UPDRS and NMSS. According to published recommendations,[34] items were substituted with case-specific means on the UPDRS-I and UPDRS-II if 1 item was missing and on the UPDRS-III if 7 or fewer items were missing. On the NMSS, sensitivity analyses were performed to choose an imputation strategy. The case-specific mean of the entire scale yielded the highest number of substitutions without changing the summary data scores (means, medians, and measures of variance) of the total sample, and this strategy was therefore chosen as the imputation strategy.

The prevalence of individual NPSs is presented as frequencies and percentage of the total sample of those with NPI data. For the determinant analysis, both univariate analysis and multivariate logistic regression analyses were performed with the presence of clinically relevant NPSs as the dependent variable.[35] Univariate between-group differences were evaluated with an unpaired-samples *t* tests for normally distributed variables and the Mann-Whitney test for nonnormally distributed variables. Categorical variables were evaluated with the χ^2 test. Independent variables with an association with the dependent variable with a *P* value ≤0.1 in the univariate test were included in the multivariate models. To prevent collinearity, bivariate correlation coefficients were calculated between these included independent variables. If variables had a $\rho > 0.5$, only the variable with the highest correlation with the dependent variable was included in the multivariate model. In the multivariate analysis, a backward-stepping selection procedure was applied with entry $P < 0.05$, removal $P < 0.10$, classification cut-off 0.5, and maximum 20 iteration. Descriptives are reported with means and standard deviations for normally-distributed variables and with median and minimal–maximal values for nonnormally distributed variables. The results were considered statistically significant if the Bonferroni-corrected $P < 0.05$. All analyses were performed using SPSS 22.0 (IBM, Armonk, NY).

Results

The clinical characteristics of the participants with completed NPI scores (N = 625) are given in Table 2. Data were missing ≥20% for the verbal fluency, clock drawing test, and Charlson

TABLE 2 *Characteristics of the sample of late-stage parkinsonism patients*

Characteristic	Value
Sample size, n	625
Women, n (%)	284 (45.4)
Hoehn and Yahr score, n (%)	
Stage 2	5 (0.8)
Stage 2.5	14 (2.2)
Stage 3	30 (4.8)
Stage 4	362 (57.9)
Stage 5	214 (34.2)
Country, n (%)	
United Kingdom	101 (16.1)
Germany	152 (24.3)
France	76 (12.2)
Sweden	105 (16.8)
The Netherlands	84 (13.4)
Portugal	107 (17.1)
Self-reported presence of dementia, n (%)	237 (37.9)
Cognitive impairment defined as MMSE <26, n (%)	402 (53.5)
Self-reported diagnosis of Parkinson's disease, n (%)	546 (87.4)
Current psychotropic drug use, n (%)	
Any psychotropic drug	423 (67.7)
Antidepressant	235 (37.6)
SSRI	109 (17.4)
Mirtazepine	53 (8.5)
Tricyclic	20 (3.2)
Venlafaxine	19 (3.0)
Other	34 (5.4)
Anxiolytic	66 (10.6)
Psychostimulant	3 (0.4)
Antipsychotic	156 (25.0)
Quetiapine	88 (14.1)
Clozapine	65 (10.4)
Typical (contra-indicated)	3 (0.5)
Antidementia drug	159 (25.4)
Rivastigmine	118 (18.9)
Memantine	42 (6.7)
Donezepil	14 (2.2)
Hypnotic	125 (20.0)
Age, median (min–max)	77 (24–96)
Disease duration in years, median (min–max)	14 (7–62)
Years of education, median (min–max)	9 (0–25)
Schwab and England score, median (min–max)	30 (0–80)
Levodopa equivalent daily dose, median (min–max)	815 (0–4834)

Abbreviations: MMSE, Mini Mental State Examination; SSRI, selective serotonin reuptake inhibitor.

