Impairment and disability in late-stage parkinsonism

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CHAPTER 1. Introduction

"As the debility increases and the influence of the will over the muscles fades away, the tremulous agitation becomes more vehement. It now seldom leaves him for a moment; but even when exhausted nature seizes a small portion of sleep, the motion becomes so violent as not only to shake the bed-hangings, but even the floor and sashes of the room. The chin is now almost immoveably bent down upon the sternum. The slops with which he is attempted to be fed, with the saliva, are continually trickling from the mouth. The power of articulation is lost. The urine and faeces are passed involuntarily; and at the last, constant sleepiness, with slight delirium, and other marks of extreme exhaustion, announce the wished-for release." [1]

James Parkinson on late-stage parkinsonism in the pre-levodopa era.

1.1 Disability and parkinsonism

Scientific progress in medicine has resulted in a reduced mortality in most diseases, but has not resulted in a similar reduction of disability [2]. In recent years, neurological diseases have become the leading cause of disability in the world, comprising 10.2% of global disability-adjusted life years [3]. Parkinson's disease (PD) is the fastest growing neurological disease [4, 5]. The overarching term "parkinsonism" refers to a group of neurological disorders, of which 85% of the persons are diagnosed with PD. The remaining persons, have a form of atypical parkinsonism, including vascular parkinsonism, multiple system atrophy, progressive supranuclear palsy, cortical basal degeneration or dementia with Lewy-bodies [6, 7]. In 2018, 6.2 million people in the world had PD, and this number is expected to double before the year 2040. In addition to an increase in the number of people with parkinsonism, the expected disease duration (14.8 years for women and 13.0 years for men) rises by 3 years around the year 2030, compared with people with parkinsonism living in 2010 [8]. Persons with longer disease durations are likely to become more disabled [9, 10]. Understanding disability in parkinsonism is therefore paramount in anticipating the health care needs of the future population and in setting the research goals of researchers.

1.2 Disease course and staging systems

Two-hundred years ago, James Parkinson already acknowledged the disabling nature of parkinsonism, in his seminal paper 'An essay on the shaking palsy', in which he calls the nature of parkinsonism "highly afflictive" [1]. In this iconic manuscript he reiterates the typical disease course from "slight and nearly imperceptible" at the start of the disease, to exhausting and violent at the end-stage of the disease. In spite of the careful descriptions by James Parkinson, it lacks a thorough systematic depiction of the course of disability. In the wake of the development of the first therapeutic agent for parkinsonism (levodopa), systematic staging on the extent of disability became a necessary step in evaluating drug treatments [11]. To this end, the Hoehn and Yahr-staging system for PD was developed. This included a description of the later stages of the disease: stage 4 and 5 (table 1) [12]. The Hoehn and Yahr stages describe the disease course from the onset of motor symptoms to the deterioration of functional mobility. No equivalent staging system is available for the other forms of parkinsonism.

Table 1. Disease stage classification, combining PD-related disability and impairments

Stage	Hoehn and Yahr Scale	Modified Hoehn and Yahr Scale
1	Unilateral involvement only usually with minimal or no functional disability	Unilateral involvement only
1.5	-	Unilateral and axial involvement
2	Bilateral or midline involvement without impairment of balance	Bilateral involvement without impairment of balance
2.5	-	Mild bilateral disease with recovery on pull test
3	Bilateral disease: mild to moderate disability with impaired postural reflexes; physically independent	Mild to moderate bilateral disease; some postural instability; physically independent
4	Severely disabling disease; still able to walk or stand unassisted	Severe disability; still able to walk or stand unassisted
5	Confinement to bed or wheelchair unless aided	Wheelchair bound or bedridden unless aided

In the post-levodopa era, the typical disease course of PD changed and now also includes phenomena that result from therapeutic management, like motor fluctuations and other adverse events, like orthostatic hypotension of psychotic symptoms [13]. Also, new insights and better recognition of pathology resulted in an understanding that the disease course of PD includes many non-motor symptoms, many of which may manifest well before presentation of the first motor symptoms (figure 2) [14, 15]. In spite of these new insights, the Hoehn and Yahr-staging system is still operationally the most robust staging system as researchers have most experience with this scale and because it is easy to implement. Another scale, the Schwab and England score, supplements the Hoehn and Yahr scale. This score measures the person's ability to perform daily tasks and was initially developed to evaluate deep-brain surgery in persons with PD [16]. It focuses less on motor symptoms.

1.3 Impacts of impairments

Disability is conceptually distinct from impairment, disease severity and quality of life, but in practice, these entities are interrelated [17] (see Box 1). The pathway through which person's impairments result in disability, can be complex and highly individual [18]. At the group level, multiple impairments frequently contribute to disability. Early in the disease course, gait and balance problems are the most important determinants of disability [19-22]. With further disease progression, other motor features such as motor fluctuations and dystonia, correlate strongly with

disability [21]. Dyskinesia has a modest association with disability [21]. Non-motor symptoms that have a strong correlation with disability are: cognitive dysfunction [22-24], psychosis [22], urinary incontinence, apathy [22] and depression [22, 25]. Pain correlates moderately with disability [26]. Only weak correlations were seen for orthostatic hypotension and sleep disturbance [21]. Data suggest that most of these impairments are frequent in late-stage disease. Debilitating motor symptoms that are common are dysarthria and falls [27-29], which are both present in more than 80% of persons after 15 years of disease duration [9]. Swallowing difficulties are also common [27, 30], as they are present in more than 50% of 15-year survivors [9]. Importantly, swallowing difficulties are strongly associated with higher mortality due to pneumonia [31]. Of the debilitating non-motor symptoms, depression, apathy and anxiety are present in approximately half of persons [9, 32]. The presence of dementia seems inevitable with time [14, 33, 34], as it has been described in >80% of 20-year of disease survivors [10, 35]. Other symptoms seem to diminish in prevalence over time, like tremor and treatment-responsive motor fluctuations [36-38]. Also, specifically for late-stage parkinsonism (LSP), the beneficial treatment effect of dopaminergic drugs, while maintained for the core motor features [33, 39, 40], diminish when it comes to treating major problems like speech problems, postural instability, dementia, most neuropsychiatric features and autonomic dysfunction [29, 41, 42].

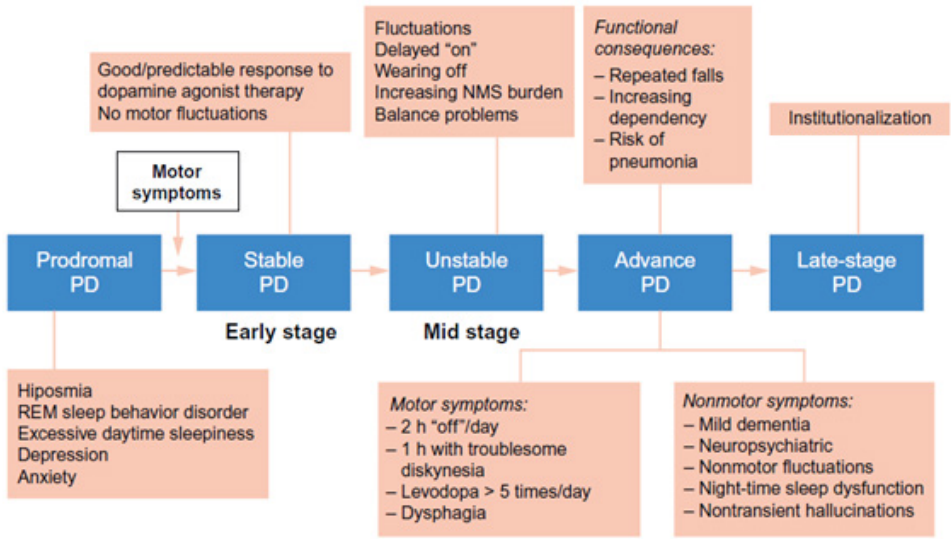

Figure 2. Post levodopa disease course of Parkinson's disease

Adapted from Chaudhuri, K.R. & Fung, V.S.C. (Eds.) (2016). Fastfacts. (4th ed.), UK: Health Press.

Box 1. The concept of disability

In the International Classification of Functioning, Disability and Health, the World Health Organizations defines disability as two separate entities: 1. activity limitations, defined as "difficulties in the execution of a task or action by an individual", and 2. participation restrictions, defined as "problems with the involvement in life situations" [43] (see figure 3). Specifically, disability affects the activities necessary for daily living, the instrumental activities of daily living and functional mobility [17]. Impairments are defined as: "problems in body functions and structures" [43]. Disease severity refers to the clinical expression of the biology of the disease and is defined as the amount of impairment or disability that result from a specific pathophysiological process [12]. Quality of life captures the personal values and perspectives of the person on the consequences of the disease, including the amount of disability [44]. Within the syndromes of parkinsonism, impairments mostly are motor symptoms, signs of autonomic dysfunctions, cognitive impairments and neuropsychiatric symptoms [45, 46]. Disability is increased with higher disease severity and worse quality of life in parkinsonism [21, 47].

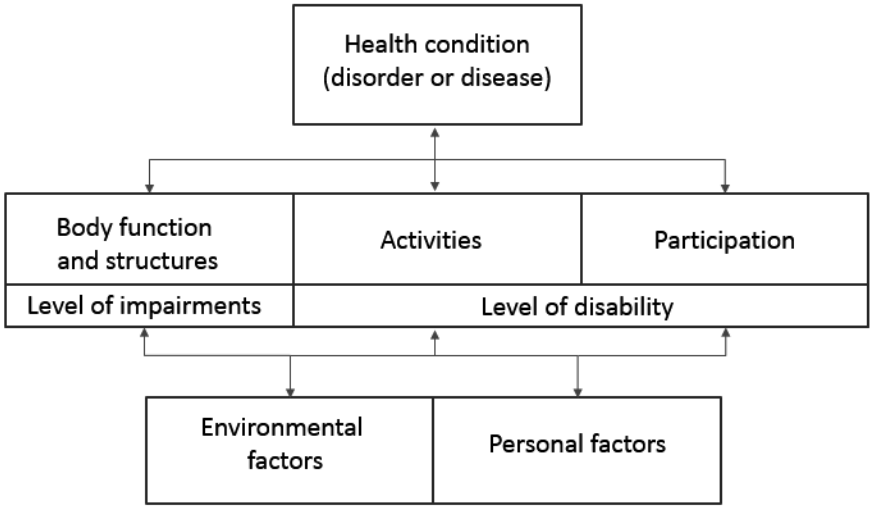

Figure 3 Conceptual representation of disability and impairments in the ICF-model*

**ICF=International Classification of Functioning, Disability and Health*

1.4 Societal response

Societally, facilitating knowledge on movement disorders is a central element in the response to the increase in PD-related disability. ParkinsonNet has been a prime example of knowledge development and implementation by means of a nationwide networking community consisting of specifically trained PD healthcare professionals [48]. ParkinsonNet has the infrastructure to implement quality monitoring and facilitate multidisciplinary collaborations as it is organized in regional sub-units. Also it develops specialized trainings (e.g. recently a blended learning tool for palliative care for PD was launched [49]). Institutionally, several health care organizations (including long-term care organizations) started organizing PD-care centrally [50]. This allows for better training of health care professionals and generates more experience with specialized care needs as higher numbers of people with parkinsonism are encountered. Currently, the government and insurance agencies in the Netherlands are showing increased interest in these centers of expertise [51]. However, all these initiatives run into the problem of a lack of systematic scientific data on late-stage disease.

1.5 Rationale for studying late-stage parkinsonism

LSP is an underserved and understudied population. Elderly care for people with LSP is suggested to be suboptimal and can be improved [52], as exemplified by the findings of one study performed in nursing home residents who experienced wearing-off for most of the day and who nevertheless received seemingly low dose of levodopa [28]. Existing expert-opinion and scientific data are of unclear status, as both expert- and research centers are difficult to visit for persons with LSP. Methodological issues hamper scientific studies as they typically had a small sample size or were performed in a single center, complicating the generalizability of the findings [24, 26, 28]. Lastly, major trials deliberately excluded persons with dementia, therefore probably excluding also persons with LSP [53].

The current thesis aims to improve the existing knowledge on impairments and disability in LSP. Late-stage parkinsonism (LSP) will be defined as Hoehn and Yahr stages 4 and 5, or a Schwab and England score ≤ 50%, to also include those persons who were disabled due to non-motor symptoms. In the following chapters, the results of a large cross-sectional study, a selective analysis of a sample of nursing home residents and a pragmatic trial will be presented to give insight into the complexity and treatability of disability in late-stage parkinsonism.

1.6 Thesis outline

The following research questions will be addressed in this thesis:

Chapter 2. *What are the frequencies of motor and non-motor features in LSP and what is the impact on disability?*
This chapter describes the general characteristics of a multinational sample of nearly 700 persons with LSP and the prevalence of common and less-common motor and non-motor impairments will be reported. Also, the correlation of these impairments with disability will be shown.

Chapter 3. *What are the prevalence and determinants of neuropsychiatric features in LSP?*
This chapter reports the prevalence and determinants of neuropsychiatric symptoms in the same cohort as in the previous chapter. Neuropsychiatric symptoms are widely recognized to strongly associate with disability, but it is unknown whether disability is also an important determinant of neuropsychiatric symptoms. This chapter includes a determinant analysis on a wide range of disease and treatment related characteristics.

Chapter 4. *What are the prevalence and prescribed treatments of orthostatic hypotension in nursing home residents with PD?*
Here, a specific, but frequently unrecognized issue (namely orthostatic hypotension) is studied in a cohort of nearly 70 nursing home residents diagnosed with PD. These persons are highly disabled, as they are unable to live independently. Risk factors for orthostatic hypotension (cardiovascular diseases, use of antihypertensive drugs) and prescribed treatments are reported in relation to the prevalence of this impairment.

Chapter 5. *What is the feasibility and efficacy of recommendations by a movement disorder expert on activities of daily living?*
This chapter shows the results of a pragmatic randomized controlled trial evaluating the impact of an intervention consisting of a letter with recommendations written by a movement disorder expert. The primary outcome is disability. Several motor and non-motor impairments, as well as quality of life were secondary outcomes.

Chapter 6. *General Discussion*
Finally, the results are discussed and interpreted with the aim of furthering understanding of impairments and disability in late-stage parkinsonism.

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CHAPTER 2. The late-stage of parkinsonism's – motor and non-motor complications

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2.1 Abstract

Introduction There is little information on the late stages of parkinsonism.

Methods We conducted a multicenter study in 692 patients with late stage parkinsonism in six European countries. Inclusion criteria were disease duration of ≥7 years and either Hoehn and Yahr stage ≥4 or Schwab and England score of 50 or less.

Results Average disease duration was 15.4 (SD 7.7) years and mean total UPDRS score was 82.7 (SD 22.4). Dementia according to MDS-criteria was present in 37% of patients. Mean levodopa equivalence dose was 874.1 (SD 591.1) mg/d. Eighty two percent of patients reported falls, related to freezing (16%) or unrelated to freezing (21% of patients) or occurring both related and unrelated to freezing (45%), and were frequent in 26%. Moderate-severe difficulties were reported for turning in bed by 51%, speech by 43%, swallowing by 16% and tremor by 11%. Off-periods occurred in 68% and were present at least 50% of the day in 13%, with morning dystonia occurring in 35%. Dyskinesias were reported by 45% but were moderate or severe only in 7%. Moderate-severe fatigue, constipation, urinary symptoms and nocturia, concentration and memory problems were encountered by more than half of participants. Hallucinations (44%) or delusions (25%) were present in 63% and were moderate-severe in 15%. The association with overall disability was strongest for severity of falls/ postural instability, bradykinesia, cognitive score and speech impairment.

Conclusion These data suggest that current treatment of late stage parkinsonism in the community remains insufficiently effective to alleviate disabling symptoms in many patients.

2.2 Introduction

The clinical features of Parkinson's disease (PD), including motor and non-motor features, are well recognized. However, whilst many studies have concentrated on the earlier features of the disease and their treatment, there is surprisingly little information on the clinical problems encountered in the late stages of PD, even though this is the population with the greatest impairment requiring significant medical and non-medical management. Whilst many motor and non-motor can be present even in the early stages of PD, including mild slowness, anxiety, depression, sleep disturbances, constipation and orthostatic hypotension, they are typically less common and less severe than in advancing disease, and others, like motor complications, freezing and hallucinations are rare [1-4]. Most studies including patients in later disease stages addressed specific features such as hallucinations, are single-center or had small sample sizes [5-7]. In specialist practice, the proportion of patients in the late stages is also underrepresented as they are often too disabled to attend hospital or office-based appointments and do not receive adequate care [7]. Knowledge about the motor and non-motor features of late stage parkinsonism is required to inform appropriate management of and service provision for these patients. Therefore, we here describe the results of a cross-sectional investigation of the clinical features of late stage parkinsonism from a large, European cohort study.

2.3 Methods

Study design

The Care of Late Stage Parkinsonism (CLaSP) study is a longitudinal multicenter cohort study of patients with late stage parkinsonism in the six European health care systems (UK, Germany, The Netherlands, France, Portugal and Sweden), identified from primary care, care of the elderly, neurology and palliative care settings. Details of the protocol were published previously [8].

Inclusion Criteria

Patients were eligible for enrolment if they had been diagnosed for at least seven years with parkinsonism and were classified as Hoehn and Yahr stage (HY) 4 or 5 in the "On"-state OR had developed significant disability (Schwab and England stage ≤ 50%) in the "On"-state [9]. Established clinical criteria (UK Parkinson's Disease Society Brain Bank Diagnostic Criteria [10]) were applied to distinguish subjects with PD from those with one of the different atypical parkinsonian syndromes.

Exclusion criteria

Patients with a diagnosis of "symptomatic PD" such as normal pressure hydrocephalus or drug-induced parkinsonism, except if persisting following discontinuation of the causative drug, were excluded. Patients with parkinsonism with a clear history of dementia occurring by history before the onset of Parkinsonism were also excluded.

Data collection

Assessments were undertaken during home visits or outpatient appointments. Due to concentration problems, fatigue or fluctuations of symptoms, we conducted assessments either on one or two separate home visits or two outpatient appointments within two weeks. All clinical data were entered in a central anonymized data management system.

Outcome measures

The following instruments were used to comprehensively collect motor and non-motor features of late stage parkinsonism: the Unified Parkinson's disease Rating Scale (UPDRS) including its four parts: Mentation, Behavior and Mood (part I), Activities of Daily Living (part II), Motor Examination (part III), and Complications of Therapy (part IV) [11]. This scale was chosen instead of the MDS-UPDRS for the following reasons: At the design stage and start of the study, there were insufficient data available on the MDS-UPDRS to allow for sample size calculation using the experiences of daily living parts, particularly at the more severe end of the spectrum of disease. As the scale was specifically designed to be more sensitive at the mild stage of the disease [12], it was unclear whether this may have affected its sensitivity at the more severe stages. Sub-scores were derived for speech (item 18), facial expression (item 19), tremor (item 20 and 21), rigidity (item 22), bradykinesia (items 23-26), postural instability and gait impairment (PIGD; items 27-29) and body hypokinesia (item 30) [13]. Treatment complications were measured with the UPDRS – part 4 (UPDRS-IV), which were summarized for dyskinesia (items 32-34) and off-periods (items 36-39) [13]. In addition, the Hoehn and Yahr scale (HY) was used to describe disease stage [14]. To assess the occurrence and severity of non-motor symptoms, the Non-Motor Symptom Scale (NMSS) was used [15]. We recorded previous diagnoses of dementia. Assessment of cognitive function was performed using the Mini-Mental State Examination (MMSE) [16] and the Pill questionnaire to assess functional impact [17]. For diagnosis of dementia, the Movement Disorders Society criteria for dementia level I [17] were applied. As some patients were unable to perform all tasks on the MMSE due to motor impairment, we also calculated a percentage score out of the total completed items to account for physical limitations

in completion e.g. due to speech impairment or dexterity and re-applied the criteria. Disability was assessed with the Schwab & England Scale [9] with scores ranging from 0 (complete dependence/bedridden) to 100% (complete independence). The dopaminergic medication dose was calculated using the levodopa equivalent daily dose (LEDD) [18].