comorbidity score, which were therefore excluded from analysis. On the NPI, missing data ranged from 69 (10.0%) for hallucinations to 78 (11.3%) for aberrant motor behavior. Elation and disinhibition had a prevalence <5% in the total sample and therefore were not analyzed further. The most common reason for missing data was the absence of a (informal) caregiver to complete the information, which is required for the application of this scale (n = 53). Those participants who missed all NPI items (n = 67; 9.7%) were younger (median age 75 vs. 77 years; $P < 0.01$), had better cognitive performance (median MMSE total 25 vs. 24; $P = 0.01$), and had lower doses of dopaminergic medication (median levodopa equivalent daily dose 687.5 vs. 815; $P < 0.01$). No differences were found on disease duration, gender, Hoehn and Yahr stage, or Schwab and England score. There were no missing data for age, medication use, or Hoehn and Yahr stage.

Prevalence of NPSs

In 92.2% (576/625) of the participants, at least 1 of the NPSs was present, and at least 1 of the clinically relevant NPS was present in 75.5% (472/625) of the participants (Table 3). The median number of NPSs in each patient was 3 and of clinically relevant NPSs 2 per patient. The most frequent NPSs on the NPI were depression (n = 372; 60.2%), apathy (n = 309; 49.7%), and anxiety (n = 274; 44.1%), and the most frequent clinically relevant symptoms were apathy (n = 242; 38.9%), depression (n = 213; 34.5%), and anxiety (n = 148; 23.8%).

Determinant Analysis

The results of the univariate test are shown in Supplementary Appendix B. In the multivariate analyses (Tables 4–7), for most NPSs, the strongest associations were seen with other NPSs. The presence of hallucinations was predicted by the presence of delusions (odds ratio [OR], 1.482; Wald, 44.60; $P < 0.001$), and conversely the presence of delusion was predicted by the presence of hallucinations (OR, 1.454; Wald, 69.76; $P < 0.001$). Agitation was predicted by the severity of irritability (OR, 1.551; Wald, 41.59; $P < 0.001$) and depression (OR, 1.196; Wald, 15.27; $P = 0.002$), and conversely irritability

TABLE 3 *Prevalence of neuropsychiatric symptoms as assessed on the Neuropsychiatric Inventory*

	Total Sample		
Symptom	Sample Size, n	Prevalence of Symptom (F ≥ 1), n (%)	Prevalence of Clinically Relevant Symptom (FxS ≥4), n (%)
Delusions	621	147 (23.7)	88 (14.2)
Hallucinations	623	257 (41.3)	129 (20.7)
Agitation/aggression	619	182 (29.4)	82 (13.2)
Depression	618	372 (60.2)	213 (34.5)
Anxiety	621	274 (44.1)	148 (23.8)
Elation/euphoria	621	25 (4.0)	9 (1.4)
Apathy/indifference	622	309 (49.7)	242 (38.9)
Disinhibition	619	49 (7.9)	26 (4.2)
Irritability/lability	620	184 (29.7)	80 (12.9)
Aberrant motor behavior	614	153 (24.9)	111 (18.1)

Abbreviations: F, frequency; S, severity

TABLE 4 *Multivariate logistic analysis on determinants of clinically relevant neuropsychiatric symptoms in late-stage parkinsonism**

Dependent Variable	Independent Variable	Measured with	β	SE	Wald Statistic	*P* Value	Odds Ratio (95% Confidence Interval)
Delusion	Dressing	UPDRS-II item 10	0.439	0.180	5.914	0.15	1.551 (1.089-2.209)
(NPI-item A)	**Hallucinations**	**NPI item B**	**0.374**	**0.045**	**69.764**	**<0.001**	**1.454 (1.331-1.587)**
	Agitation	NPI item C	0.134	0.059	5.091	0.24	1.143 (1.018-1.284)
	Constant		-4.448	0.607	63.669	<0.001	
Model coefficients: N complete cases = 548 (79.2%), χ^2 = 123.54, df 3, *P* value <0.001, log likelihood = 30.82, Nagelkerke R^2 = 0.37							
Hallucinations	Years of education	–	−0.089	0.040	5.110	0.60	0.915 (0.846-0.988)
(NPI-item B)	**Cognitive performance**	**MMSE total score**	**−0.088**	**0.021**	**17.072**	**<0.001**	**0.915 (0.878-0.955)**
	Light-headedness	NMSS item 1	0.090	0.038	5.656	0.43	1.094 (1.016-1.179)
	Daytime sleepiness	**NMSS item 3**	**0.143**	**0.036**	**15.424**	**0.002**	**1.154 (1.074-1.239)**
	Delusion	**NPI item A**	**0.393**	**0.059**	**44.595**	**<0.001**	**1.482 (1.320-1.664)**
	Anxiety	NPI item E	0.086	0.045	3.622	1.00	1.090 (0.997-1.192)
	Elation/euphoria	NPI item F	0.250	0.152	2.692	1.00	1.284 (0.953-1.731)
	Aberrant motor behavior	NPI item J	0.085	0.048	3.143	1.00	1.089 (0.991-1.196)
	Sleep and night-time behavior disorders	NPI item K	0.118	0.040	8.660	0.08	1.125 (1.040-1.217)
	Constant	–	−0.866	0.582	2.215	1.00	
Model coefficients: N complete cases = 500 (72.3%), χ^2 = 167.47, df 9, *P* value <0.001, log likelihood = 318.76, Nagelkerke R^2 = 0.46							
Agitation	LEDD	–	−0.001	0.001	3.951	1.00	0.999 (0.998-1.000)
(NPI-item C)	Cognitive performance	MMSE total score	−0.054	0.026	4.161	0.90	0.948 (0.900-0.998)
	Falling (unrelated to freezing)	UPDRS-II item 13	0.224	0.126	3.129	1.00	1.251 (0.976-1.602)
	Depression	**NPI item D**	**0.179**	**0.046**	**15.273**	**0.002**	**1.196 (1.094-1.309)**
	Elation/euphoria	NPI item F	0.430	0.186	5.311	0.46	1.536 (1.066-2.214)
	Irritability	**NPI item I**	**0.439**	**0.068**	**41.587**	**<0.001**	**1.551 (1.357-1.772)**
	Constant		−2.203	0.671	10.759	0.02	
Model coefficients: N complete cases = 505 (73.0%), χ^2 = 112.27, df 6, *P* value <0.001, log likelihood = 231.18, Nagelkerke R^2 = 0.40							

*Shown are backward-stepping logistic regression models with clinically relevant NPI items (Frequency x Severity ≥4) as dependent variables based on data from the total sample.
Abbreviations: SE, standard error; NPI, Neuropsychiatric Inventory; UPDRS-II, Unified Parkinson Disease Rating Scale, Part II; MMSE, Mini-Mental State Examination; NMSS, Non-Motor Symptoms Scale; LEDD, levodopa equivalent daily dose; F, frequency; S, severity.

TABLE 5 *Multivariate logistic analysis on determinants of clinically relevant neuropsychiatric symptoms in late-stage parkinsonism**