To determine the prevalence of motor and non-motor problems, we report the number and percentage of patients who had score of at least 1 on UPDRS items reflecting motor problems, and of at least 1 on the severity scores of the NMSS reflecting non-motor problems. For presence of impulse control disorders, we applied the question assessing this complication from the MDS-UPDRS. In addition, we report the prevalence of moderate to severe problems as defined by a score of 3 on the UPDRS items (moderately or severe impaired) and of at least 2 on the severity scores of the NMSS (some or severe distress to the patient).

Statistical analyses

Descriptive data are presented as either mean and standard deviation (SD) or median and interquartile range (IQR) and percentages. We performed an unpaired samples T-test to compare Schwab and England score between men and woman. Continuous variables were evaluated with Pearson or Spearman correlation coefficients, depending on the distribution of data. For multivariate analysis, multivariate logistic regression models were built using Schwab and England scores as outcome measure. If p-value was ≤ 0.1 in univariate analysis, variables were included in the multivariate analysis. To prevent collinearity between independent variables, bivariate correlations were calculated between all independent variables. If variables had a rho >0.5, they were collinear and the variable with the highest correlation with the outcome measure was included in the final model. A backward stepping approach was used to select the final model using maximum likelihood estimates to discriminate between steps. Results were considered statistically significant if the Bonferroni-corrected p-value was <0.05.

Ethical approval

The study was approved by the ethical review board of each individual center. Written informed consent was obtained from all participants. In case the patients were unable to sign, consent was given by the legal representative, mostly a spouse or family member, in accordance with the country-specific legal requirements.

2.4 Results

Overall, 752 patients participated in the study. Twenty-three patients were excluded due to disease severity of milder degree (Hoehn and Yahr <3 and S&E >50%), and 37 participants due to a disease duration of less than <7 years. All remaining 692 participants were included in the further analysis. All scales had missing data <8%.

Clinical features and complications
Disease duration was 15.4 (SD 7.7) years and most participants were in H&Y stage 4 and 5 (92.5%). The remaining 7.5% had Schwab and England scores ≤50 but Hoehn and Yahr stage <4. Mean age was 76.1 (SD 8.4) years and 54% were men. Mean total UPDRS score was 82.7 (SD 22.4). The prevalence of motor problems as assessed on the UPDRS is shown in figure 1, and of non-motor problems in figure 2. The mean UPDRS part I score was 5.3 (SD 3.2) out of a maximum score of 16, part II 26.8 (SD 7.6) out of 52, part III 45.6 (SD 15.0) out of 108 and part IV 5.1 (SD 3.5) out of 23. A previous diagnosis of dementia was present in 37%.

Dementia diagnosed according to the MDS-criteria for dementia was present in 40% of patients if all questions that were not completed were rated as errors, and in 37% if the MMSE was calculated as a percentage of questions that were completed. Eighty two percent of patients reported falls, either only related to freezing (16%) or unrelated to freezing (21% of patients) or occurring both related and unrelated to freezing (45%), and were frequent in 26%. Help was required for turning in bed by 51%, moderate-severe speech impairment was reported in 43% and moderate to severe swallowing problems and in 16%. Off periods occurred in 68% and were present at least 50% of the day in 13%, with morning dystonia occurring in 35%. Moderate-severe tremor was reported by 11%, and dyskinesias by 45% but were moderate or severe only in 7%. The average LEDD was 874.1 (SD 591.1) mg/d and correlations of LEDD with clinical features and complications were all negligible (rho<0.2).

The NMSS showed at least one moderate to severe non-motor symptom in 651 participants (98.6%) and the average participant had 15.7 non-motor symptoms and 11.4 moderate-severe non-motor symptoms. Hallucinations occurred in 44% and delusions in 25%. Impulse control disorders were present in 16.5% and severe in 4.5%. For further individual symptom frequencies see figure 2 and supplementary materials.

Table 1. Patient characteristics

	Mean (SD)	N (%)
Age (years)		76.1 (8.4)
Gender (% women)		319 (46.1)
Country, number (%)		
United Kingdom		123 (17.8)
Germany		192 (27.7)
France		76 (11.0)
Sweden		107 (15.5)
The Netherlands		85 (12.3)
Portugal		109 (15.8)
Years of education	10.0 (3.9)	
Disease duration in years	15.4 (7.7)	
Schwab and England score	33.9 (16.0)	
Hoehn and Yahr score		
Stage 2		5 (0.7)
Stage 2.5		14 (2.0)
Stage 3		33 (4.8)
Stage 4		411 (59.4)
Stage 5		229 (33.1)
UPDRS-I	5.3 (3.2)	
UPDRS-II	26.8 (7.6)	
UPDRS-III	45.6 (15.0)	
UPDRS-IV	5.1 (3.5)	
UPDRS-total score	82.7 (22.4)	
Previous diagnosis of dementia (% yes)		255 (36.8)
Advanced treatment		
Neurosurgery		58 (8.4)
GPI		1 (0.1)
STN		51 (7.4)
Unknown		6 (0.9)
Apomorphine		34 (4.9)
Pen		10 (1.4)
Pump		27 (3.9
Levodopa/carbidopa intestinal gel		28 (4.0)

UPDRS = Unified Parkinson's Disease Rating Scale; GPI = Globus Pallidus Interna; STN = Subthalamic nucleus.

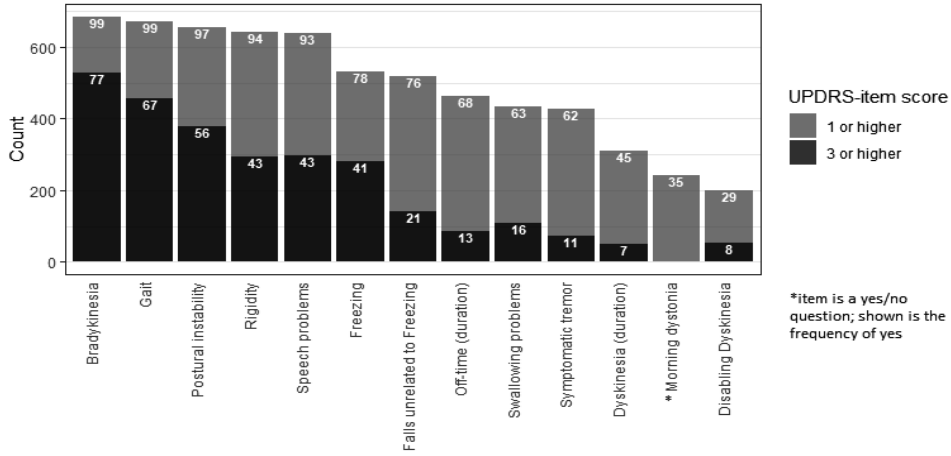

Figure 1. Frequency and percentage (within bars) of motor symptoms

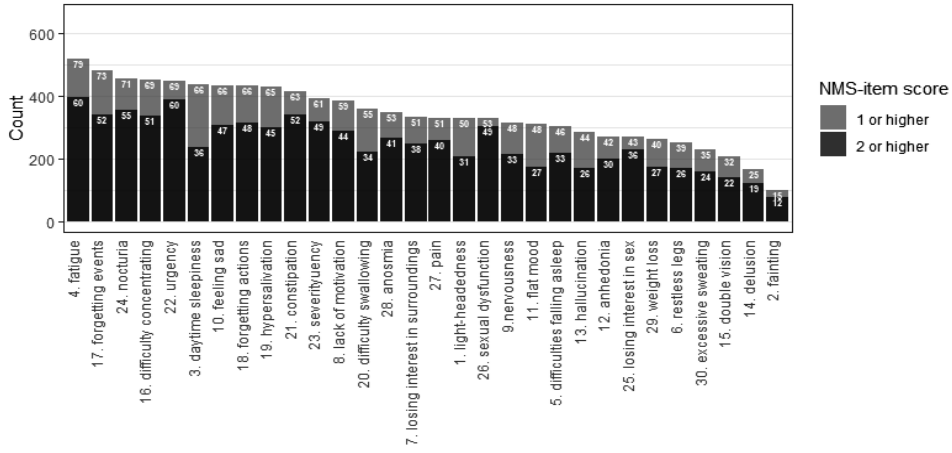

Figure 2. Frequency and percentage (within bars) of non-motor symptoms

Relationship of clinical features with disability

Overall Schwab and England disability score was 33.9 (SD16.0) out of a maximum (most independent) score of 100. In the multivariate regression analysis with Schwab and England score as dependent variable, and using all clinical features that were significant in the univariate analysis with $p<0.1$ without collinearity, the clinical features with predicting disability score in this late stage sample of parkinsonism were Hoehn and Yahr stage, MMSE score, bradykinesia, tremor, PIGD and speech ability.

Table 2. Multivariate analysis of predictors of disability

	Predictors	Measure	Beta	95% confidence interval	T statistic	P-value*	VIF
Schwab and	Age	-	-0.102	-0.203 to -0.001	-1.981	1.00	1.159
England scale	Disease stage	Hoehn and Yahr score	-2.810	-4.420 to -1.200	-3.482	0.02	1.537
	Cognitive performance	MMSE total score	0.460	0.309 to 0.610	6.006	<0.001	1.440
	Speech	UPDRS item 18	-2.369	-3.492 to -1.247	-4.145	<0.001	1.049
	Facial expression	UPDRS item 19	-1.131	-2.247 to -0.015	-1.991	1.00	1.625
	Tremor	UPDRS item 20 +21	-0.318	-0.503 to -0.134	-3.384	0.02	1.943
	Bradykinesia	UPDRS items 23-26	-0.385	-0.534 to -0.235	-5.061	<0.001	1.747
	PIGD	UPDRS items 27-30	-0.863	-1.174 to -0.552	-5.453	<0.001	1.511
	Off-periods	UPDRS items 36-39	0.395	-0.075 to 0.865	1.650	1.00	1.081
	Losing interest in surrounding	NMSs item 7	-0.256	-0.472 to -0.046	-2.331	0.44	1.267
	Difficulty swallowing	NMSs item 20	-0.203	-0.434 to 0.028	-1.729	1.00	1.159
	Urgency	NMSs item 22	-0.176	-0.343 to -0.009	-2.067	0.86	1.123
	Weight loss	NMSs item 29	-0.223	-0.446 to 0	-1.965	1.00	1.057
	Constant	-	71.085	59.655 to 82.515	12.216	<0.001	
Model coefficients: number of complete cases = 583 (84.2%), F-statistic = 54.524, p-value <0.001, R-square = 0.56							

*MMSE = Mini-Mental State Examination; UPDRS = Unified Parkinson's Disease Rating Scale; NMSs = Non-Motor Symptoms scale; *p-values are Bonferroni corrected*

2.5 Discussion

We delineate the clinical features and complications of the late stages of PD based on the largest study in this population to date. In this study, we purposefully included patients that were no longer seen in specialist clinics. The results from nearly 700 patients from six different countries are therefore likely to be representative of this underserved population. Unlike many earlier studies [19], gender distribution in our sample appeared representative of the PD population, with almost as many women as men, reflective of the greater longevity in women but higher prevalence of PD in men.

The severity of disease in this cohort was reflected in the high motor and non-motor scores on the UPDRS motor and ADL parts and the NMSS. Compared to results of other clinical studies, the UPDRS scores and frequencies on non-motor symptoms were higher than in patients with early disease [20, 21], but also than in patients who have advanced but not necessarily late disease [22]. However, motor complications including off-periods and dyskinesias, which are characteristic of PD leading to advanced therapies, were present only in 45% of this late stage population and moderate to severe in 7% [22-25]. Despite a large variety of symptomatic and supportive treatment options, most patients had moderate to severe motor and non-motor problems. The most common problems included falls, even in patients already bed-bound, off-periods for more of 50% of the day, speech and swallowing problems, and autonomic and psychiatric complications such as constipation and bladder problems, fatigue and dementia.

Amongst the individual features of late stage parkinsonism, whilst a high rate of falls, hallucinations and dementia was expected, it is noteworthy that despite moderate doses of levodopa only a small proportion had moderate to severe dyskinesia. It is likely that, as in other phases of the disease, considerable heterogeneity exists and many no longer develop dyskinesias. This is also in keeping with previous reports that only approximately 50% of patients in the late stage of PD have a significant response to levodopa. Alternatively, some patients may not have received high enough doses of dopaminergic medications to develop dyskinesia, in agreement with previous findings in a study of Dutch nursing homes where many patients appeared to be relatively undertreated (3). Similarly, only 11% had moderate to severe tremor despite high overall motor scores, in keeping with the observations that many patients with the tremor subtype lose their tremor and develop the akinetic rigid subtype with longer follow-up [26, 27]. It is also noteworthy that a proportion of 16.5% of patients had moderate to severe impulse control disorders, even in the

advanced stages of the disease, indicating that these should be proactively screened for in this population, and not just in the higher risk group of younger men [28].

Disability, as assessed by the Schwab and England scale, was strongly influenced by the presence of motor severity as assessed by the Hoehn and Yahr stage, overall bradykinesia and axial features but also speech impairment. This highlights the importance of communication problems in mediating patients' dependence on others. The other main predictor of disability was cognitive status whilst other clinical features such as nocturia, hypersalivation or pain had little or relationship to disability scores, and neuropsychiatric symptoms or autonomic dysfunction were no longer strongly related to disability once these factors were accounted for. This is likely to be a reflection of the instrument used which assesses level of physical dependence on others, for which these features may be less relevant than for quality of life or broader or instrumental disability measures or quality of life measures. In this severely affected disease population, it is important to stress, however, that individual symptoms, which may not be a frequent problem or a predictor of disability in the overall group once other factors are accounted for, may it still be a major burden for the individual patient.

Knowledge of the frequency of specific motor and particularly non-motor complications at this disease stage should inform both clinical management and future research studies in this vulnerable population. Whilst treatment for many of these complications exist, potential side effects on other parkinsonian features such as orthostatic hypotension or comorbidities such as ischemic heart disease often limit their use [29]. This highlights the importance of finding new pharmacological or non-pharmacological options suitable for patients in this disease phase and providing care and support using other strategies. Many patients in the late stages no longer receive specialist input, which may be due to difficulties attending or the assumption that this will not provide useful benefit. However, adjustment of antiparkinsonian medication may improve some levodopa-responsive motor as well as non-motor features, discontinuation of medications that are no longer needed and may cause side effects may improve non-motor problems, and treatment of specific non-motor features, e.g. depression, constipation or hallucinations, may lead to overall improvement of quality of life [30]. Different models of care that allow patients to receive specialist input in non-specialist settings, may be beneficial to these patients [7, 31, 32]. In particularly, palliative care approaches that incorporate PD-expertise may be well suited to address some of the non-levodopa responsive treatments with MDT input, non-pharmacological options and non-PD medications.

The high frequency of motor and non-motor symptoms also emphasized the need for the development of a pragmatic tool to improve recognition of these symptoms. The great variety in treatment strategies across patients observed in our study furthermore highlights the need to develop dedicated protocols and guidelines for management in this late stage population, to further harmonize treatment, and to ascertain that patients in advanced stages of PD – with their complex phenotype – receive the best possible care. With the increasing population age and rising prevalence of PD expected over the next decades there is a growing challenge to deliver the appropriate care to patients who reach the late stages of this disorder [33]. This study is the first study that specifically characterizes the clinical features of patients with late stage parkinsonism across several European countries. Combining the detailed assessments of patients in six different countries and across neurology, geriatric and palliative care settings, provides comprehensive knowledge on this hitherto little studied population. This information can then inform how best to provide effective care for this severely affected patient group and contribute to improved practices for clinical care.