Dependent Variable	Independent Variable	Measured with	β	SE	Wald Statistic	*P* Value	Odds Ratio (95% Confidence Interval)
Depression	**Hygiene**	**UPDRS-II item 11**	**0.495**	**0.126**	**15.334**	**0.003**	**1.641 (1.281–2.103)**
(NPI-item D)	Daytime sleepiness	NMSS item 3	−0.078	0.033	5.460	0.53	0.925 (0.867–0.988)
	Pain	NMSS item 27	0.064	0.027	5.511	0.53	1.066 (1.011–1.124)
	Weight loss	**NMSS item 29**	**0.109**	**0.032**	**11.235**	**0.02**	**1.115 (1.046–1.188)**
	Agitation	NPI item C	0.189	0.067	8.018	0.14	1.208 (1.060–1.377)
	Anxiety	**NPI item E**	**0.287**	**0.047**	**36.972**	**<0.001**	**1.332 (1.214–1.461)**
	Apathy	**NPI item G**	**0.156**	**0.034**	**21.119**	**<0.001**	**1.169 (1.094–1.249)**
	Sleep and night-time behavior disorders	**NPI item K**	**0.095**	**0.034**	**7.665**	**0.006**	**1.100 (1.028–1.177)**
	Constant	–	−3.550	0.417	72.633	<0.001	
Model coefficients: N complete cases = 496 (71.7%), χ^2 = 187.11, df 8, *P* value <0.001, log likelihood = 455.66, Nagelkerke R^2 = 0.43							
Anxiety	Female gender	–	0.642	0.260	6.116	0.31	1.9101 (1.143–3.162)
(NPI-item E)	Cognitive performance	MMSE total score	0.049	0.025	3.845	1.00	1.050 (1.000–1.102)
	Turning in bed and adjusting clothes	UPDRS-II item 12	0.248	0.129	3.707	1.00	1.281 (0.996–1.648)
	Falling (unrelated to freezing)	UPDRS-II item 13	−0.224	0.100	4.983	0.62	0.800 (0.657–0.973)
	Body bradykinesia	UPDRS-III item 31	−0.283	0.153	3.428	1.00	0.753 (0.558–1.017)
	Dyskinesia	UPDRS-IV items 32–34	0.132	0.058	5.213	0.53	1.141 (1.019–1.278)
	Restless legs	NMSS item 6	0.064	0.033	3.619	1.00	1.066 (0.998–1.138)
	Lost interest in sex	**NMSS item 25**	**0.090**	**0.024**	**13.827**	**0.005**	**1.094 (1.043–1.147)**
	Delusion	NPI item A	−0.118	0.069	2.910	1.00	0.889 (0.776–1.018)
	Hallucination	NPI item B	0.133	0.057	5.435	0.48	1.142 (1.021–1.277)
	Depression	**NPI item D**	**0.234**	**0.040**	**33.791**	**<0.001**	**1.264 (1.168–1.368)**
	Apathy	NPI item G	0.066	0.039	2.807	1.00	1.068 (0.989–1.153)
	Irritability/lability	**NPI item I**	**0.191**	**0.059**	**10.566**	**0.03**	**1.210 (1.079–1.358)**
	Constant	–	−4.336	0.881	24.215	<0.001	
Model coefficients: N complete cases = 524 (75.7%), χ^2 = 165.63, df 13, *P* value <0.001, Log likelihood = 403.09, Nagelkerke R^2 = 0.41							

*Shown are backward-stepping logistic regression models with clinically relevant NPI items (Frequency x Severity ≥4) as dependent variables based on data from the total sample. Bold font indicates a bonferroni-corrected significance of p<0.05.

Abbreviations: SE, standard error; NPI, Neuropsychiatric Inventory; UPDRS-II, Unified Parkinson Disease Rating Scale, Part II; MMSE, Mini-Mental State Examination; UPDRS-III, Unified Parkinson Disease Rating Scale, Part III; UPDRS-IV, Unified Parkinson Disease Rating Scale, Part IV; NMSS, Non-Motor Symptoms Scale; LEDD, levodopa equivalent daily dose; F, frequency; S, severity.

TABLE 6 *Multivariate logistic analysis on determinants of clinically relevant neuropsychiatric symptoms in late-stage parkinsonism**

Dependent Variable	Independent Variable	Measured with	β	SE	Wald Statistic	*P* Value	Odds Ratio (95% Confidence Interval)
Apathy	**Cognitive performance**	**MMSE total score**	**−0.121**	**0.019**	**39.231**	**<0.001**	**0.886 (0.853–0.920)**
(NPI-G)	Freezing when walking	UPDRS-II item 14	0.177	0.089	3.929	1.00	1.194 (1.002–1.422)
	Off periods	UPDRS-IV items 36–39	−0.172	0.069	6.269	0.32	0.842 (0.736–0.963)
	Daytime sleepiness	NMSS item 3	0.059	0.033	1.00	1.00	1.061 (0.994–1.132)
	Fatigue	NMSS item 4	0.067	0.030	5.001	0.68	1.069 (1.008–1.134)
	Losing interest in sex	**NMSS item 25**	**0.087**	**0.023**	**14.141**	**0.005**	**1.091 (1.042–1.141)**
	Depression	**NPI item D**	**0.166**	**0.041**	**16.045**	**0.002**	**1.180 (1.088–1.280)**
	Anxiety	NPI item E	0.106	0.046	5.317	0.57	1.112 (1.016–1.216)
	Sleep and night-time behavior disorders	NPI item K	0.095	0.034	7.655	0.16	1.100 (1.028–1.176)
	Appetite and eating changes	NPI item L	0.085	0.040	4.515	0.92	1.089 (1.007–1.178)
	Constant		0.014	0.503	0.001	1.00	
Model coefficients: N complete cases = 493 (71.2%), χ^2 = 191.48, df 10, *P* value <0.001, log likelihood = 454.52, Nagelkerke R^2 = 0.44							
Irritability	Cognition	MMSE total score	0.063	0.031	4.215	0.76	1.065 (1.003–1.131)
(NPI-I)	Cutting foods and handling utensils	UPDRS-II item 9	0.328	0.171	3.683	0.94	1.388 (0.993–1.939)
	Delusion	NPI item A	0.121	0.054	5.007	0.43	1.128 (1.015–1.254)
	Agitation	**NPI item C**	**0.344**	**0.063**	**29.501**	**<0.001**	**1.410 (1.246–1.596)**
	Anxiety	**NPI item E**	**0.151**	**0.045**	**11.358**	**0.01**	**1.163 (1.065–1.270)**
	Sleep and night-time behavior disorders	NPI item K	0.113	0.042	7.388	0.12	1.120 (1.032–1.215)
	Constant		−5.677	1.001	32.171	<0.001	
Model coefficients: N complete cases = 516 (74.6%), χ^2 = 96-48, df 6, *P* value <0.001, log likelihood = 270.40, Nagelkerke R^2 = 0.34							

*Shown are backward-stepping logistic regression models with clinically relevant NPI items (Frequency x Severity ≥4) as dependent variables based on data from the total sample. Bold font indicates a bonferroni-corrected significance of p<0.05.

Abbreviations: SE, standard error; NPI, Neuropsychiatric Inventory; MMSE, Mini-Mental State Examination; UPDRS-II, Unified Parkinson Disease Rating Scale, Part II; UPDRS-IV, Unified Parkinson Disease Rating Scale, Part IV; NMSS, Non-Motor Symptoms Scale; LEDD, levodopa equivalent daily dose; F, frequency; S, severity.

TABLE 7 *Multivariate logistic analysis on determinants of clinically relevant neuropsychiatric symptoms in late-stage parkinsonism**

Dependent Variable	Independent Variable	Measured with	β	SE	Wald Statistic	*P* Value	Odds Ratio (95% Confidence Interval)
Aberrant motor behavior (NPI J)	Tremor	UPDRS-II item 16	−0.435	0.145	9.058	0.06	0.647 (0.487–0.859)
	Sensory complaints related to Parkinson's disease	UPDRS-II item 17	−0.241	0.120	4.034	0.90	0.786 (0.621–0.994)
	Dyskinesia	**UPDRS-IV items 32–34**	**0.217**	**0.061**	**12.561**	**0.008**	**1.243 (1.102–1.402)**
	Off periods	UPDRS-IV items 36–39	−0.143	0.078	3.367	1.00	0.867 (0.744–1.010)
	Constipation	NMSS item 21	−0.085	0.033	6.731	0.18	0.919 (0.862–0.980)
	Urgency	NMSS item 22	0.048	0.026	3.403	1.00	1.050 (0.997–1.105)
	Delusion	**NPI item A**	**0.171**	**0.052**	**10.629**	**0.02**	**1.186 (1.071–1.315)**
	Hallucinations	NPI item C	0.102	0.049	4.439	0.70	1.108 (1.007–1.218)
	Disinhibition	NPI item H	0.155	0.078	3.978	0.92	1.168 (1.003–1.361)
	Appetite and eating changes	NPI item L	0.108	0.041	6.876	0.18	1.114 (1.028–1.208)
	Constant		−1.701	0.306	30.867	<0.001	