2.7 Supplementary materials

Appendix A. Prevalence of motor problems in late stage parkinsonism

Motor feature	UPDRS item	Sample, number	Prevalence of any symptoms number (%)*	Prevalence of moderate or severe problems number (%)**
Speech problems	UPDRS-2 item 5	688	637 (92.6)	298 (43.3)
Swallowing problems	UPDRS-2 item 7	689	432 (62.7)	108 (15.7)
Falls unrelated to Freezing	UPDRS-2 item 13	681	519 (76.2)	142 (20.9)
Freezing	UPDRS-2 item 14	679	532 (78.4)	281 (41.4)
Symptomatic tremor	UPDRS-2 item 16	689	428 (62.1)	73 (10.6)
Rigidity	UPDRS-3 item 22	685	641 (93.6)	295 (43.1)
Bradykinesia	UPDRS-3 item 23 - 26	685	684 (98.8)	528 (77.1)
Gait	UPDRS-3 item 29	682	672 (98.5)	456 (66.9)
Postural instability	UPDRS-3 item 30	674	655 (97.2)	378 (56.1)
Dyskinesia (duration)	UPDRS-4 item 32	688	310 (45.1)	51 (7.4)
Disabling Dyskinesia	UPDRS-4 item 33	687	201 (29.0)	52 (7.5)
Off-time (duration)	UPDRS-4 item 39	682	462 (67.7)	87 (12.8)
Morning dystonia	UPDRS-4 item 35	688	241 (35.0)	NA***

UPDRS = Unified Parkinson's Disease Rating Scale; **UPDRS item severity score ≥ 1; **UPDRS item severity score ≥ 3; *** Not Applicable, as item is yes/no question*

Appendix B. Prevalence of non-motor problems in late stage parkinsonism

Non-motor symptoms as assessed on the Non-Motor Symptoms scale	Sample, number	Prevalence of any symptoms number (%)**	Prevalence of moderate or severe symptoms number (%)***	Sum score (Frequency x Severity score), mean (SD)
1. light-headedness	656	331 (50.4)	209 (31.4)	2.6 (3.6)
2. fainting	657	99 (15.1)	80 (12.2)	0.8 (2.3)
3. daytime sleepiness	661	439 (66.4)	237 (35.9)	3.6 (3.9)
4. fatigue	658	520 (79.0)	396 (60.2)	5.5 (4.4)
5. difficulties falling asleep	659	305 (46.3)	219 (33.2)	3.4 (4.6)
6. restless legs	655	252(38.5)	171 (26.1)	2.4 (3.8)
7. losing interest in surroundings	659	335 (50.8)	250 (37.9)	3.4 (4.3)
8. lack of motivation	658	385 (58.5)	290 (44.1)	4.2 (4.6)
9.nervousness	658	317 (48.2)	215 (32.7)	2.6 (3.7)
10. feeling sad	659	435 (66.0)	307 (46.6)	3.7 (4.0)
11. flat mood	657	312 (47.5)	174 (26.5)	2.5 (3.6)
12. anhedonia	658	273 (41.5)	199 (30.2)	2.8 (4.2)
13. hallucination	659	287 (43.6)	172 (26.1)	2.4 (3.8)
14. delusion	659	167 (25.3)	123 (18.7)	1.5 (3.2)
15. double vision	654	207 (31.7)	142 (21.7)	2.0 (3.6)
16. difficulty concentrating	660	455 (68.9)	337 (51.1)	4.9 (4.6)
17. forgetting events	659	481 (73.0)	342 (51.9)	5.0 (4.6)
18. forgetting actions	655	433 (66.1)	317 (48.4)	4.8 (4.8)
19. hypersalivation	661	430 (65.1)	300 (45.4)	4.4 (4.4)
20. difficulty swallowing	661	360 (54.5)	222 (33.6)	3.0 (3.9)
21. constipation	658	415 (63.1)	340 (51.7)	4.4 (4.5)
22. urgency	654	448 (68.5)	390 (59.6)	6.0 (5.1)
23. frequency	651	395 (60.7)	319 (49.0)	5.0 (5.0)
24. nocturia	650	458 (70.5)	356 (54.8)	5.9 (5.0)
25. losing interest in sex	634	273 (43.1)	229 (36.1)	4.1 (5.2)
26. sexual dysfunction	621	331 (53.3)	304 (49.0)	5.3 (5.5)
27. pain	656	332 (50.6)	260 (39.6)	3.6 (4.4)
28. anosmia	653	348 (53.3)	268 (41.0)	4.4 (4.9)
29. weight loss	657	263 (40.0)	174 (26.5)	2.4 (3.8)
30. excessive sweating	659	231 (35.1)	161 (24.4)	2.1 (3.6)
Impulse control disorders*	599	99 (16.5%)	27 (4.5%)	

*SD = Standard Deviation; *individual question from the MDS-UPDRS (presence ≥1, moderate or severe ≥3); **NMSs severity score ≥ 1; ***NMSs severity score ≥ 2.*

Appendix C. Results of univariate association analysis of demographic and clinical features with disability

	Schwab and England score		
	Women	Men	p-value
Gender, number (%)	34.4 (16.2)	33.3 (15.8)	0.498
	Spearman's rank	**p-value**	
Age in years	-0.148	<0.001	
Disease duration in years	0.001	0.985	
Years of education	0.040	0.308	
Hoehn and Yahr stage	-0.615	<0.001	
Cognition			
MMSE-total	0.503	<0.001	
Medications			
LEDD in mg	0.143	<0.001	
UPDRS 3			
18. Speech	-0.534	<0.001	
19. Facial expression	-0.387	<0.001	
20. and 21. Tremor at rest (head, upper and lower extremity right and left) and postural tremor (upper extremity right and left)	-0.069	0.075	
22. Rigidity (head, upper and lower extremity right and left)	-0.454	<0.001	
23 -26. Bradykinesia items right and left	-0.594	<0.001	
27-30. gait and postural imbalance	-0.656	<0.001	
31. Body bradykinesia	-0.542	<0.001	
UPDRS 4			
Sum of dyskinesia items	0.185	<0.001	
Sum of Off-period items	0.156	<0.001	
NMSs, f x s scores			
1. light-headedness	-0.018	0.641	
2. fainting	-0.018	0.641	
3. daytime sleepiness	-0.200	<0.001	
4. fatigue	-0.173	<0.001	
5. difficulties falling asleep	0.036	0.354	
6. restless legs	0.041	0.299	
7. losing interest in surroundings	-0.393	<0.001	
8. lack of motivation	-0.382	<0.001	
9.nervousness	-0.112	0.004	
10. feeling sad	-0.131	0.001	

table continues

	Spearman's rank	p-value
11. flat mood	-0.149	<0.001
12. anhedonia	-0.216	<0.001
13. hallucination	-0.232	<0.001
14. delusion	-0.264	<0.001
15. double vision	-0.006	0.875
16. difficulty concentrating	-0.353	<0.001
17. forgetting events	-0.335	<0.001
18. forgetting actions	-0.343	<0.001
19. hypersalivation	-0.102	0.009
20. difficulty swallowing	-0.293	<0.001
21. constipation	-0.153	<0.001
22. urgency	-0.272	<0.001
23. frequency	-0.199	<0.001
24. nocturia	-0.060	0.122
25. losing interest in sex	-0.073	0.059
26. sexual dysfunction	-0.127	0.001
27. pain	0.031	0.433
28. anosmia	0.046	0.235
29. weight loss	-0.151	<0.001
30. excessive sweating	0.013	0.735
Impulse control disorder		
MDS-UPDRS item DDS	0.126	0.002

MMSE = Mini-Mental State Examination; LEDD = Levodopa Equivalent Daily Dose; UPDRS = Unified Parkinson's Disease Rating Scale; NMSs = Non-Motor Symptoms Scale; MDS-UPDRS = Movement Disorders Society – Unified Parkinson's Disease Rating Scale

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CHAPTER 3. The prevalence and determinants of neuropsychiatric symptoms in late-stage parkinsonism

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

Background Late-stage parkinsonism (PD) is an insufficiently studied population. Whilst neuropsychiatric symptoms, e.g. psychosis, depression, anxiety and 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 (NPI), with frequency x severity score ≥4 indicating clinically relevant symptoms. Determinants analyzed were demographic characteristics, medication, and motor and non-motor symptoms. Univariate and multivariate logistic analyses were performed on predictors of clinically relevant neuropsychiatric symptoms.

Results Six hundred and twenty-five patients were recruited in whom the NPI could be completed. In 92.2% (576/625) of patients, at least one 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 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 pro-actively explore other psychiatric comorbidities once a neuropsychiatric symptom is recognized.

3.2 Introduction

Late-stage parkinsonism (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 non-motor symptoms [1-3], including neuropsychiatric symptoms (NPS) such as psychosis, depression, anxiety, apathy and behavioral problems. The presence of NPS is associated with a decreased quality of life, increased caregiver burden and an increased risk of institutionalization [4-7]. Two small cohort studies suggest NPS to be highly prevalent in late-stage PD [2, 3]. In the first study in 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, in 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 NPS 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 NPS 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 NPS in the overall group of patients with late-stage PD.

3.3 Methods

Study design

We examined the prevalence and correlates of NPS in patients in the Care of Late-Stage Parkinsonism-cohort (CLaSP-study), which is a longitudinal cohort study aimed to evaluate the needs of patients in late-stage PD. This paper presents a detailed analysis of the extensive baseline measurements. Further details of the study have been described in full detail elsewhere [22]. In brief, CLaSP included centers in London (United Kingdom), Lund (Sweden), Munich (Germany), Marburg (Germany), Nijmegen (The Netherlands), Bordeaux (France) and Lisbon (Portugal), and included patients with (a) a clinical diagnosis of parkinsonism, (b) a disease

duration of at least 7 years and (c) a Hoehn and Yahr stage 4 or 5 in "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) 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 Committee 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 Regionala etikprovningsnamnden: Lund (EPN Regional Ethics Name: Lund). JPND NC 559–002, Marburg: Ethik-Kommission bei der Landesarztekammer Hessen (Ethics Commission at the State Medical Association Hesse). MC 309/2014, Munich: Ethikkommission bei der LMU Munchen (Ethics committee at the LMU Munchen). 193–14, Nijmegen: Radboud universitair medisch centrum, Concernstaf Kwaliteit en Veiligheid, Commissie Mensgebonden Onderzoek Regio Arnhem-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 understands potential risks and benefits of the study. If patients were unable, 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

NPS were assessed with the Neuropsychiatric Inventory – Nursing home version (NPI) [25]. The NPI was originally developed for use in research with dementia patients and was suggested for use in PD-patients to assess NPS by the Movement Disorder Society [26]. The NPI scores 10 NPS: delusion, hallucination, agitation, depression, anxiety, euphoria, apathy, disinhibition, irritability, aberrant motor behavior, and two items associated with NPS: 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 0-4 and from 0-3 respectively, with higher scores indicating higher

frequency or higher severity. Multiplying frequency with severity scores produces a composite score ranging from 0-12. NPS with a composite score ≥4 are considered clinically relevant [27, 28].

Demographic, disease- or treatment related variables that were considered as potential predictors of NPS in PD included age, gender, years of education, disease duration, disease severity, co-morbidity, and a range of motor and non-motor features (see table 1). Disease severity was assessed using Hoehn and Yahr stage [23]. Motor function was measured with the Unified Parkinson Disease Rating Scale – part 3 (UPDRS-III) [24]. The UPDRS-III consist of 14 items, from which subscores were derived for speech (item 18), facial expression (item 19), tremor (item 20 and 21), rigidity (item 22), bradykinesia (items 23-26), postural instability and gait impairment (PIGD; 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 assessment of cognitive performance. Activities of daily living were assessed with the UPDRS – part 2 (UPDRS-II) [24]. Treatment complications were measured with the UPDRS – part 4 (UPDRS-IV), which were summarized for LID (items 32-34) and off-periods (items 36-39) [24]. NPI-items other than the dependent variable were used as independent variables. Other non-motor features were measured with the non-motor symptoms scale (NMSS) in the domains 1) cardiovascular, 2) sleep/fatigue, 6) gastrointestinal tract, 7) urinary, 8) sexual function and 9) miscellaneous [31]. The NMSS measures a composite of severity (0-3) x frequency (0-4) for each item. Co-morbid diseases were assessed using the Charlson Comorbidity Index [32]. The dopaminergic medications were recalculated to levodopa equivalent daily doses (LEDD) [33]. Psychotropic drug use was collected for antidepressants, antipsychotics, anti-dementia drugs, anxiolytics and hypnotics.

Statistical analysis

Results were first examined for missing data. Variables were excluded from further analysis when >20% of the data was 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 one item was missing and on the UPDRS-III if 7 or less 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.

Table 1. Demographic, disease- and treatment-related variables included in analysis

Demographics	*Non-motor 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 nighttime 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	
MMSE total score	urgency	speech
	frequency	salivation
Motor function (UPDRS III)	nocturia	swallowing
speech	losing interest in sex	handwriting
facial expression	sexual dysfunction	cutting food and handling utensils
tremor	pain	dressing
rigidity	anosmia	personal hygiene
bradykinesia	weight loss	turning in bed
postural instability and gait impairment	excessive sweating	falling (unrelated to freezing)
body hypokinesia	*Neuropsychiatric symptoms*	freezing when walking
	delusions	walking
Motor complications (UPDRS IV)	hallucinations	tremor
dyskinesia	agitation/aggression	sensory complaints related to Parkinson
off-periods	depression	
	anxiety	Treatment
	elation/euphoria	levodopa equivalent daily dose

MMSE = Mini Mental State examination, UPDRS = Unified Parkinson Disease Rating scale. The following variables were not included due to missing data: Charlson comorbidity index, verbal fluency, clock drawing test.

Prevalence of individual NPS 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 analysis were performed with the presence of clinically relevant NPS as the dependent variable [35]. Univariate between-group differences were evaluated with an unpaired samples T-test for normally distributed variables and the Mann-Whitney test for non-normally distributed variables. Categorical variables were evaluated with the chi-square 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 mean and standard deviation for normally distributed variables and with median and minimal-maximal values for non-normally distributed variables. Results were considered statistically significant if the Bonferroni-corrected p<0.05. All analysis was performed using SPSS 22.0 (IBM, Armonk, NY).

3.4 Results

The clinical characteristics of the participants with completed NPI-scores (N=625) are given in table 2. Data was missing ≥20% for the Verbal fluency, Clock Drawing test, and Charlson 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 lower than 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 LEDD 687.5 vs. 815; p<0.01). No differences were found on disease duration, gender, Hoehn and Yahr stage and Schwab and England score. There were no missing data for age, medication use and Hoehn and Yahr stage.

Prevalence of NPS

In 92.2% (576/625) of the participants at least one of the NPS was present and at least one of the clinically relevant NPS was present in 75.5% (472/625) of the participants (table 3). The median number of NPS in each patient was three and of clinically relevant NPS two per patient. The most frequent NPS 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

Results of the univariate test are shown in the supplementary appendix B. In the multivariate analyses (table 4-7), for most NPS, the strongest associations were seen with other NPS. The presence of hallucinations was predicted by the presence of delusions (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 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 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).

Table 2. Characteristics of the sample of late-stage parkinsonism patients

	Number (%)
Sample size	625
Gender (% women)	284 (45.4%)
Hoehn and Yahr score	
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	
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	237 (37.9%)
Cognitive impairment defined as MMSE < 26	402 (53.5%)
Self-reported diagnosis of Parkinson's disease	546 (87.4%)
Current psychotropic drug use	
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)
Anti-dementia drug	159 (25.4)
-Rivastigmine	118 (18.9)
-Memantine	42 (6.7)
-Donezepil	14 (2.2)
Hypnotic	125 (20.0)

table continues

	Median (min-max)
Age	77 (24-96)
Disease duration in years	14 (7-62)
Years of education	9 (0-25)
Schwab and England score	30 (0-80)
Levodopa equivalent daily dose	815 (0-4834)

MMSE = Mini-Mental State Examination; SSRI = Selective Serotonin Reuptake Inhibitor

Table 3. Prevalence of neuropsychiatric symptoms as assessed on the Neuropsychiatric Inventory

	Sample size, number	**Prevalence of symptoms (F≥1), number (%)**	**Prevalence of clinically relevant symptoms (FxS≥4), number (%)**
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%)

F = frequency; FxS = frequency x severity

In several models other predictors than NPS 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 two NPS: anxiety (OR 1.332; Wald = 36.97; p=<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 two NPS: 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).

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

Dependent variable	Independent variables	Measured with
Delusion	Dressing	UPDRS-II item 10
(NPI-item A)	**Hallucinations**	**NPI item B**
	Agitation	NPI item C
	Constant	
Model coefficients: N complete cases = 548 (79.2%), chi-square =123.54, df 3, p-value <0.001, Log likelihood = 30.82, Nagelkerke R-square = 0.37		

Dependent variable	Independent variables	Measured with
Hallucinations	Years of education	-
(NPI-item B)	**Cognitive performance**	**MMSE total score**
	Lightheadedness	NMSS item 1
	Daytime sleepiness	**NMSS item 3**
	Delusion	**NPI item A**
	Anxiety	NPI item E
	Elation/euphoria	NPI item F
	Aberrant motor behavior	NPI item J
	Sleep and nighttime behavior disorders	NPI item K
	Constant	-
Model coefficients: N complete cases = 500 (72.3%), chi-square = 167.47, df 9, p-value <0.001, Log likelihood = 318.76, Nagelkerke R-square = 0.46		

Dependent variable	Independent variables	Measured with
Agitation	LEDD	-
(NPI-item C)	Cognitive performance	MMSE total score
	Falling (unrelated to freezing)	UPDRS-II item 13
	Depression	**NPI item D**
	Elation/euphoria	NPI item F
	Irritability	**NPI item I**
	Constant	
Model coefficients: N complete cases = 505 (73.0%), chi-square =112.27, df 6, p-value <0.001, Log likelihood = 231.18, Nagelkerke R-square = 0.40		

**Shown are backward stepping logistic regression models with clinically relevant NPI items (FxS ≥ 4) as dependent variables based on data from the total sample. NPI = Neuropsychiatric Inventory; UPDRS = Unified Parkinson disease Rating Scale; NMSS = Non-motor Symptoms Scale; MMSE = Mini-mental state examination; LEDD = Levodopa equivalent daily dose.*

Beta	S.E.	Wald statistic	P-value	Odds ratio (95% confidence interval)
0.439	0.180	5.914	0.15	1.551 (1.089-2.209)
0.374	**0.045**	**69.764**	**<0.001**	**1.454 (1.331-1.587)**
0.134	0.059	5.091	0.24	1.143 (1.018-1.284)
-4.448	0.607	63.669	<0.001	

Beta	S.E.	Wald statistic	P-value	Odds ratio (95% confidence interval)
-0.089	0.040	5.110	0.60	0.915 (0.846-0.988)
-0.088	**0.021**	**17.072**	**<0.001**	**0.915 (0.878-0.955)**
0.090	0.038	5.656	0.43	1.094 (1.016-1.179)
0.143	**0.036**	**15.424**	**0.002**	**1.154 (1.074-1.239)**
0.393	**0.059**	**44.595**	**<0.001**	**1.482 (1.320-1.664)**
0.086	0.045	3.622	1.00	1.090 (0.997-1.192)
0.250	0.152	2.692	1.00	1.284 (0.953-1.731)
0.085	0.048	3.143	1.00	1.089 (0.991-1.196)
0.118	0.040	8.660	0.08	1.125 (1.040-1.217)
-0.866	0.582	2.215	1.00	

Beta	S.E.	Wald statistic	P-value	Odds ratio (95% confidence interval)
-0.001	0.001	3.951	1.00	0.999 (0.998-1.000)
-0.054	0.026	4.161	0.90	0.948 (0.900-0.998)
0.224	0.126	3.129	1.00	1.251 (0.976-1.602)
0.179	**0.046**	**15.273**	**0.002**	**1.196 (1.094-1.309)**
0.430	0.186	5.311	0.46	1.536 (1.066-2.214)
0.439	**0.068**	**41.587**	**<0.001**	**1.551 (1.357-1.772)**
-2.203	0.671	10.759	0.02	

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

Dependent variable	Independent variables	Measured with
Depression	**Hygiene**	**UPDRS-II item 11**
(NPI-item D)	Daytime sleepiness	NMSS item 3
	Pain	NMSS item 27
	Weight loss	**NMSS item 29**
	Agitation	NPI item C
	Anxiety	**NPI item E**
	Apathy	**NPI item G**
	Sleep and nighttime behavior disorders	**NPI item K**
	Constant	-
Model coefficients: N complete cases = 496 (71.7%), chi-square = 187.11, df 8, p-value <0.001, Log likelihood = 455.66, Nagelkerke R-square = 0.43		
Dependent variable	**Independent variables**	**Measured with**
Anxiety	Female gender	-
(NPI-item E)	Cognitive performance	MMSE total score
	Turning in bed and adjusting clothes	UPDRS-II item 12
	Falling (unrelated to freezing)	UPDRS-II item 13
	Body bradykinesia	UPDRS-III item 31
	Dyskinesia	UPDRS-IV items 32-34
	Restless legs	NMSS item 6
	Lost interest in sex	**NMSS item 25**
	Delusion	NPI item A
	Hallucination	NPI item B
	Depression	**NPI item D**
	Apathy	NPI item G
	Irritability/lability	**NPI item I**
	Constant	-
Model coefficients: N complete cases = 524 (75.7%), chi-square = 165.63, df 13, p-value <0.001, Log likelihood = 403.09, Nagelkerke R-square = 0.41		

**Shown are backward stepping logistic regression models with clinically relevant NPI items (FxS ≥ 4) as dependent variables based on data from the total sample. NPI = Neuropsychiatric Inventory; UPDRS = Unified Parkinson disease Rating Scale; NMSS = Non-motor Symptoms Scale; MMSE = Mini-mental state examination; LEDD = Levodopa equivalent daily dose.*