Model coefficients: N complete cases = 522 (75.4%), χ^2 = 90.62, df 10, *P* value <0.001, log likelihood = 389.30, Nagelkerke R^2 = 0.27

*Shown are backward-stepping logistic regression models with clinically relevant NPI items (Frequency x Severity ≥4) as dependent variables based on data from the total sample. Bold font indicates a bonferroni-corrected significance of p<0.05.. Potential collinearity (ρ > 0.5) resulting in the restriction of 1 variable into the model was found for the following set of variables: gait impairment (UPDRS-III postural instability and gait impairment score, UPDRS-II items 15 walking, and 10 dressing), psychosis (NPI items A and B), dysphagia (UPDRS-II items 6 hypersalivation and 7 swallowing, NMSs questions 19 hypersalivation, and 20 difficulty swallowing), urological dysfunction (NMSS questions 22 urgency and 23 frequency), sexuality (NMSS questions 25 losing interest in sex and 26 sexual dysfunction), activities of daily living (UPDRS-II items 8 handwriting, 9 cutting foods and handling utensils, 10 dressing, 11 hygiene, and 12 turning in bed and adjusting clothes).
Abbreviations: SE, standard error; NPI, Neuropsychiatric Inventory; UPDRS-II, Unified Parkinson Disease Rating Scale, Part II; UPDRS-IV, Unified Parkinson Disease Rating Scale, Part IV; MMSE, Mini-Mental State Examination; NMSS, Non-Motor Symptoms Scale; LEDD, levodopa equivalent daily dose; UPDRS-III, Unified Parkinson Disease Rating Scale, Part III; F, frequency; S, severity.

was predicted by agitation scores (OR, 1.410; Wald, 29.50; $P < 0.001$) as well as anxiety (OR, 1.163; Wald, 11.36; $P = 0.01$).

In several models, other predictors than NPSs were found. The presence of hallucinations was inversely predicted by the degree of cognitive performance (OR, 0.915; Wald, 17.07; $P < 0.001$) and correlated positively with daytime sleepiness (OR, 1.154; Wald, 15.42; $P = 0.002$), For depression, the ability to undertake personal hygiene tasks (OR, 1.641; Wald, 15.33; $P = 0.003$), sleep problems (OR, 1.100; Wald, 7.67; $P = 0.006$), and weight loss (OR, 1.115; Wald, 11.24; $P = 0.02$) were the strongest predictors in addition to the following 2 NPSs: anxiety (OR, 1.332; Wald, 36.97; $P \leq 0.001$) and apathy (OR, 1.669; Wald, 21.12; $P < 0.001$). For anxiety, the main predictor variables were loss of interest in sex (OR, 1.094; Wald, 13.83; $P = 0.005$) and again the following 2 NPSs: depression (OR, 1.264; Wald, 33.79; $P < 0.001$) and irritability (OR, 1.210; Wald, 10.57; $P = 0.03$). For apathy, the strongest determinants were a lower cognitive performance (OR, 0.886; Wald, 39.23; $P < 0.001$), loss of interest in sex (OR, 1.091; Wald, 14.14; $P = 0.005$), and the presence of depression (OR, 1.180; Wald, 16.05; $P = 0.002$). For aberrant motor behavior, LID was the strongest predictor (OR, 1.243; Wald, 12.56; $P = 0.008$), followed by the presence of delusion (OR, 1.186; Wald, 10.63; $P = 0.02$).

Discussion

We found that NPSs are highly prevalent in the late stage of PD and that these are clinically relevant in the vast majority of patients. Most patients had at least 2 NPSs occurring together. Although each NPS has a unique set of disease-related determinants, the strongest predictors for most NPSs were the presence of other NPSs.

Multiple prevalence estimates of NPSs in PD have been published, ranging from 14% to 69% for individual NPSs and 61% to 89% for the overall presence of any NPSs,[8,36–42] but there are no previous studies examining their combined prevalence in the overall late-stage disease population. Although there are publications available for cohorts of patients with Parkinson's disease with dementia (PDD)[27] and long disease durations,[43] late-stage Parkinsonism differs as it is defined by the notion of having become dependent on others for daily living.[1] These patients have, by nature of their dependencies, difficulty in participating with study protocol and visits, and do not frequently participate in studies. Earlier studies in this population did not have appropriate sample sizes to definitely answer our research questions (sample size <100).[2,3] Our high prevalence figures for NPSs do resemble the prevalence of NPSs in a cohort with 537 PDD participants[4,44] in whom the prevalence of hallucinations, depression, and apathy was 44%, 57%, and 54%, respectively. That study recruited participants from a multicenter trial on rivastigmine using the presence of mild to moderate severe dementia (MMSE, 10–24) as inclusion criterion. In the current study of patients with late-stage PD, in whom 36% had a self-reported diagnosis of dementia and 53% had cognitive

impairment as defined by a MMSE <26, the corresponding rate of hallucinations, depression, and apathy were very similar at 41%, 60%, and 50%. The percentage of clinically relevant symptoms in our study is also similar to the findings in the PDD cohort, with the exception of clinically relevant depression and aberrant motor behavior, which were slightly higher in our late-stage PD population (35% vs. PDD 21% for depression, 18% vs. PDD 13% for aberrant motor behavior). It is likely that there is considerable overlap between the 2 cohorts with comparable mechanisms, although our study selected participants primarily based on motor stage and disease duration. Both cohorts shared characteristics such as worse cognitive performance, functional dependence, daytime sleepiness, and motor complications. There is an ongoing controversy on the underlying pathology of PDD, which is likely to include diffuse Lewy body distribution in the cortical areas as well as Alzheimer's disease pathology.[45] Our results that NPSs are common in late-stage PD with and without dementia suggest that NPSs are not necessarily restricted to those with dementia, but can be hypothesized to reflect the wider spread of pathology in all patients in late-stage PD.

Of note, the most consistent predictors of NPSs in general was the presence of other NPSs. This association may suggest that these determine each other, such as a depression resulting from hallucinations, but more likely suggest that they are manifestations of the same syndrome (eg, anxiety and depression) or a common cause attributed to jointly affected brain regions. Multiple studies have investigated the complex interrelationship of NPSs in PD using factor and hierarchical cluster analyses.[4,18,40,46,47] In the previously mentioned cohort of PDD, the following 5 separate profiles of NPSs were suggested: (1) low overall NPI scores; (2) high depression, anxiety, and apathy scores and low scores on other NPS items; (3) high apathy scores and low scores on other NPS items; (4) high scores on all items, especially on agitation and irritability; and (5) high scores on hallucinations and delusion and low scores on other items. Our results with the late-stage PD patient population are in keeping with these profiles with an interrelation between depression, anxiety, and apathy (profile 2); correlation between irritability, agitation, anxiety, and apathy (profile 4); and correlation between delusion and hallucinations (profile 5). However, we have not performed cluster analysis to confirm these findings as it was outside the scope of the current study. Other associations in this study are in keeping with the different expressions of NPSs, concomitant cognitive impairment, or medication side effects, such as the association of depression with agitation or the association of delusions with aberrant motor behavior. We also found an association of aberrant motor behavior with LID. Although aberrant motor behavior is largely defined by repetitive tasks such as pacing and undoing buttons, there is also overlap with LID and an urge to move.[48] Another explanation for this association is that late-stage PD patients may not be able to display aberrant motor behavior as a result of severe motor impairment, with the exception of those who have a good motor response with LID and are able to display aberrant motor behavior.