Beta	S.E.	Wald statistic	P-value	Odds ratio (95% confidence interval)
0.495	**0.126**	**15.334**	**0.003**	**1.641 (1.281-2.103)**
-0.078	0.033	5.460	0.53	0.925 (0.867-0.988)
0.064	0.027	5.511	0.53	1.066 (1.011- 1.124)
0.109	**0.032**	**11.235**	**0.02**	**1.115 (1.046-1.188)**
0.189	0.067	8.018	0.14	1.208 (1.060-1.377)
0.287	**0.047**	**36.972**	**<0.001**	**1.332 (1.214-1.461)**
0.156	**0.034**	**21.119**	**<0.001**	**1.169 (1.094-1.249)**
0.095	**0.034**	**7.665**	**0.006**	**1.100 (1.028-1.177)**
-3.550	0.417	72.633	<0.001	

Beta	S.E.	Wald statistic	P-value	Odds ratio (95% confidence interval)
0.642	0.260	6.116	0.31	1.9101 (1.143-3.162)
0.049	0.025	3.845	1.00	1.050 (1.000-1.102)
0.248	0.129	3.707	1.00	1.281 (0.996-1.648)
-0.224	0.100	4.983	0.62	0.800 (0.657-0.973)
-0.283	0.153	3.428	1.00	0.753 (0.558-1.017)
0.132	0.058	5.213	0.53	1.141 (1.019-1.278)
0.064	0.033	3.619	1.00	1.066 (0.998-1.138)
0.090	**0.024**	**13.827**	**0.005**	**1.094 (1.043-1.147)**
-0.118	0.069	2.910	1.00	0.889 (0.776-1.018)
0.133	0.057	5.435	0.48	1.142 (1.021-1.277)
0.234	**0.040**	**33.791**	**<0.001**	**1.264 (1.168-1.368)**
0.066	0.039	2.807	1.00	1.068 (0.989-1.153)
0.191	**0.059**	**10.566**	**0.03**	**1.210 (1.079-1.358)**
-4.336	0.881	24.215	<0.001	

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

Dependent variable	Independent variables	Measured with
Apathy	**Cognitive performance**	**MMSE total score**
(NPI-G)	Freezing when walking	UPDRS-II item 14
	Off-periods	UPDRS-IV items 36-39
	Daytime sleepiness	NMSS item 3
	Fatigue	NMSS item 4
	Losing interest in sex	**NMSS item 25**
	Depression	**NPI item D**
	Anxiety	NPI item E
	Sleep and nighttime behavior disorders	NPI item K
	Appetite and eating changes	NPI item L
	Constant	
Model coefficients: N complete cases = 493 (71.2%), chi-square =191.48, df 10, p-value <0.001, Log likelihood = 454.52, Nagelkerke R-square = 0.44		

Dependent variable	Independent variables	Measured with
Irritability	Cognition	MMSE total score
(NPI-I)	Cutting foods and handling utensils	UPDRS-II item 9
	Delusion	NPI item A
	Agitation	**NPI item C**
	Anxiety	**NPI item E**
	Sleep and nighttime behavior disorders	NPI item K
	Constant	
Model coefficients: N complete cases = 516 (74.6%), chi-square =96-48, df 6, p-value <0.001, Log likelihood = 270.40, Nagelkerke R-square = 0.34		

**Shown are backward stepping logistic regression models with clinically relevant NPI items (FxS ≥ 4) as dependent variables based on data from the total sample. NPI = Neuropsychiatric Inventory; UPDRS = Unified Parkinson disease Rating Scale; NMSS = Non-motor Symptoms Scale; MMSE = Mini-mental state examination; LEDD = Levodopa equivalent daily dose.*

Beta	S.E.	Wald Statistic	P-value	Odds ratio (95% confidence interval)
-0.121	**0.019**	**39.231**	**<0.001**	**0.886 (0.853-0.920)**
0.177	0.089	3.929	1.00	1.194 (1.002-1.422)
-0.172	0.069	6.269	0.32	0.842 (0.736-0.963)
0.059	0.033	1.00	1.00	1.061 (0.994-1.132)
0.067	0.030	5.001	0.68	1.069 (1.008- 1.134)
0.087	**0.023**	**14.141**	**0.005**	**1.091 (1.042-1.141)**
0.166	**0.041**	**16.045**	**0.002**	**1.180 (1.088-1.280)**
0.106	0.046	5.317	0.57	1.112 (1.016-1.216)
0.095	0.034	7.655	0.16	1.100 (1.028-1.176)
0.085	0.040	4.515	0.92	1.089 (1.007-1.178)
0.014	0.503	0.001	1.00	

Beta	S.E.	Wald Statistic	P-value	Odds ratio (95% confidence interval)
0.063	0.031	4.215	0.76	1.065 (1.003-1.131)
0.328	0.171	3.683	0.94	1.388 (0.993-1.939)
0.121	0.054	5.007	0.43	1.128 (1.015-1.254)
0.344	**0.063**	**29.501**	**<0.001**	**1.410 (1.246-1.596)**
0.151	**0.045**	**11.358**	**0.01**	**1.163 (1.065-1.270)**
0.113	0.042	7.388	0.12	1.120 (1.032-1.215)
-5.677	1.001	32.171	<0.001	

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

Dependent variable	Independent variables	Measured with
Aberrant motor behavior (NPI J)	Tremor	UPDRS-II item 16
	Sensory complaints related to Parkinson	UPDRS-II item 17
	Dyskinesia	**UPDRS-IV items 32-34**
	Off-periods	UPDRS-IV items 36-39
	Constipation	NMSS item 21
	Urgency	NMSS item 22
	Delusion	**NPI item A**
	Hallucinations	NPI item C
	Disinhibition	NPI item H
	Appetite and eating changes	NPI item L
	Constant	

Model coefficients: N complete cases = 522 (75.4%), chi-square =90.62, df 10, p-value <0.001, Log likelihood = 389.30, Nagelkerke R-square = 0.27

*Shown are backward stepping logistic regression models with clinically relevant NPI items (FxS ≥ 4) as dependent variables based on data from the total sample. Bonferroni corrected critical p-value <0.05. Potential collinearity (rho>0.5) resulting in the restriction of one variable into the model was found for the following set of variables:
gait impairment (UPDRS-III PIGD 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).
NPI = Neuropsychiatric Inventory; UPDRS = Unified Parkinson disease Rating Scale; NMSS = Non-motor Symptoms Scale; MMSE = Mini-mental state examination; LEDD = Levodopa equivalent daily dose.

Beta	S.E.	Wald statistic	P-value	Odds ratio (95% confidence interval)
-0.435	0.145	9.058	0.06	0.647 (0.487-0.859)
-0.241	0.120	4.034	0.90	0.786 (0.621-0.994)
0.217	**0.061**	**12.561**	**0.008**	**1.243 (1.102-1.402)**
-0.143	0.078	3.367	1.00	0.867 (0.744-1.010)
-0.085	0.033	6.731	0.18	0.919 (0.862-0.980)
0.048	0.026	3.403	1.00	1.050 (0.997-1.105)
0.171	**0.052**	**10.629**	**0.02**	**1.186 (1.071-1.315)**
0.102	0.049	4.439	0.70	1.108 (1.007-1.218)
0.155	0.078	3.978	0.92	1.168 (1.003-1.361)
0.108	0.041	6.876	0.18	1.114 (1.028-1.208)
-1.701	0.306	30.867	<0.001	

3.5 Discussion

We found that NPS 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 two NPS occurring together. Although each NPS has a unique set of disease-related determinants, the strongest predictors for most NPS were the presence of other NPS.

Multiple prevalence estimates of NPS in PD have been published, ranging from 14% to 69% for individual NPS and 61% to 89% for overall presence of any NPS [8, 36-42], but there are no previous studies examining their combined prevalence in the overall late-stage disease population. While there are publications available for cohorts of patients with Parkinson dementia [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 NPS do resemble the prevalence of NPS in a cohort with 537 PD dementia (PDD) participants [4, 44] in whom prevalence of hallucinations, depression and apathy was 44%, 57% and 54%, respectively [4]. 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 two cohorts with comparable mechanisms, although our study selected participants primarily based on motor stage and disease duration. Both cohorts share characteristics like worse cognitive performance, functional dependence, daytime sleepiness and motor complications. There is an ongoing controversy on the underlying pathology of PD dementia, which is likely to include diffuse Lewy body distribution in the cortical areas as well as Alzheimer pathology [45]. Our results that NPS are very common in late-stage PD with and without dementia suggest that NPS

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 NPS in general was the presence of other NPS. 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, e.g. anxiety and depression, or a common etiology due to jointly affected brain regions. Multiple studies have investigated the complex interrelationship of NPS in PD, using factor and hierarchical cluster analyses [4, 18, 40, 46, 47]. In the earlier mentioned cohort of PDD, five NPS separate profiles 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 score on other items. Our results in 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 NPS, concomitant cognitive impairment or medication side effects, such as the association of depression with agitation, or association of delusions with aberrant motor behavior. We also found an association of aberrant motor behavior with LID. Whilst 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, due to severe motor impairment, with the exception of those that 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 association 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 determinant for depression [55].

It is noteworthy that, once other NPS are accounted for, in this population with virtually uniformly severe motor impairment, other motor and non-motor aspects of the disease were not strongly associated with the occurrence of NPS. Whilst some of this may be explained by 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 NPS 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 NPS. Therefore, no conclusions can be drawn on potential undertreatment with psychotropic drugs or on the contribution of specific dopaminergic treatments (like dopamine agonist). Another limitation is the cross-sectional design of the study. As a result of this, we cannot infer the causality between determinant and outcome. The number of patients with dementia or cognitive decline is relatively low compared to 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. Due to the nature of the condition, our selection criteria and the primary assessment measure of NPS requiring a carer, we were at risk of being unable to complete the assessment in several participants, resulting in missing data. In order 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 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.

3.6 Conclusion

We demonstrated that NPS are highly prevalent in late-stage PD and that they predict the presence of other NPS. Clinicians involved in the care for patients with late-stage PD should be aware of the frequent occurrence of NPS in this specific disease group and pro-actively explore other psychiatric comorbidity once NPS are recognized. Future research should work to shed more light on the common etiology of NPS and develop tailored interventional and supportive strategies for this disease group.

3.7 Supplementary materials

Appendix A. Prevalence of neuropsychiatric symptoms in all late-stage versus typical disease of the CLaSP-cohort as assessed on the Neuropsychiatric Inventory

	Sample size, number	Prevalence of symptoms (F≥1), number (%)
		Late-stage parkinsonism
Delusions	621	147 (23.7%)
Hallucinations	623	257 (41.3%)
Agitation/aggression	619	182 (29.4%)
Depression	618	372 (60.2%)
Anxiety	621	274 (44.1%)
Elation/euphoria	621	25 (4.0%)
Apathy/indifference	622	309 (49.7%)
Disinhibition	619	49 (7.9%)
Irritability/lability	620	184 (29.7%)
Aberrant motor behavior	614	153 (24.9%)

Prevalence of clinically relevant symptoms (FxS≥4), number (%)	Sample size, number	Prevalence of symptoms (F≥1), number (%)	Prevalence of clinically relevant symptoms (FxS≥4), number (%)
	Patients with Parkinson Disease		
88 (14.2%)	542	129 (23.8%)	78 (14.4%)
129 (20.7%)	544	218 (40.1%)	114 (21.0%)
82 (13.2%)	541	167 (30.9%)	79 (14.6%)
213 (34.5%)	539	334 (62.0%)	195 (36.2%)
148 (23.8%)	542	255 (47.0%)	142 (26.2%)
9 (1.4%)	542	24 (4.4%)	9 (1.7%)
242 (38.9%)	543	279 (51.4%)	220 (40.5%)
26 (4.2%)	540	47 (8.7%)	24 (4.4%)
80 (12.9%)	541	162 (29.9%)	76 (14.0%)
111 (18.1%)	535	132 (24.7%)	99 (18.5%)

Appendix B. Univariate associations between presence of clinically relevant neuropsychiatric items (FxS≥4), measured with neuropsychiatric inventory (NPI) and clinical and demographic characteristics

	NPI item A. Delusion			**NPI item B, Hallucinations**
	Yes	No	P-value	Yes
Age in years, mean (SD)	77.5 (6.9)	76.3 (8.4)	0.22	77.4 (6.5)
Gender, number (%)				
Women	35	246	0.27	55
Men	53	287		74
Disease duration in years, median (range)	15 (37)	14 (62)	0.81	14 (57)
Years of education, median (range)	9.5 (18)	9 (24)	0.83	9 (20)
Hoehn and Yahr stage, number (%)				
Stage 2	1	4		0
Stage 2 ½	1	13	0.05	5
Stage 3	5	25		6
Stage 4	39	321		55
Stage 5	42	170		63
Medications				
LEDD in mg	875 (2810)	800 (4835)	0.27	800 (2551)
Cognitive function				
MMSE total score	20 (26)	25 (30)	0.09	19 (28)
UPDRS 2				
5. Speech				
0	4	41	0.30	4
1	13	120		25
2	24	143		37
3	29	151		35
4	17	77		26
6. Salivation				
0	21	126	0.66	31
1	16	129		24
2	18	97		22
3	21	102		30
4	11	77		20
7. Swallowing				
0	30	197	0.74	38
1	23	132		35
2	23	117		28
3	8	71		20
4	3	15		6
8. Handwriting				
0	0	14	0.06	1
1	2	34		7
2	12	103		15
3	23	149		26
4	50	231		78

		NPI D. Depression			NPI item E. Anxiety		
No	P-value	Yes	No	P-value	Yes	No	P-value
76.2 (8.6)	0.08	76.8 (7.4)	76.4 (8.5)	0.54	76.5 (8.9)	76.5 (8.0)	0.99
228	0.48	113	167	<0.01	85	196	<0.01
266		100	238		63	277	
14 (62)	0.67	14 (62)	14 (46)	0.71	15 (62)	14 (55)	0.17
10 (24)	0.02	9 (22)	9 (23)	0.02	9 (20)	9 (24)	0.29
5		2	3		2	3	
9	<0.01	7	7	0.03	7	7	0.17
24		9	21		6	24	
307		107	253		83	278	
149		88	121		50	161	
820 (4835)	0.66	875 (4835)	790 (3490)	0.23	875 (4834)	799 (3470)	0.23
25 (30)	<0.01	22 (30)	25 (30)	<0.01	23 (27)	24 (30)	0.26
							0.34
41	0.13	12	33	0.60	7	38	
109		44	90		32	102	
130		55	107		39	126	
145		69	110		50	130	
69		32	64		18	77	
							0.20
117	0.53	52	95	0.97	36	111	
122		46	97		25	121	
93		41	73		32	82	
93		43	80		34	90	
68		30	58		19	68	
							0.62
190	0.25	68	158	0.47	58	169	
121		54	101		36	121	
112		53	86		27	112	
59		31	48		20	59	
12		6	11		5	12	
							0.45
13	<0.01	1	13	<0.01	2	12	
29		8	27		5	31	
100		29	84		23	91	
146		63	107		44	127	
205		110	173		71	212	

table continues

	NPI item A. Delusion			**NPI item B, Hallucinations**
	Yes	No	P-value	Yes
9. Cutting foods and handling utensils				
0	2	46	<0.01	2
1	8	98		12
2	18	135		24
3	36	163		48
4	22	90		41
10. Dressing				
0	0	5	<0.01	0
1	2	53		3
2	8	139		15
3	29	165		35
4	48	170		74
11. Hygiene				
0	0	10	<0.01	0
1	2	75		4
2	14	150		23
3	38	187		49
4	33	110		51
12. Turning in bed and adjusting clothes	0	27	<0.01	2
0	9	100		13
1	23	141		28
2	18	120		33
3	37	144		51
4				
13. Falling (unrelated to freezing)				
0				
1	25	120	0.29	30
2	30	169		34
3	14	125		31
4	3	39		6
	13	75		24
14. Freezing when walking				
0	17	119	0.53	22
1	8	70		13
2	17	123		24
3	26	128		35
4	17	86		31
15. Walking				
0	0	5	0.07	0
1	4	13		4
2	14	113		20
3	42	297		65
4	27	103		38
16. Tremor				
0	32	202	0.52	38
1	23	163		47
2	25	110		32
3	5	40		6
4	2	17		4

		NPI D. Depression			NPI item E. Anxiety		
No	P-value	Yes	No	P-value	Yes	No	P-value
							0.19
46	<0.01	6	41	<0.01	5	42	
94		28	76		20	86	
130		46	106		38	116	
153		78	122		56	144	
70		53	59		27	84	
							0.48
5	<0.01	1	4	<0.01	1	4	
52		15	38		11	43	
132		40	105		35	112	
161		54	139		41	154	
144		102	118		58	160	
							0.11
10	<0.01	0	10	<0.01	1	9	
73		16	59		15	61	
144		42	121		29	137	
175		74	150		59	165	
92		80	64		42	101	
25	<0.01	2	23	<0.01	3	25	0.04
96		23	85		17	92	
136		48	112		39	124	
107		57	83		36	103	
130		82	101		53	129	
116	0.28	61	82	<0.01	49	104	0.02
166		50	148		37	161	
109		40	98		30	110	
35		16	26		14	28	
64		43	46		18	70	
114	0.05	46	88	<0.01	35	100	0.49
65		28	50		14	64	
117		36	102		29	111	
119		48	105		41	113	
73		52	53		26	78	
							0.38
5	0.04	0	5	<0.01	1	4	
13		4	13		3	14	
107		38	88		30	97	
277		106	232		74	266	
91		36	66		38	91	
							0.21
196	0.12	63	170	0.02	46	187	
141		68	118		45	142	
102		56	78		37	98	
39		19	24		15	29	
16		6	14		3	17	

table continues

	NPI item A. Delusion			**NPI item B, Hallucinations**
	Yes	No	P-value	Yes
17. Sensory complaints related to Parkinson				
0	37	209	0.18	56
1	21	108		26
2	13	107		14
3	12	98		26
4	4	8		4
UPDRS 3				
18. Speech				
0	2	23	0.22	1
1	14	140		20
2	36	177		49
3	24	141		37
4	10	49		19
19. Facial expression				
0	1	9	0.29	1
1	9	105		16
2	38	217		51
3	29	144		45
4	9	55		13
20. and 21. Tremor at rest (head, upper and lower extremity right and left) and postural tremor (upper extremity right and left)	0 (14)	1 (28)	0.45	1 (14)
22. Rigidity (head, upper and lower extremity right and left)	10 (20)	7 (20)	0.55	9 (20)
23 -26. Bradykinesia items right and left	21 (29)	18 (32)	0.71	22 (30)
27-30. gait and postural imbalance	12 (13)	10 (16)	0.97	12 (14)
31. Body bradykinesia				
0	3	12	0.17	1
1	1	37		3
2	26	166		31
3	30	189		53
4	28	129		38
UPDRS 4				
Sum of dyskinesia items	1 (8)	0 (10)	0.20	0 (8)
Sum of wearing-off items	2 (6)	2 (7)	0.55	2 (6)
NMSs, F x S scores				
1. light-headedness	1 (12)	0 (12)	0.91	3 (12)
2. fainting	0(12)	0 (12)	0.53	0 (12)
3. daytime sleepiness	4(12)	2 (12)	0.01	4 (12)
4. fatigue	6 (12)	4 (12)	0.08	7 (12)
5. difficulties falling asleep	1 (12)	0 (12)	0.06	1 (12)
6. restless legs	0 (12)	0 (12	0.42	0 (12)
19. hypersalivation	4 (12)	3 (12)	0.14	3 (12)