We also found an association between loss of libido and anxiety and apathy, which may be the result of the NPS itself, loss of libido leading to anxiety, or the common underlying mechanism affecting related brain areas. Other results align with previously literature such as associations of cognitive performance with hallucinations and apathy,[49–51] the association of daytime sleepiness with hallucinations,[52] the association of weight loss with depression,[53,54] and the findings of dependence in personal hygiene as a determinant for depression.[55]

It is noteworthy that, once other NPSs are accounted for, in this population with virtually uniformly severe motor impairment, other motor and nonmotor aspects of the disease were not strongly associated with the occurrence of NPSs. Although some of this may be explained by the lack of sensitivity of the rating scales used, it can be hypothesized that the pathology in other areas than those determining motor function is the overriding factor for the occurrence of these symptoms.

Strengths and Limitations

This is the largest study to date in this difficult-to-reach population. We demonstrate the high prevalence and severity of NPSs in this population. This study's limitations include the heterogeneity of the sample as we included patients with any type of parkinsonism. However, only a small percentage of patients did not have a diagnosis of PD (n = 80; 12%), and the results restricted to those with a diagnosis of Parkinson's disease were similar. We allowed for the inclusion of patients already using psychotropic drugs. The current prevalence estimates could be an underestimation as a result of this. We did not include treatment variables in the analysis because these can be both causes and consequences of NPSs. Therefore, no conclusions can be drawn on potential undertreatment with psychotropic drugs or on the contribution of specific dopaminergic treatments (such as dopamine agonist). Another limitation is the cross-sectional design of the study. As a result, we cannot infer the causality between determinant and outcome. The number of patients with dementia or cognitive decline is relatively low compared with another cohort with similar disease duration.[56,57] This could indicate a recruitment bias where patients with dementia were less likely to participate. On the other hand, one of the key strengths of the study includes its size and the strong efforts to include patients not currently in specialist care. Because of the nature of the condition, our selection criteria, and the primary assessment measure of NPSs requiring a carer, we were at risk of being unable to complete the assessment in several participants, resulting in missing data. To mitigate this, we took considerable care to allow for frequent breaks in the assessment and spreading of assessments across multiple visits. We further performed an elaborate missing data analysis prior to analysis to ensure that participants and variables were included where possible. We believe that these steps allowed for a high study quality despite the challenges of recruitment and assessment in this population.

We demonstrated that NPSs are highly prevalent in late-stage PD and that they predict the presence of other NPSs. Clinicians involved in the care for patients with late-stage PD should be aware of the frequent occurrence of NPSs in this specific disease group and proactively explore other psychiatric comorbidities once NPSs are recognized. Future research

should work to shed more light on the common causes of NPSs and develop tailored interventional and supportive strategies for this disease group.

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Author Roles

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Disclosures

Ethical Compliance Statement: The study was conducted in compliance with the Helsinki Declaration and approved by the ethical committees of all participating study sites (London, Camden, and Islington NRES Committees 14/LO/0612; Bordeaux, South West, and Overseas Protection Committee III [South West and Overseas Protection Committee], 2014-A01501–46; Lisbon, Centro Hospitalar Lisboa Norte, DIRCLN-19SET2014–275; Lund, EPN regional ethics name Lund, JPND NC 559–002; Marburg, Ethics Commission at the State Medical Association Hesse, MC 309/2014; Munich, ethics committee at the LMU Munchen, 193–14; Nijmegen, Radboud University Medical Center, Group Staff Quality and Safety Human Research Committee, Arnhem-Nijmegen region, DJ/CMO300). To obtain consent, detailed oral and written information were given to the patients and their informant to ensure that the patient fully understood the potential risks and benefits of the study. If patients were unable to provide consent, consent was obtained with the legal representative, in accordance with national law. We confirm that we have read the Journal's position on issues involved in ethical publication and affirm that this work is consistent with those guidelines.

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Supporting Information

Supporting information may be found in the online version of this article.

Appendix A. Frequencies of neuropsychiatric symptoms in the subgroup of patients with typical Parkinson's disease.

Appendix B. Univariate associations between the presence of neuropsychiatric symptoms and predictors.