		NPI D. Depression			NPI item E. Anxiety		
No	P-value	Yes	No	P-value	Yes	No	P-value
190	0.08	68	176	0.02	50	193	0.21
103		43	85		26	103	
106		53	67		37	84	
86		43	68		29	83	
8		5	6		4	8	
							0.50
24	<0.01	7	18	0.39	6	19	
134		48	108		36	118	
165		66	143		46	168	
129		64	101		44	120	
40		24	36		12	47	
							0.05
9	0.13	3	7	0.87	7	8	
99		36	79		32	83	
205		91	160		60	195	
128		56	116		41	132	
51		23	42		8	55	
1 (28)	0.59	2 (28)	1 (27)	0.17	1 (24)	1 (28)	0.85
7 (20)	<0.01	8 (20)	7 (20)	0.02	7 (20)	7 (20)	0.67
18 (32)	<0.01	22 (30)	18 (32)	<0.01	19 (32)	19 (32)	0.93
10 (16)	<0.01	12 (16)	10 (16)	<0.01	11 (16)	10 (16)	0.59
							0.05
8	0.05	2	7	0.19	5	10	
35		7	31		8	30	
161		65	124		52	140	
168		82	135		59	160	
119		53	106		24	133	
0 (10)	0.65	0 (8)	0 (10)	0.86	1 (9)	0 (10)	0.01
2 (7)	0.66	2 (6)	2 (7)	0.17	3 (6)	2 (7)	0.02
0 (12)	<0.01	1 (12)	0 (12)	<0.01	1 (12)	0 (12)	<0.01
0 (12)	0.05	0 (12)	0 (12)	0.14	0 (12)	0 (12)	0.28
2 (12)	<0.01	3 (12)	2 (12)	0.09	4 (12)	2 (12)	<0.01
4 (12)	<0.01	6 (12)	4 (12)	<0.01	6 (12)	4 (12)	<0.01
0 (12)	0.20	2 (12)	0 (12)	<0.01	2 (12)	0 (12)	0.02
0 (12)	0.75	0 (12)	0 (12)	0.68	0 (12)	0 (12)	0.10
3 (12)	0.22	3 (12)	3 (12)	0.68	3.5 (12)	3 (12)	0.70

table continues

	NPI item A. Delusion			NPI item B, Hallucinations
	Yes	No	P-value	Yes
20. difficulty swallowing	1 (12)	1 (12)	0.45	2 (12)
21. constipation	3 (12)	3 (12)	0.68	3 (12)
22. urgency	8 (12)	6 (12)	0.09	9 (12)
23. frequency	4 (12)	4(12)	0.67	6 (12)
24. nocturia	4 (12)	6 (12)	0.97	8 (12)
25. losing interest in sex	0 (12)	0 (12)	0.73	0 (12)
26. sexual dysfunction	4 (12)	4 (12)	0.73	7 (12)
27. pain	1 (12)	0 (12)	0.26	1 (12)
28. anosmia	4 (12)	2 (12)	0.36	2 (12)
29. weight loss	0 (12)	0 (12)	0.55	0 (12)
30. excessive sweating	0 (12)	0 (12)	<0.01	0 (12)
NPI FxS scores				
A. Delusions	-	-	-	3 (12)
B. Hallucinations	6 (12)	0 (12)	<0.01	-
C. Agitation/aggression	1 (12)	0 (12)	0.10	0 (12)
D. Depression/Dysphoria	4 (12)	1 (12)	0.97	4 (12)
E. Anxiety	0 (12)	0 (12)	0.04	1 (12)
F. Elation/euphoria	0 (6)	0 (9)	0.73	0 (12)
G. Apathy / indifference	0 (12)	0 (12)	0.49	6 (12)
H. Disinhibition	0 (8)	0 (12)	0.84	0 (12)
I. Irritability /lability	0 (12)	0 (12)	0.72	0 (12)
J. Aberrant motor behavior	0 (12)	0 (12)	0.71	0 (12)
K. Sleep and nighttime behavior disorders	0 (12)	0 (12)	0.15	1 (12)
L. Appetite and eating changes	0 (12)	0 (12)	0.70	0 (12)

MMSE = Mini-Mental State Examination; LEDD = Levodopa Equivalent Daily Dose; UPDRS = Unified Parkinson's Disease Rating Scale; NMSs = Non-Motor Symptoms Scale; NPI = Neuropsychiatric Inventory; F x S = frequency x severity score

		NPI D. Depression			NPI item E. Anxiety		
No	P-value	Yes	No	P-value	Yes	No	P-value
1 (12)	0.10	2 (12)	1 (12)	0.17	1 (12)	1 (12)	0.30
4 (12)	0.27	4 (12)	2 (12)	<0.01	6 (12)	2 (12)	<0.01
6 (12)	<0.01	7 (12)	6 (12)	0.09	6 (12)	6 (12)	0.48
3 (12)	<0.01	6 (12)	3 (12)	0.03	4 (12)	4 (12)	0.99
4 (12)	0.19	8 (12)	4 (12)	0.03	4 (12)	6 (12)	0.24
0 (12)	0.74	6 (12)	0 (12)	<0.01	9(12)	0 (12)	<0.01
3 (12)	0.21	12 (12)	1 (12)	<0.01	12 (12)	1 (12)	<0.01
0 (12)	0.66	4 (12)	0 (12)	<0.01	4 (12)	0 (12)	0.02
3 (12)	0.83	4 (12)	1 (12)	0.15	4 (12)	2 (12)	0.37
0 (12)	<0.01	1 (12)	0 (12)	<0.01	0 (12)	0 (12)	0.04
0 (12)	0.95	0 (12)	0 (12)	0.08	0 (12)	0 (12)	0.85
0 (12)	<0.01	0 (12)	0 (12)	<0.01	0 (12)	0 (12)	<0.01
-	-	0 (12)	0 (12)	<0.01	0.5 (12)	0 (12)	<0.01
1 (12)	<0.01	0 (12)	0 (12)	<0.01	0 (12)	0 (12)	<0.01
0 (12)	<0.01	-	-	-	4 (12)	1 (12)	<0.01
0 (12)	<0.01	3 (12)	0 (12)	<0.01	-	-	-
0 (6)	0.05	0 (9)	0 (6)	0.53	0 (9)	0 (6)	0.59
0 (12)	<0.01	6 (12)	0 (12)	<0.01	4 (12)	0 (12)	<0.01
0 (12)	0.03	0 (12)	0 (12)	0.91	0 (12)	0 (12)	0.87
0 (12)	<0.01	0 (12)	0 (12)	<0.01	0 (12)	0 (12)	<0.01
0 (12)	<0.01	0 (12)	0 (12)	0.02	0 (12)	0 (12)	0.34
0 (12)	<0.01	1 (12)	0 (12)	<0.01	1 (12)	0 (12)	0.05
0 (12)	0.13	0 (12)	0 (12)	<0.01	0 (12)	0 (12)	0.56

Appendix B (continued). Associations between presence of clinically relevant neuropsychiatric items (FxS≥4), measured with neuropsychiatric inventory (NPI) and clinical and demographic characteristics

	NPI item C. Agitation			**NPI item I, Irritability / lability**
	Yes	no	P	Yes
Age in years, mean (SD)	76.7 (9.6)	76.5 (7.9)	0.77	77.0 (9.1)
Gender, number (%)				
Women	38	243	0.85	37
Men	44	294		43
Disease duration in years, median (range)	15 (57)	14 (62)	0.76	13 (62)
Years of education, median (range)	9 (20)	10 (24)	0.12	9 (20)
Hoehn and Yahr stage, number (%)				
Stage 2				
Stage 2 ½	1	4	0.05	2
Stage 3	3	11		2
Stage 4	5	25		3
Stage 5	35	325		39
	38	172		34
Medications				
LEDD in mg	644 (2309)	836 (4834)	<0.01	740 (2376)
Cognition				
MMSE total score, median (range)	22 (29)	24 (30)	<0.01	23 (29)
UPDRS 2				
5. Speech				
0	4	41	0.28	7
1	16	117		14
2	19	145		20
3	24	156		23
4	19	76		16
6. Salivation				
0	18	129	0.87	19
1	21	123		18
2	16	99		18
3	18	105		18
4	9	78		7
7. Swallowing				
0	26	202	0.04	28
1	20	134		19
2	14	125		15
3	19	60		17
4	3	14		1
8. Handwriting				
0	0	14	<0.01	1
1	0	36		4
2	13	100		13
3	14	157		14
4	54	228		48

		NPI G Apathy			NPI item J. Aberrant motor behavior		
No	P	Yes	No	P	yes	No	P
76.4 (8.0)	0.54	77.0 (7.7)	76.1 (8.5)	0.20	76.2 (6.0)	76.6 (8.6)	0.56
245 295	0.88	105 137	177 203	0.44	51 60	228 275	0.91
14 (60)	0.28	14 (37)	14 (57)	0.90	45 (56)	14 (62)	0.36
9 (24)	0.33	9 (21)	10 (25)	<0.01	9 (25)	9 (25)	0.59
3 12 27 321 177	0.15	1 6 12 108 115	4 8 18 253 97	<0.01	0 3 5 54 49	5 11 25 306 156	0.08
825 (4835)	0.20	798 (4835)	836 (3470)	0.13	803 (2810)	825 (4835)	0.73
24 (30)	0.35	21 (30)	25 (27)	<0.01	22 (29)	24 (30)	<0.01
38 119 146 155 80	0.69	9 41 62 79 51	36 93 103 102 44	<0.01	6 18 26 36 25	38 115 138 144 66	0.07
128 126 96 106 81	0.55	51 53 44 57 37	97 91 71 67 51	0.35	28 26 18 23 16	118 118 94 101 69	0.98
200 137 122 62 17	0.15	74 59 55 43 11	154 97 85 35 7	<0.01	40 24 27 18 2	186 130 112 57 16	0.53
13 32 100 158 234	0.08	0 7 22 63 150	14 29 92 108 134	<0.01	1 7 14 29 60	13 29 100 141 217	0.18

table continues

	NPI item C. Agitation			**NPI item I, Irritability / lability**
	Yes	no	P	Yes
9. Cutting foods and handling utensils				
0	2	46	<0.01	2
1	8	96		11
2	13	140		9
3	35	164		35
4	24	88		23
10. Dressing				
0	0	5	0.02	1
1	4	51		3
2	16	128		18
3	20	175		22
4	42	176		36
11. Hygiene				
0	0	10	<0.01	1
1	5	72		6
2	15	148		17
3	31	194		27
4	31	111		29
12. Turning in bed and adjusting clothes	2	24	0.09	4
0	7	101		5
1	20	141		19
2	23	117		19
3	30	152		33
4				
13. Falling (unrelated to freezing)				
0				
1	24	119	0.03	24
2	17	182		21
3	17	122		13
4	3	39		6
	18	70		13
14. Freezing when walking				
0	19	117	0.28	17
1	6	71		9
2	16	122		12
3	18	136		17
4	19	85		22
15. Walking				
0	0	5	0.05	0
1	3	14		5
2	16	109		13
3	36	303		36
4	27	103		25
16. Tremor				
0	26	207	0.25	26
1	33	154		28
2	17	115		19
3	5	40		5
4	1	19		2

		NPI G Apathy			NPI item J. Aberrant motor behavior		
No	P	Yes	No	P	yes	No	P
46	<0.01	8	40	<0.01	6	42	0.04
93		20	86		14	92	
143		52	101		27	124	
165		97	110		33	165	
90		70	41		30	78	
4	0.21	1	4	<0.01	1	4	<0.01
52		9	46		8	47	
125		37	109		12	134	
174		68	127		39	155	
183		127	92		51	161	
9	0.04	2	8	<0.01	1	9	0.03
70		17	59		5	72	
147		39	128		28	139	
198		92	132		46	174	
114		92	51		31	107	
23	0.02	5	22	<0.01	4	23	0.45
104		9	90		15	94	
141		51	112		33	128	
121		61	78		22	117	
149		106	76		37	139	
120	0.31	66	80	<0.01	22	120	0.55
177		53	146		39	161	
127		45	95		21	118	
35		23	19		8	34	
76		52	35		19	64	
119	0.06	51	85	<0.01	29	104	0.24
69		25	53		12	66	
126		46	94		19	121	
137		52	102		26	128	
82		64	40		23	76	
5	0.02	0	5	<0.01	1	4	0.52
12		6	11		5	12	
113		38	88		18	109	
302		114	227		62	277	
106		84	46		25	98	
208	0.76	89	144	0.70	55	179	0.02
158		70	118		33	155	
115		53	81		17	111	
39		22	23		6	38	
18		8	12		0	18	

table continues

	NPI item C. Agitation			NPI item I, Irritability / lability
	Yes	no	P	Yes
17. Sensory complaints related to Parkinson				
0	40	204	0.25	33
1	16	112		17
2	12	108		17
3	13	98		12
4	0	12		0
UPDRS 3				
18. Speech				
0	2	23	0.01	3
1	13	140		20
2	33	179		24
3	18	147		20
4	15	44		13
19. Facial expression				
0	0	10	0.54	1
1	14	100		13
2	36	217		37
3	20	153		20
4	11	53		9
20. and 21. Tremor at rest (head, upper and lower extremity right and left) and postural tremor (upper extremity right and left)	2 (17)	1 (28	0.64	1 (18)
22. Rigidity (head, upper and lower extremity right and left)	9 (18)	7 (20)	0.01	7 (20)
23 -26. Bradykinesia items right and left	21 (30)	19 (32)	0.01	20 (30)
27-30. gait and postural imbalance	12 (12)	10 (16)	0.02	11 (13)
31. Body bradykinesia				
0	0	9	0.59	1
1	3	35		6
2	24	166		28
3	31	187		27
4	23	135		18
UPDRS 4				
Sum of dyskinesia items	0 (8)	0 (10)	0.70	0 (9)
Sum of wearing-off items	2 (5)	2 (7)	0.31	2 (5)
NMSs, F x S scores				
1. light-headedness	0 (12)	0 (12)	0.86	0 (12)
2. fainting	0 (12)	0 (12)	0.53	0 (12)
3. daytime sleepiness	3 (12)	2 (12)	0.15	3 (12)
4. fatigue	6 (12)	4 (12)	0.54	4 (12)
5. difficulties falling asleep	2 (12)	0 (12)	0.02	2 (12)
6. restless legs	0 (12)	0 (12)	0.59	0 (12)
19. hypersalivation	4 (12)	3(12)	0.46	4 (12)

		NPI G Apathy			NPI item J. Aberrant motor behavior		
No	P	Yes	No	P	yes	No	P
212	0.69	100	145	0.51	56	186	0.09
112		51	77		22	106	
104		50	71		17	102	
98		37	75		14	97	
11		3	9		1	9	
22	0.33	5	20	<0.01	2	22	0.02
134		46	108		25	128	
188		77	136		32	180	
144		72	94		34	130	
47		40	19		18	38	
8	0.87	3	7	<0.01	0	9	0.23
102		36	79		17	97	
216		96	159		45	207	
153		66	107		33	140	
56		39	25		16	45	
1 (28)	0.68	1 (24)	1 (28)	0.83	0 (18)	1 (28)	0.03
7 (20)	0.96	10 (20)	6 (20)	<0.01	7 (20)	7 (12)	0.67
19 (32)	0.13	22 (30)	17 (32)	<0.01	21 (30)	19 (32)	0.02
10 (16)	0.17	12 (14)	10 (16)	<0.01	11 (15)	10 (16)	0.02
8	0.87	3	6	<0.01	2	7	0.69
32		9	29		7	31	
162		55	137		32	157	
191		94	125		36	182	
141		79	79		34	120	
0 (10)	0.94	0 (9)	0 (10)	0.29	1 (9)	0 (9)	0.09
2 (7)	0.59	2 (7)	2 (6)	0.03	2 (6)	2 (7)	0.02
0 (12)	0.91	1 (12)	0 (12)	0.08	0 (12)	1 (12)	0.92
0 (12)	0.13	0 (12)	0 (12)	0.24	0 (12)	0 (12)	0.45
2 (12)	0.30	4 (12)	2 (12)	<0.01	3 (12)	2 (12)	0.22
6 (12)	0.33	8 (12)	4 (12)	<0.01	4 (12)	6 (12)	0.17
0 (12)	0.03	0 (12)	0 (12)	0.37	1 (12)	0 (12)	0.29
0 (12)	0.46	0 (12)	0 (12)	0.67	0 (12)	0 (12)	0.42
3 (12)	0.81	4 (12)	3 (12)	0.25	4 (12)	3 (12)	0.60

table continues

	NPI item C. Agitation			**NPI item I, Irritability / lability**
	Yes	no	P	Yes
20. difficulty swallowing	2 (12)	1(12)	0.23	1 (12)
21. constipation	4 (12)	3(12)	0.12	4 (12)
22. urgency	8 (12)	6 (12)	0.35	8 (12)
23. frequency	5 (12)	4(12)	0.54	6 (12)
24. nocturia	6 (12)	4(12)	0.75	8 (12)
25. losing interest in sex	3 (12)	0 (12)	0.08	4(12)
26. sexual dysfunction	9 (12)	4 (12)	0.14	8 (12)
27. pain	2 (12)	0 (12)	0.70	4 (12)
28. anosmia	4 (12)	3 (12)	0.83	0 (12)
29. weight loss	0 (12)	0 (12)	0.09	0 (12)
30. excessive sweating	0 (12)	0 (12)	0.68	0 (12)
NPI-NH FxS scores				
A. Delusions	0 (12)	0 (12)	<0.01	0 (12)
B. Hallucinations	2 (12)	0 (12)	<0.01	2 (12)
C. Agitation/aggression	-	-	-	4 (12)
D. Depression/Dysphoria	6 (12)	0 (12)	<0.01	4 (12)
E. Anxiety	3 (12)	0 (12)	<0.01	4 (12)
F. Elation/euphoria	0 (9)	0 (6)	<0.01	0 (9)
G. Apathy / indifference	6 (12)	0 (12)	<0.01	4 (12)
H. Disinhibition	0 (12)	0 (12)	<0.01	0 (12)
I. Irritability /lability	4 (12)	0 (9)	<0.01	-
J. Aberrant motor behavior	0 (12)	0 (12)	<0.01	0 (12)
K. Sleep and nighttime behavior disorders	0 (12)	0 (12)	0.07	4 (12)
L. Appetite and eating changes	0 (12)	0 (12)	0.15	0 (12)

MMSE = Mini-Mental State Examination; LEDD = Levodopa Equivalent Daily Dose; UPDRS = Unified Parkinson's Disease Rating Scale; NMSs = Non-Motor Symptoms Scale; NPI = Neuropsychiatric Inventory; F x S = frequency x severity score

		NPI G Apathy			NPI item J. Aberrant motor behavior		
No	P	Yes	No	P	yes	No	P
1 (12)	0.39	2 (12)	1 (12)	<0.01	2 (12)	1 (12)	0.45
3 (12)	0.37	4 (12)	2 (12)	<0.01	2(12)	4 (12)	0.09
6 (12)	0.18	8 (12)	4 (12)	<0.01	8 (12)	6 (12)	0.01
4 (12)	0.16	6 (12)	2 (12)	<0.01	6 (12)	3 (12)	0.03
4 (12)	0.13	6 (12)	4 (12)	0.23	8 (12)	4 (12)	0.10
0 (12)	0.02	4 (12)	0 (12)	<0.01	0 (12)	0 (12)	0.99
4 (12)	0.13	12 (12)	1 (12)	<0.01	4(12)	4 (12)	0.63
0 (12)	0.11	1 (12)	0 (12)	0.85	0 (12)	1 (12)	0.52
4(12)	0.48	4 (12)	2 (12)	0.52	4 (12)	2 (12)	0.71
0 (12)	0.22	0 (12)	0 (12)	<0.01	0 (12)	0 (12)	0.41
0 (12)	0.03	0 (12)	0 (12)	0.42	0 (12)	0 (12)	0.05
0 (12)	<0.01	0 (12)	0 (12)	<0.01	1 (12)	0 (12)	<0.01
0 (12)	<0.01	0 (12)	1 (12)	<0.01	2 (12)	0 (12)	<0.01
0 (12)	<0.01	0 (12)	0 (12)	<0.01	0 (12)	0 (12)	<0.01
1 (12)	<0.01	0 (12)	4 (12)	<0.01	3 (12)	1 (12)	0.01
0 (12)	<0.01	0 (12)	1 (12)	<0.01	0 (12)	0 (12)	0.28
0 (6)	0.08	0 (9)	0 (6)	0.77	0 (6)	0 (9)	<0.01
0 (12)	<0.01	-	-	-	4 (12)	0 (12)	<0.01
0 (12)	<0.01	0 (8)	0 (12)	0.14	0 (12)	0 (12)	<0.01
-	-	0 (12)	0 (12)	<0.01	0 (12)	0 (12)	<0.01
0 (12)	<0.01	0 (12)	0 (12)	<0.01	-	-	-
0 (12)	<0.01	0 (12)	0 (12)	<0.01	1 (12)	0 (12)	<0.01
0 (12)	0.09	0 (12)	0 (12)	0.01	1 (12)	0 (12)	<0.01

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CHAPTER 4. Prevalence and prescribed treatments of orthostatic hypotension in institutionalized patients with Parkinson's Disease

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4.1 Abstract

Background Orthostatic hypotension (OH) in Parkinson's disease (PD) is a common non-motor sign that can be hard to recognize and treat. OH prevalence and treatment in institutionalized PD-patients remains unknown.

Objective The aim of this study was to explore the prevalence and prescribed treatments of OH in institutionalized patients with PD.

Method A cross-sectional study of nursing homes in the south-east of the Netherlands identified 64 residents with PD (inclusion criteria: MMSE >18). Assessments included blood pressure measurement, both supine and in the upright position (after 1 minute and after 3 minutes of standing), and 2 questions on cardiovascular items including falls of the validated Non-Motor Symptom Scale (NMSS). OH was defined according to the consensus guidelines. OH was considered as 'probably symptomatic' if patients had a concomitant frequency score >1 on the selected NMSS items, and 'probably asymptomatic' for a frequency score of 0. If OH was not present, but patients had a frequency score >1, OH was considered as 'possibly symptomatic'.

Results The prevalence of OH was 51.6%, almost equally divided into probably symptomatic and probably asymptomatic cases. Another 20.6% had possibly symptomatic OH. Importantly, only two patients with symptomatic OH had an OH diagnosis noted in their medical records. Five received domperidone, one received fludrocortisone, and none received midodrine.

Conclusion One half of institutionalized PD patients had OH, of whom half were probably symptomatic. OH was rarely noted in the medical records, suggesting underdiagnosis. Finally, OH was rarely treated, suggesting undertreatment.

4.2 Introduction

Parkinson's disease (PD) in institutionalized patients has a profound impact on quality of life and is characterized by a wide range of motor and non-motor signs [1, 2]. Orthostatic hypotension (OH) is a common non-motor trait, defined as a blood pressure drop within three minutes of standing of at least 20 mmHg systolic or at least 10 mmHg diastolic [3]. OH has a prevalence in PD ranging from 30% to 64.9% [4], and can be symptomatic, causing symptoms like generalized weakness, lightheadedness, head and neck pain, vertigo, falls and syncope [5]. However, it can also be asymptomatic, making it clinically less relevant. Patients can describe symptoms reminiscent of OH without measurements showing a blood pressure drop, either because the symptoms are not due to OH or because the blood pressure was measured at a time when OH was not pronounced. The prevalence of symptomatic orthostatic hypotension has been estimated to be about 19% [6, 7], with a large proportion of PD-patients (30%) having asymptomatic OH. Treatment of OH can be pharmacological and non-pharmacological. Suggested pharmacological treatments include midodrine and fludrocortisone [8, 9]. In Dutch guidelines, domperidone is suggested as a treatment for OH [10].

No studies have specifically addressed the prevalence of OH in institutionalized PD-patients, even though the prevalence in these severely affected patients might be particularly high. It is currently unclear how often OH is recognized and treated in long-term care settings. Prior work suggests that misdiagnosis and undertreatment are common among institutionalized PD-patients[2, 11], and this may be especially the case for an elusive symptom such as OH. The aim of this study was to explore the prevalence of OH in PD patients living in Dutch nursing homes, and to determine whether it is recognized and treated adequately.

4.3 Materials and Methods

Population

The study, described in detail previously [1, 2], was performed in 12 large nursing home organizations in the South of the Netherlands between January and November 2010. Only residents receiving long-term care were included. Eligible residents were identified through medical files of elderly care physicians and registries of pharmacists identifying all nursing home residents who used antiparkinsonian medication (defined according to the Anatomical Therapeutic Chemical (ATC) classification system: N04). All nursing home medical charts were reviewed, and all primary and secondary diagnoses were recorded. All prescribed medication

was recorded, and fludrocortisone, midodrine and domperidone were specifically registered for analysis. For most residents, the hospital outpatient file was present in the nursing home and was also reviewed. A single researcher (NW) with experience in the field of movement disorders confirmed the diagnosis of PD according to the UK Parkinson's Disease Brain Bank criteria [12]. Participants scoring less than 18 on the Mini-Mental State Examination (MMSE)—representing moderate to severe cognitive decline, which could hamper obtaining reliable clinimetrics [13]—were excluded. Participants currently or recently treated with (typical) antipsychotic drugs or other offensive drugs, defined by an extensive review [14], were also excluded. An exception was made for patients in whom a diagnosis had been made prior to the start of the offending drug [11].

Measurement

OH was measured according to a standard protocol consisting of three measurements with a routine sphygmomanometer [15]. A first measurement was carried out after at least 10 minutes of supine rest. The second and third measurements were performed following standing up, after 1 and 3 minutes respectively [3]. A nurse or nurse assistant carried out the measurement after instruction by a movement disorder specialist (NW). Patients able to stand, with or without help of caregiver, were included. Patients who could not stand for 3 minutes due to motor problems were excluded. Patients who could not stand for 3 minutes due to OH were included. Symptoms of orthostatic intolerance were determined using two questions of the first domain of the Non-motor Symptom Scale (NMSS): "Lightheadedness, dizziness, weakness on standing", and "Falling because of fainting /blacking out". Answers comprise frequency (range 0-4) and severity (range 0-3) assessing the symptom, if present, over the last month. Participants presenting with frequency ≥1 on either of these were determined as having orthostatic symptoms. The severity is scored as mild (causing little distress or disturbance), moderate (causing some distress or disturbance) or severe (causing major distress or disturbance) [16]. We defined the following combinations of OH and symptoms: probably symptomatic OH denotes patients with orthostatic symptoms and OH, possibly symptomatic OH concerns those with orthostatic symptoms but no OH. Probably asymptomatic OH concerned patients with OH but without orthostatic symptoms; finally, no OH describes patients without OH and without symptoms. All current medication was retrieved from the nursing home medical chart. Antihypertensive medications considered were diuretics, B-adrenergic antagonist, calcium antagonist and ACE-inhibitors or angiotensin receptor antagonist. Co-morbid disorders were retrieved from medical files and classified according to the ICD-10 coding system. Cardiovascular disease

was considered present if medical files showed cerebrovascular accident (ICD-10: I60-I69, G45), myocardial infarction (ICD-10: I21, I22, I252), heart failure (ICD-10 I50), peripheral vascular disease (ICD-10: I71, I79.0, I73.9, R02, Z95.8, Z95.9) or other cardiovascular diseases (I0-I99). Also, hypertension (ICD-10: I10-I15) and diabetes mellitus (ICD-10: E10-E14) were extracted from medical files.

Statistics

For descriptive statistics SPSS version 20.0.0.1 (2011) was used. Taking antihypertensives, history of hypertension, history of diabetes mellitus and history of cardiovascular disease were analyzed as potential confounding variables in an explorative analysis, using the chi-square test. A critical p-value of 0.05 was applied.

4.4 Results

Of 258 patients considered, 152 patients were diagnosed with PD; 73 met the inclusion criteria of MMSE >18. Blood pressure measurements were available for 64 patients, with no measurement (N=7) and failed third measurement (N=2) explaining the remainder of the group (Figure 1). One patient completed the blood pressure measurement but not the NMSS questionnaire. This patient was left out of the further analyses. The mean age of patients was 78.8 years; disease duration was 9.9 years. The majority of patients had advanced disease (85.9% Hoehn & Yahr stage ≥4). The prevalence of OH was 51.6% (Table 1).

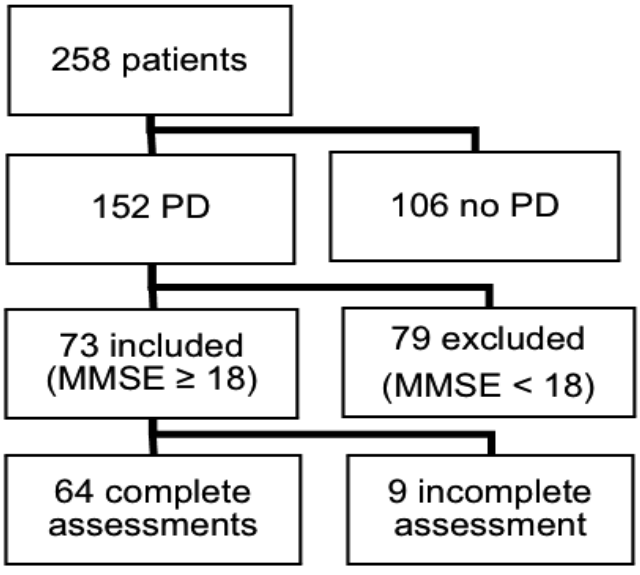

Figure 1. Flow-chart of study sample
PD = Parkinson's disease, MMSE= Mini mental state examination

Table 1. Patient characteristics (n=64)

Characteristic	Value
Age (in years), mean (SD)	78.8 (6.5)
Gender, n (% women)	36 (56.3%)
Disease duration (in years), mean (SD)	9.9 (6.8)
Length of nursing home stay (in months), mean (SD)	20.8 (25.0)
Hoehn and Yahr stage, n (%)	
2	1 (1.6%)
3	8 (12.5%)
4	26 (40.6%)
5	29 (45.3%)
Orthostatic hypotension, n (%)	33 (51.6%)

OH was recognized in 52.4% of the population; 25.4% had probably symptomatic OH and 27.0% had probably asymptomatic OH. 46.0% of all patients reported orthostatic symptoms. 20.6% had possible symptomatic OH and 27.0% had no OH (Table 2).6 reported orthostatic symptoms as a major source of distress, 8 as causing some distress and 15 as causing little distress.

Table 2. Cross-table of orthostatic hypotension and orthostatic symptoms (n=63)

		Orthostatic symptoms? n (%)		
		Yes*	No**	
Orthostatic hypotension? n (%)	Yes	16 (25.4)	17 (27.0)	33 (52.4)
	No	13 (20.6)	17 (27.0)	30 (47.6)
		29 (46.0)	34 (54.0)	63 (100)

** NMSS Domain 1, item 1 or 2 frequency≥1; ** NMSS, Domain 1, item 1 and 2 frequency = 0*

Three diagnosis alluding to OH were found in medical files: “collapse”, “prone to collapse” and “autonomic dysfunction”. A diagnosis was present in the medical files of one patient with probably symptomatic OH, one patient with probably asymptomatic OH and one patient with possibly symptomatic OH. Six patients were treated with either domperidone or fludrocortisone. None received midodrine. Domperidone was prescribed for two patients with probable symptomatic OH and three patients with possible symptomatic OH. Fludrocortisone was prescribed to one patient with possibly symptomatic OH and one patient with no OH (Table 3).

Comorbidity was frequently present: 35 patients had a history of cardiovascular disease, 17 patient's hypertension and 11 patients had diabetes mellitus. Another 32 patients were using antihypertensives (Table 3). No statistically significant differences between OH-groups were found on comorbidity and use of antihypertensive medication.

Table 3. Reported confounding variables, treatment and diagnosis in medical file

	Overall *N=63*	Probable symptomatic OH *N=16*	Probable asymptomatic OH *N=17*	Possible symptomatic OH *N=13*	No OH *N=17*
Potential confounding variables					
Taking antihypertensives, n (%) *	32 (50.8)	7 (43.8)	10 (58.8)	5 (38.5)	9 (52.9)
History of hypertension, n (%) *	17 (26.9)	3 (18.8)	5 (29.4)	5 (38.5)	4 (23.5)
History of cardiovascular disease, n (%) *	35 (55.6)	8 (50)	8 (47.1)	8 (61.5)	11 (64.7)
History of diabetes mellitus, n (%) *	11 (17.4)	2 (12.5)	2 (11.8)	5 (38.5)	2(11.8)
Pharmacological treatment of OH					
Fludrocortisone, n (%)	2 (3.2)	0	0	1 (1.6)	1 (1.6)
Domperidone, n (%)	5 (7.9)	2 (3.2)	0	3 (4.8)	0
Diagnosis in medical file					
History of OH, n (%)	3 (4.8)	1 (1.6)	1 (1.6)	1 (1.6)	0

** no statistically significant difference; OH = Orthostatic Hypotension*

4.5 Discussion

In this relatively small sized cohort study the prevalence of OH in institutionalized PD patients was 51.6%. In a systematic review in 2011 prevalence in PD-patients was estimated lower at 30% [4]. As no comparison was made in this study with unmedicated PD-patients, less disabled PD-patients or non-PD nursing home residents no conclusions can be drawn on why prevalence seems higher in our cohort. Several hypotheses can be made based on this study. A potential determinant of OH is PD progression. An earlier study showed that OH is equally prevalent in mild, moderate and severe PD [17]. However, the average HY stage of 4.3 in our cohort is much higher than the HY stage in any cohort published earlier

[4, 17]. Other determinants of OH are cardiovascular disease, diabetes mellitus and antihypertensive medication [18, 19]. These factors were shown to be present in > 50% of patients and could potentially explain the increased prevalence in this patient group. No differences in frequency of determinants were found between PD-patients with and without OH in an explorative analysis. This could be because our study was underpowered to detect a difference due to the small sample size. More research is warranted to explain the finding of high OH prevalence in institutionalized PD-patients.

About half of patients had probably symptomatic OH. In this paper we defined three degrees of probability linking patient's symptoms with the outcome of an orthostatic blood pressure measurement. The Consensus statement [3] defines OH as a blood pressure fall, but does not provide guidelines how to link symptoms with this sign. There are several reasons why studying this relation is complex. First, a fall of systolic blood pressure of 20 mm Hg is abnormal, but whether it causes clinically manifest cerebral hypoperfusion probably depends more on the level of the nadir than on the magnitude of the drop. In other words, a systolic drop from 60 to 40 mmHg can be clinically more relevant than a drop of 180 to 80 mm Hg [20]. Second, the manifestation of OH can differ during the course of the day, with symptoms typically presenting most frequently in the morning. Also, OH can worsen due to the variable presence of exacerbating factors like heat, food, alcohol, exercise, activities which increased intrathoracic pressure (e.g. coughing, defecating) and certain drugs [21, 22]. Third, the reliability of self-reported symptoms can be biased as patients have difficulty distinguishing symptoms of OH from other symptoms, e.g. balance problems or benign paroxysmal positional vertigo [23, 24].

Several other methodological issues could hamper the interpretation of our findings. First, an inherent risk of selection bias is associated with cohorts with a small sample size. We tried to minimize the risk of selection with a double search recruitment strategy identifying virtually all eligible residents in the approached nursing homes. Second, PD-patients with an MMSE <18 were excluded from this study. The prevalence of OH is known to be high (50%) in patients with PD and dementia [25], so the prevalence observed here is likely an underestimate. Third, we followed the definition of classical OH, so initial OH (occurring very rapidly after rising, hence missed by the traditional blood pressure measurements) and delayed OH (occurring after prolonged standing, well beyond the second measurement taken after 3 min of standing) may have been missed also resulting in a probable underestimation [26, 27]. Finally, we did not use an Ewing test battery as our measurement routine of

autonomic dysfunction. We focused on OH as a clinically most relevant expression of autonomic failure. To do so, we diagnosed OH using a validated and clinically widely used measurement technique, tailored to this particular group of patients who are not capable of visiting an outpatient clinic equipped with a tilt table [6, 7, 28] In addition, we went further than merely measuring a blood pressure drop and wanted to gain insight into the symptoms of OH. The Non-Motor Symptom Scale is suggested for evaluating the presence and severity of OH-related symptoms in a Movement Disorder Task Force-review of dysautonomia rating scales [29]. There is however an inherent risk of informational bias associated our measurement routine.

4.6 Conclusion

Probably symptomatic OH was present in 25.4% of our institutionalized patient population. An additional 20.6% had possibly symptomatic OH. Only three patients had a diagnosis alluding to OH in the medical record, suggesting a marked under-diagnosis of OH. A minority of symptomatic patients received fludrocortisone or domperidone, despite sometimes debilitating symptoms upon rising or standing, suggesting undertreatment. As the clinical manifestations of OH can be very burdensome, a more robust approach to address these complaints is needed.

4.7 References

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CHAPTER 5. Optimizing treatment in undertreated late-stage parkinsonism: a pragmatic randomized trial

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5.1 Abstract

Background Treatment of patients with late-stage parkinsonism is often sub-optimal.

Objective To test the effectiveness of recommendations by a movement disorder specialist with expertise in late-stage parkinsonism.

Methods Ninety-one patients with late-stage parkinsonism considered undertreated were included in a pragmatic multi-center randomized-controlled trial with six-month follow-up. The intervention group received a letter with treatment recommendations to their primary clinician based on an extensive clinical assessment. Controls received care as usual. The primary outcome was the Unified Parkinson Disease Rating Scale (UPDRS) part-II (Activities of Daily Living). Other outcomes included quality-of-life (PDQ-8), mental health (UPDRS-I), motor function (UPDRS-III), treatment complications (UPDRS-IV), cognition (Mini-mental-state-examination), non-motor symptoms (Non-Motor-Symptoms-scale), health status (EQ-5D-5L) and levodopa-equivalent-daily-dose (LEDD). We also assessed adherence to recommendations. In addition to intention-to-treat analyses, a per-protocol analysis was conducted.

Results Sample size calculation required 288 patients, but only 91 patients could be included. Treating physicians followed recommendations at least partially in 37 (64%) patients. The intention-to-treat analysis showed no difference in primary outcome (between-group difference = -1.2, p = 0.45), but there was greater improvement for PDQ-8 in the intervention group (between-group difference = -3.7, p=0.02). The per-protocol analysis confirmed these findings, and showed less deterioration in UPDRS-part I, greater improvement on UPDRS-total score and greater increase in LEDD in the intervention group.

Conclusion The findings suggest that therapeutic gains may be reached even in this vulnerable group of patients with late-stage parkinsonism, but also emphasize the need for better strategies to implement specialist recommendations to further improve outcomes.

5.2 Introduction

Late-stage parkinsonism (LSP) is characterized by a high burden of motor and non-motor symptoms, resulting in dependence in daily functioning, low quality of life and, ultimately, an increased risk of institutionalization and death [1, 2]. Studies suggest that treatment in LSP is often suboptimal [1, 3, 4]. In a Dutch nursing home population, 44% of patients reported to be "off" most of the day[4] and received a seemingly too low dose of dopaminergic treatment. Also, patients in this study perceived their professional caregivers as having insufficient knowledge of Parkinson's disease (PD) [3].

Although treatment in LSP is more complex than in earlier disease stages[1], movement disorders experts are potentially well equipped to address this complexity as they frequently treat patients with PD. However, LSP-patients may be underrepresented in their patient population, as LSP-patients are frequently unable to travel for appointments with a neurologist, or for hospital-based assessments of their condition. A model of care with a movement disorder expert's advice supporting the treatment decisions of the patient's primary physician in LSP, has not been tested for feasibility or effectiveness in LSP.

The primary aim of this European pragmatic study was to evaluate the effect of recommendations made by movement disorder experts in a population of undertreated LSP-patients on clinically relevant outcomes measures, such as activities of daily living, motor symptoms, non-motor symptoms and quality of life.

5.3 Methods

Study design

This study is part of the Care of Late-Stage Parkinsonism-study (CLaSP-study) [5]. To assess the effect of the intervention, we designed a multi-center pragmatic parallel randomized controlled trial that allowed us to observe the effectiveness embedded within existing clinical care routines in four European countries (UK, France, Sweden and the Netherlands). Centers in two other countries, who participated in the CLaSP-study, did not participate in this trial due to organizational and regulatory issues. To establish an estimation of impact, the study had a pragmatic design and was executed in routine clinical practice[6]. The study recruitment was set up to be as inclusive as possible. Allocation to the intervention versus control group followed a 3:1 ratio to ensure that as many patients as possible could potentially benefit from the intervention. The study consisted of a baseline measurement following inclusion of the patient in the study, and a follow-up measurement after six months.

Study sample

Patients recruitment took place from January 2015 until December 2017. Last follow-up measurement was June 2018. Undertreated LSP-patients formed the target population. As these patients normally do not access expert research centers, recruitment was set-up to include care-pathways outside of routine recruitment pathways like expert clinics. Care settings included in the recruitment were nursing homes (France, Sweden, the Netherlands), general practices (UK), non-research Centre hospitals (Sweden, the Netherlands), patient-advocate organizations (UK) and PD patient registries (Sweden). Patients with a disease duration of 7 years or longer were invited for participation if they either had disease stage Hoehn and Yahr stage ≥ 4 or a Schwab and England-score ≤ 50%. This allowed for inclusion of patients with disability not only due to motor but also non-motor problems, such as dementia, neuropsychiatric symptoms and autonomic dysfunction [7]. Undertreatment was defined by the presence of any insufficiently treated symptoms or problems (for full set of possible symptoms and problems see table 1). PD and atypical parkinsonian disorders were diagnosed using established clinical criteria[8-10]. Patients with atypical parkinsonism were purposely not excluded as their care needs are likely comparable to those of patients with late-stage PD[11-13]. Exclusion criteria were: 1. a diagnosis of normal pressure hydrocephalus or drug-induced parkinsonism (except if parkinsonism persisted after discontinuation of the causative drug for at least 6 months), 2. dementia prior to or at time of parkinsonism diagnosis; 3. having seen a movement disorder specialist recently (≤4 months); and 4. the patient was unable to comply with changes to treatments (for example unable to attend physiotherapy in their region).

Intervention

Our intervention consisted of a letter with specific recommendations to optimize treatment and care, formulated by a movement disorder expert, based on a comprehensive clinical assessment by the researchers, as part of the CLaSP protocol [5]. The researchers assessed the symptoms and discussed these with the movement disorder expert, who drafted the letter. Each study center assigned one expert to write this letter. To align the recommendations between the centers, the experts used an extensive, predesigned study guideline. During a face-to-face meeting, the group of movement disorder experts in the study developed this consensus-based recommendation guideline based on combined treatment recommendations of multiple European and International guidelines[14-19]. (see supplemental file). The guideline covered four distinct domains: 1. dopaminergic treatment, 2. non-dopaminergic treatment, 3. mental health medications, and 4. allied health care, social services and nursing care.

Table 1. Definition of undertreated LSP patients

More than 1 of the following:
- Troublesome motor parkinsonism (including nocturnal motor problems).
- Levodopa-induced motor complications, including Off-time >50% of waking day, moderately disabling dyskinesias or off-time dystonia.
- PD dementia (defined according to MDS Task Force definition (Dubois et al. 2007), and not treated with cholinesterase inhibitors.
- Depression not receiving adequate treatment.
- Clinically relevant neuropsychiatric symptoms, among which psychotic symptoms, agitation/ aggression; anxiety and irritability/ liability.
- Clinically relevant symptomatic orthostatic hypotension, pain, constipation, urinary symptoms, insomnia or daytime sleepiness.
- Regular falling
- Treatment with medications that are associated with exacerbation of PD-related problems: (a) typical antipsychotics other than quetiapine or clozapine, anticholinergics, benzodiazepines, pills with protein rich meal, antihypertensives in symptomatic hypotensive patients, valproate, calcium antagonists, other medications with side effect exacerbating PD motor or non-motor symptoms
- Increased risk of contractures and skin ulceration
- Inadequate management of dysphagia with risk of choking, of dysarthria or of hypersalivation
- Living in an inadequate home environment.

For each patient, the letter with recommendations was sent to the physician who was identified by the patient as being the physician responsible for the parkinsonism treatment, i.e., the primary physician. The movement disorder expert drafted the letter after the CLaSP baseline assessment, considering current and previous disease factors, review of medications and current medical and social care arrangements. The movement disorder expert sent the letter to the primary physician with the invitation to contact the expert if the recommendations were unclear or additional advice was needed. The decision to implement the recommendations remained with the patient's primary physician. Patients in the control group received care as usual during the follow-up period, but had the possibility to receive a letter with recommendations from the expert after the follow-up assessment, i.e. outside the current study window. For ethical reasons, if the assessments revealed issues requiring urgent treatment, these were communicated to the primary physicians in both treatment and control group.

Outcomes

The primary outcome was the Unified Parkinson's Disease Rating Scale – part II: activities of daily living (UPDRS-II)[20] at 6 months, and secondary outcomes were quality of life (Parkinson Disease Quality of Life Questionnaire 8-items version; PDQ-8), mental health (UPDRS-I), motor function (UPDRS-III), complications of

therapy (UPDRS-IV), total UPDRS score (UPDRS-total), cognition (Mini-mental state examination; MMSE), non-motor symptoms (Non-Motor Symptoms scale; NMSs) and health status (EQ-5D-5L). We also assessed the levodopa equivalent daily dose (LEDD)[21-26]. We chose activities of daily living as the primary outcome, because it contributes to the disease burden of patient and caregiver, and to adverse outcomes like nursing home placement[27-29]. Outcomes were assessed twice: at baseline and at the primary endpoint after six months. Assessors visited the patients mostly at home, but if possible, patients came to the study center. Process information was collected to assess implementation of the treatment recommendations and barriers to implementation. During the follow-up meeting the assessor discussed the treatment recommendations with the patient and scored recommendations as completely followed, partially followed, not followed, or unknown. The assessor contacted the primary physician for an interview to find out if recommendations were followed, and to assess barriers for implementations. For the latter, we used a structured questionnaire based on the Cabana model [30-32], which identifies barriers in knowledge, attitude or behavior for guideline adherence among neurologist and GP [31, 32]. Barriers listed in the original questionnaire that were not applicable to our intervention were removed, leaving a comprehensive list of eleven items (see table 4).

Randomization and concealment of allocation

Permuted block randomization was used, stratified by country, presence of dementia and residency (nursing home or similar/ home). Randomization was performed centrally at the Coordinating Centre for Clinical Trials (Marburg, Germany). Assessors and patients were not blinded.

Statistical analysis

A power calculation was performed to estimate the target sample size, based on the primary outcome: UPDRS – part II: activities of daily living [33] An independent sample *t*-test was used and the assumptions were a difference in change of 4.8 points between both treatment groups, a standard deviation of 10 points for difference in change and non-participating and dropout rates of 20% each. 288 patients had to be included to achieve a power of 80% with a two-sided significance level of 5%. The current study was terminated at the end of the funding period, prior to reaching the target sample size.

Missing data were substituted with an imputation strategy, preferably according to the user guidelines of each measurement instrument. As such, we used the validated protocol for handling missing data of the UPDRS[34], by which imputations were allowed if the number of missing items did not exceed 1 for the UPDRS-I, 1 for

the UPDRS-II and 7 for the UPDRS-III. No imputation was allowed for UPDRS-IV. Imputation for NMS items is possible if less than 15 items were missing. The case-specific mean of completed items was used for imputation of missing UPDRS and NMS items. No valid imputation strategies exist for the other questionnaires and analyses were performed on the available data.

For the intention-to-treat analysis, we performed multivariate linear regression analyses with the outcome measures at follow-up as dependent variables and the group (intervention or care as usual) and baseline score of the outcome measure as the independent variables, correcting for relevant covariates (i.e., presence of dementia, presence of informal caregiver, residency, age, gender and disease duration). We present the covariate-adjusted mean difference between treatment groups and the 95% confidence intervals. We also performed an exploratory per protocol analysis, only including in the intervention group those patients in whom the recommendations were completely or partially followed; all others were included in the control group. Descriptives are presented with mean and standard deviation for normally distributed variables and with median and interquartile range for non-normally distributed variables. Critical p-value for statistical significance was set at 0.05. All analyses were performed using Statistical Package of Social Sciences, version 22.

Standards protocol approvals, regulations, and patient consent

This study was in compliance with the Helsinki Declaration (World Medical Association Declaration of Helsinki 1997). Detailed oral and written information was given to the patients and their informant to ensure that the patients fully understood the potential risks and benefits of the study. Written consent was given by patients or, if patients lacked capacity, by a legal guardian, in accordance with local ethical and legal regulations. The study protocol was approved by the local ethics committees of all participating study sites (London: Camden and Islington NRES Committee 14/LO/0612, Lisbon: Centro Hospitalar Lisboa Norte, DIRCLN-19SET2014–275, Lund: EPN Regionala etikprovningsnamnden (EPN Regional Ethics Name) JPND NC 559–002, Bordeaux: CPP Sud-Ouest et Outre-Mer III 2014/85, , Marburg: Ethik-Kommission bei der Landesarztekammer Hessen (Ethics Commission at the State Medical Association Hesse, MC 309/2014). Nijmegen: Radboud universitair medisch centrum, Concernstaf Kwaliteit en Veiligheid, Commissie Mensgebonden Onderzoek Regio Arnhem-Nijmegen (Radboud university medical center, Group staff Quality and Safety Human Research Committee, Arnhem-Nijmegen region, DJ/CMO300). Inclusion was possible if patients gave their written informed consent. The protocol was registered at ClinicalTrials.gov as NCT02333175 on 07/01/2015.

Data availability
Anonymized data can be shared with qualified investigators on request.

5.4 Results

Out of the 477 patients in the overall CLaSP study in the participating centers with ethical approval, 167 had not received care by a movement disorder specialist within the last four months. Out of these 91 could be included, of whom 70 were randomized to the intervention group and 21 to the control group. Reasons for non-inclusion, including four who declined participation, are listed in figure 1. Patients in the intervention group did not differ in baseline characteristics from controls except for the presence of an informal caregiver that was more present in the intervention group in the per protocol group allocation (table 2). Overall, 58 (83%) patients in the intervention group and 18 (86%) patients in the control group completed the trial (figure 1).

In the intention-to-treat analysis, there was no difference in change in the UPDRS ADL scores, i.e. the primary outcome measure, between the intervention and control group at six months (between-group difference = -1.2, 95% CI = -4.2 to 1.8, p = 0.45). The group difference in UPDRS motor and total score showed a trend towards improvement (between-group difference = -5.1, 95% CI = -10.7 to 0.6, p = 0.08). Quality of life had improved at six months for patients in the intervention group, but had worsened in controls (PDQ-8, between-group difference = -3.7, 95% CI = -6.7 to -0.9, p=0.01; figure 2a and supplementary material). All other secondary outcomes showed no group differences.

The per-protocol analysis (figure 2b and supplementary material) confirmed these findings, showing no between-group difference in the UPDRS ADL score, but again a difference in PDQ-8 in favor of the intervention group (between-group difference = -2.7, 95% CI = -5.1 to -0.3, p=0.03). The difference in UPDRS total score as well as part I scores also reached significance (UPDRS total: between-group difference = -7.4, 95% CI = -14.6 to -0.2, p = 0.04; UPDRS part I: between-group difference = -1.1, 95% CI = -2.2 to -0.4, p = 0.04), with a trend for part III scores (between-group difference = -4.2, 95% CI = -9.2 to 0.8, p = 0.10). Finally, patients in the intervention group had a larger increase in LEDD (between-group difference = 165 mg, 95% CI = 51 to 279, p=0.01). A sensitivity analysis with presence of a caregiver as a covariate in the per-protocol analysis gave similar results (data not shown). Different definitions of the per protocol groups did not change the main results (supplementary materials).

Figure 1. Flow Diagram of recruitment of cohort and trial population

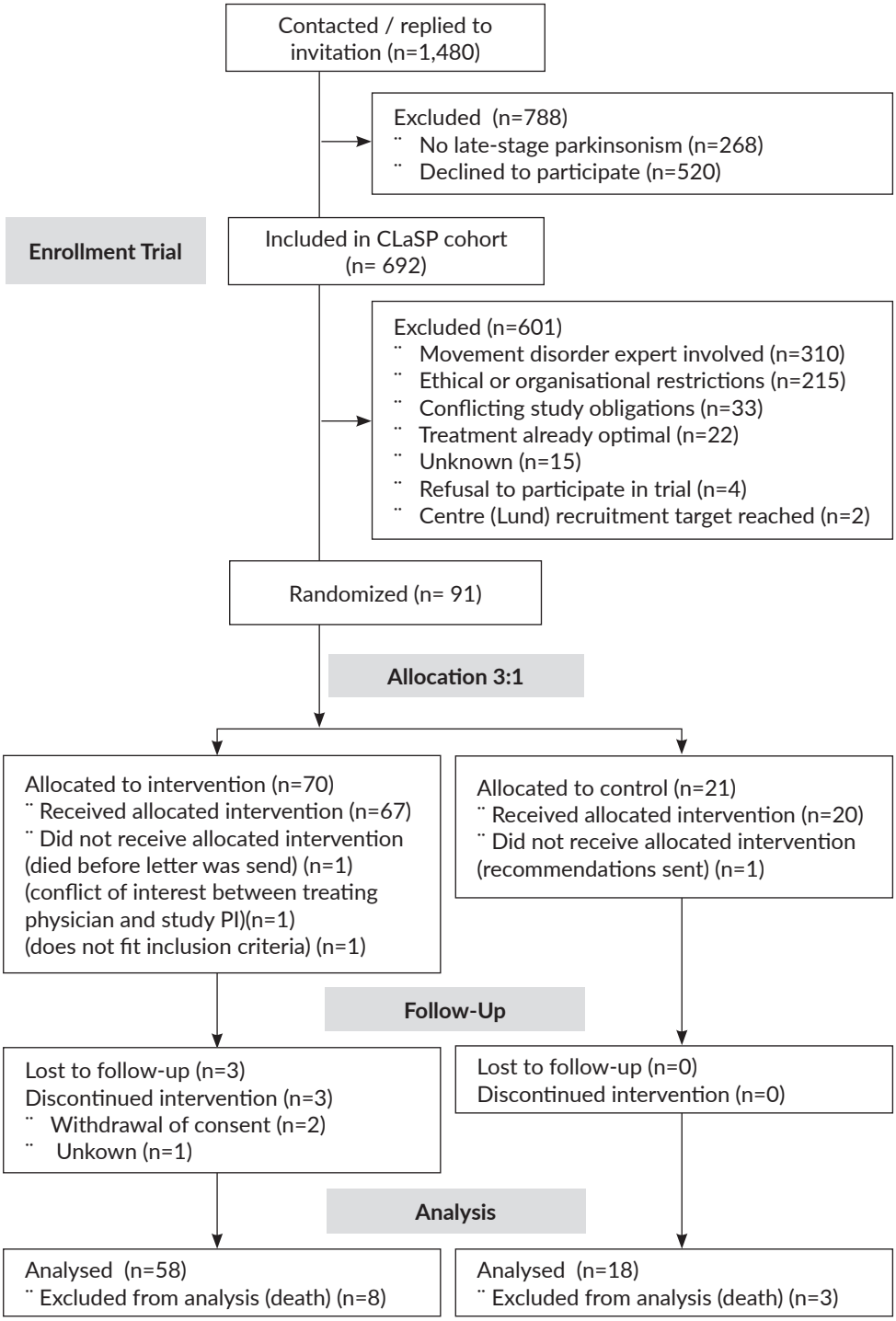
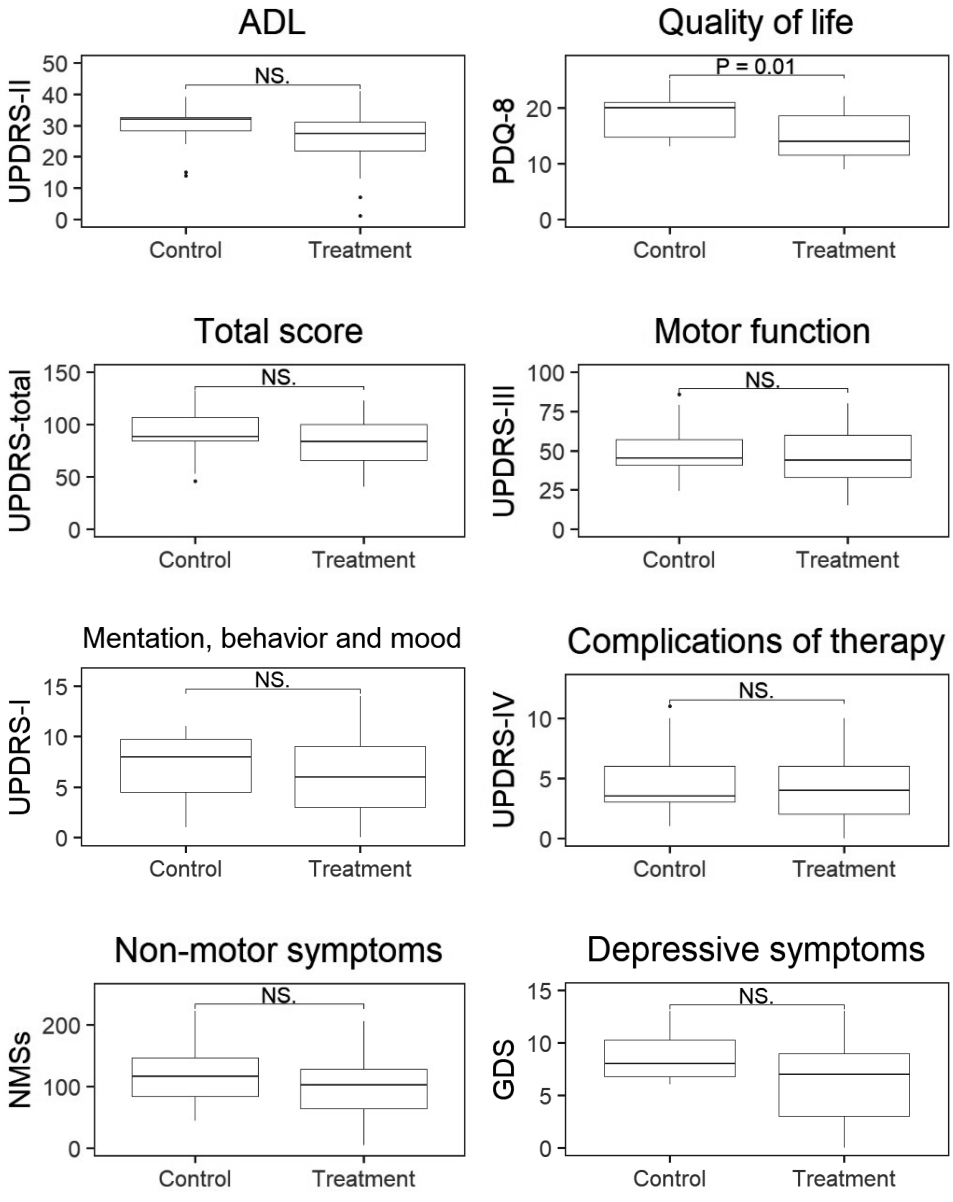


Table 2. Univariate comparative analysis of baseline characteristics

	Intention-to-treat analysis			Per-protocol analysis		
	Interven-tion	Control	P-value	Interven-tion	Control	P-value
Age, years, median (IQR)	80 (74-85)	84 (76-88)	0.15	78 (74-84)	83 (74-88)	0.11
Age of onset, years, mean (SD)	65.0 (10.3)	63.4 (13.1)	0.55	64.6 (9.8)	64.5 (13.2)	0.98
Disease duration, years, median (IQR)	14 (10-18)	16 (12-23)	0.13	14 (9-17)	15 (11-20)	0.44
Women, n (%)	36 (51)	6 (29)	0.07	17 (46)	16 (44)	0.90
Dementia, n (%)	31 (44)	9 (43)	0.91	16 (50)	12 (33)	0.38
Informal care giver present, n (%)	46 (66)	11 (52)	0.27	32 (86)	24 (67)	0.04
Living in nursing home, n (%)	42 (60)	12 (57)	0.82	18 (49)	23 (64)	0.19
Diagnosis, n (%)						
Parkinson's disease	67	20	0.93	35	35	0.57
Atypical parkinsonism	3	1		2	1	
Site, n (%)						
London	7 (10)	1 (5)		2 (5)	2 (6)	0.97
Bordeaux	4 (6)	2 (10)		2 (5)	3 (8)	
Lund	42 (60)	13 (62)		24 (65)	23 (64)	
Nijmegen	17 (24)	5 (24)		9 (25)	8 (22)	
Hoehn and Yahr stage, n (%)						
Stage 3	4 (6)	0	0.52	2 (5)	0	0.20
Stage 4	39 (56)	13 (62)		21 (57)	26 (72)	
Stage 5	27 (39)	8 (38)		14 (38)	10 (28)	

IQR = Interquartile range; SD = Standard deviation

Figure 2A. Intention-to-treat analysis CLaSP-trial



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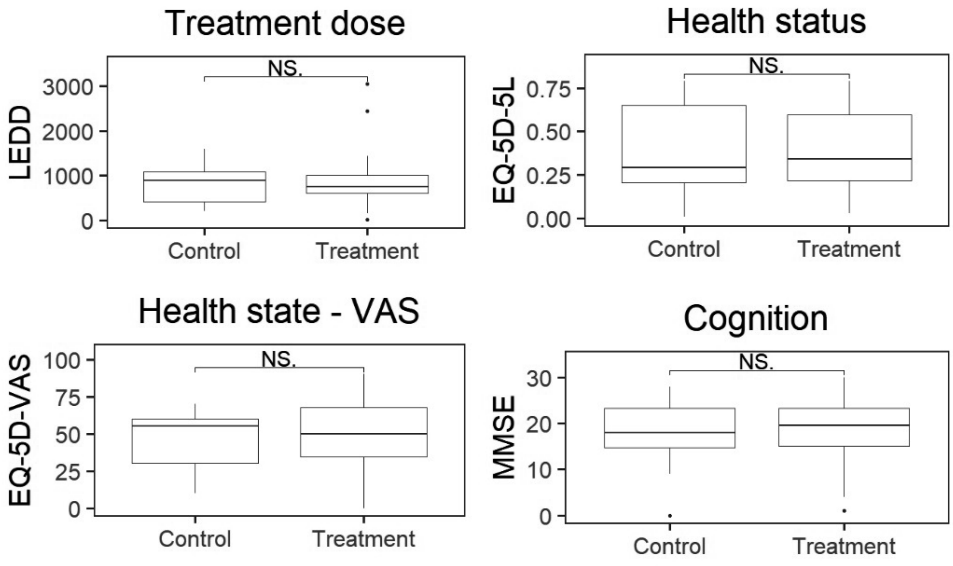
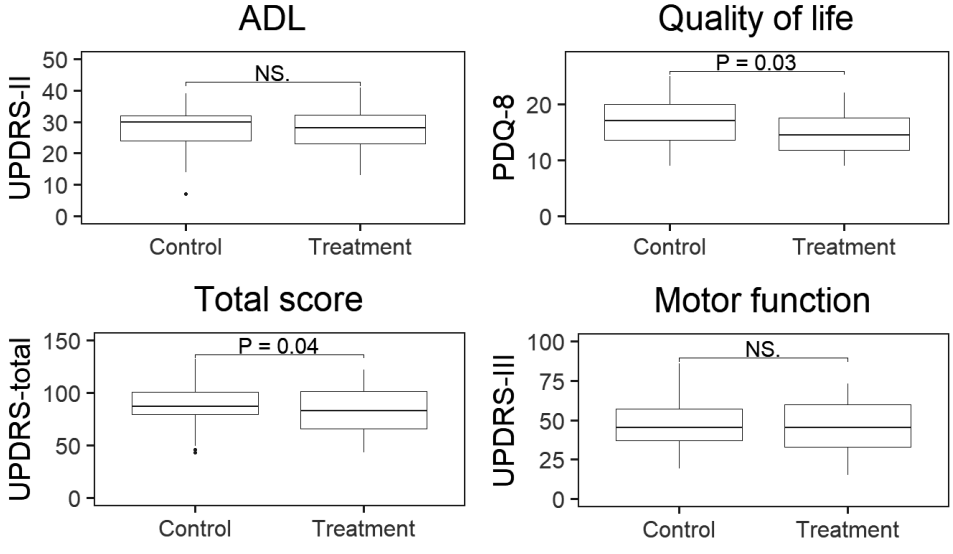


Shown are boxplots of primary and secondary outcome measures at follow-up. UPRDS = Unified Parkinson Disease Rating scale; MMSE = Mini-Mental State Examination; NMSs = Non-Motor Symptoms scale; GDS = Geriatric Depression Scale – 15 items; PDQ = Parkinson Disease Questionnaire, EQ-5D-5L = EuroQol-5 dimensions, VAS = Visual Analogue Scale, LEDD = Levodopa Equivalent Daily Dose, NS. = non-significant

Figure 2B. Per-protocol analysis CLaSP-trial



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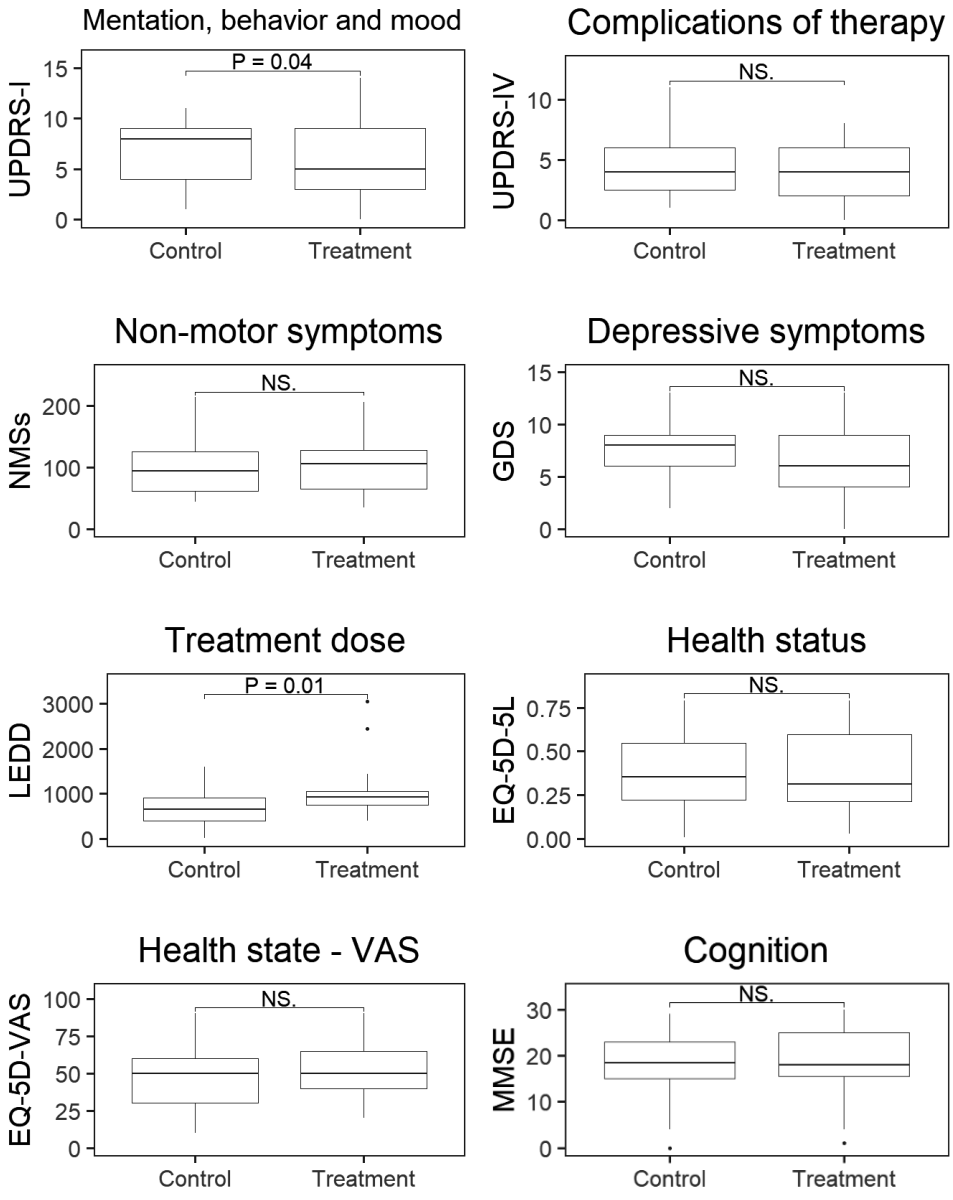

Shown are boxplots of primary and secondary outcome measures at follow-up. UPRDS = Unified Parkinson Disease Rating scale; MMSE = Mini-Mental State Examination; NMSs = Non-Motor Symptoms scale; GDS = Geriatric Depression Scale – 15 items; PDQ = Parkinson Disease Questionnaire, EQ-5D-5L = EuroQol-5 dimensions, VAS = Visual Analogue Scale, LEDD = Levodopa Equivalent Daily Dose, NS. = non-significant

Process Analysis of implementation

The primary physicians receiving the letter with recommendations followed these recommendations completely in only 16 (28%) patients and partially in 21 (36%). Recommendations were not followed in 18 (31%) and remained unclear in 3 (5%) patients. The extent to which recommendations were followed, differed per type of recommendation and ranged from 15% for referral to physiotherapist (complete or partially followed: 5/33) to 50% for recommendations about dopaminergic treatment (complete or partially followed: 20/40). In total, 36 recipients of the letter with recommendations were contacted to assess barriers for implementing recommendations. As the main reason for not following the recommendations, the physicians reported to have experienced an inability to reconcile patient's preferences with the recommendation (10 /36 = 28%), lack of time (8/36 = 22%) and lack of outcome expectancy (7/36 = 19%) (table 3). In addition to the items from the Cabana model, the open question retrieved eight additional barriers, reported in total 12 times (33%; see table 4, item 14). The most frequent additional barrier to not following recommendation was a change in physician (5/36 = 15%).

Table 3. Performance of recommendation letter as implementation strategy

Type of recommendation	Number of participants receiving recommendation	Recommendation followed			
		Yes[a]	Partially	No	Unknown
Overall	58	16 (28%)	21 (36%)	18 (31%)	3 (5%)
Per domain					
Dopaminergic treatment	40	14 (35%)	6 (15%)	7 (18%)	13 (33%)
Non-dopaminergic treatment	32	8 (25%)	3 (9%)	8 (25%)	13 (41%)
Mental health treatment	43	13(30%)	2 (5%)	12 (28%)	16(37%)
Referral to allied health care					
Physiotherapy	33	4 (12%)	1 (3%)	14 (42%)	14 (42%)
Speech and language therapy	10	4 (40%)	0	4 (40%)	2 (20%)
Occupational therapy	9	2 (22%)	0	4 (40%)	3 (33%)
Parkinson nurse	2	0	0	1 (50%)	1 (50%)
Psychosocial support	5	0	0	2 (40%)	3 (60%)
Referral to other specialties	11	1 (9%)	1 (9%)	1(9%)	8 (73%)

[a]If multiple recommendations were given the participants was scored as 'Yes' in 'Overall' if one of the recommendations was followed completely.

Table 4. Barriers of implementations of recommendations as reported by letter recipients

Number of letter recipients consulted	36
Inability to reconcile patient preference with management advice	10 (28%)
Lack of time	8 (22%)
Lack of outcome expectancy	7 (19%)
Lack of agreement with the management advice	4 (11%)
User unfriendly letter	3 (9%)
Presence of contradictory management advice	2 (6%)
Lack of self-efficacy	2 (6%)
Inertia in changing previous practice routine	1 (3%)
Lack of knowledge on the content of the management advice	1 (3%)
Lack of actuality of management advice	1 (3%)
Lack of confidence in movement disorder specialist	0
Lack of (financial) reimbursement	0
Perceived increase in malpractice liability	0
Other:	
- Recommendations were deemed inappropriate for this age and comorbidity	5 (14%)
- Lack of knowledge and experience in nursing staff who are needed for implementation	1 (3%)
- Indication not severe enough to warrant intervention	1 (3%)
- misunderstood intend of letter; thought it was only informative	1 (3%)
- Treating physician had no trusting relation with patient	1 (3%)
- Change in physician during treatment period	1 (3%)
- Recommendations send to a physician who is not the primary treating physician	1 (3%)
- Recommendation described were “too idealized”	1 (3%)

Proportions of the barriers per recipients are shown following a structured interview using the Cabana model and one open-ended question allowing other barriers to be mentioned. Multiple barriers could be report per recipient.

5.5 Discussion

Despite not reaching the required sample size, this pragmatic trial is the largest study to date in the underserved and poorly studied population of LSP. A letter to the primary physician with recommendations to optimize treatment by a specialist, based on standardized assessments by a trained assessor, did not improve the primary outcome measure of UPDRS ADL score compared to care as usual, but there was a significant improvement in quality of life scores in both the intention-to-treat and per-protocol-analysis, with an effect size exceeding the minimally important benefit [35]. In addition, there was a trend towards better outcome on the UPDRS part III as well as UPDRS total scores in the intention-to-treat population, and a

significant improvement on the UPDRS total and part I scores in the per-protocol analysis, together with a greater increase in LEDD, suggesting that adjustment of dopaminergic medication partially mediated the observed effects. This notion is also in line with earlier work showing dopaminergic undertreatment in LSP patients[3, 4], and also with other studies showing that levodopa improved motor and non-motor features in LSP patients[36-38]. The significant difference between intervention and control group in the PDQ-8 suggests that the intervention had a positive impact on the patients' overall quality of life that was not captured by the UPDRS-ADL part. Several other studies on complex multidisciplinary interventions in PD failed to show an impact on ADL-measures, indicating that these outcomes may not be sensitive enough to capture relevant change in these situations[39-42]. A quality of life measure may be a more appropriate tool, particularly in the advanced, complex stage of PD, where treatment is increasingly aiming to optimize quality of life instead of pursuing improvement of objective functioning. Social elements of the disease, like feeling embarrassed by symptoms or having trouble in personal relations, are represented in our quality of life measurement but not in the other outcome measures, which could explain the lack of finding on other outcome measures in the intention-to-treat analysis. Furthermore, patient-reported outcome measures, such as quality of life measures, are increasingly used as primary outcome measures in large trials [43, 44]. Finding a change on a patient-reported measure, like quality of life measures, but not on clinician-completed outcome measures has been reported by other trials [45, 46], indicating that patients may report improvements that are not appreciated in assessment by others, including using standardized assessment tools.

It is also noteworthy that our process evaluation revealed that whilst physicians followed recommendations to at least some degree in most patients (64% either completely or partially), many other recommendations were not followed and several barriers to implementing the recommendations were identified. These findings indicate suboptimal implementation of the advice of movement disorder experts communicated in a letter, as typically done in standard outpatient settings, and that other medical consultation models may be more appropriate for this population. This is in line with previous studies, with more elaborate interventions, that reported low adherence in interventions aiming at improving quality of disease management in elderly populations [47-51]. Perhaps the most important result of this trial is that we identified several barriers for the implementation of the advice. The most common reasons were difficulty in reconciling the advice with the patient's preference, a lack of time, a lack of outcome expectancy and change in primary physicians. This may in

part be related to the constraints of the trial, with standardized recommendations, assessments rather than ongoing care, and assessment of complex patients with a trained study assessor rather than the movement disorder specialist who made the recommendations following discussion. It has previously been shown that understanding the medicine-taking behavior of patients should be the first step in optimizing therapy, which requires knowledge and consideration of a patient's personal beliefs about their medicines [52]. However, it may also suggest that recommendations by the specialist require greater interaction with the primary care physician to adjust to the circumstances of their care, availability and access to treatments such occupational therapy, a PD specialist nurse, and wishes of patients with LSP, or that the healthcare system is ill-equipped to implement the intervention. Further work is needed to explore this, and future research should take note of these barriers in developing more elaborate interventions which are better suited to the local health care system.

The pragmatic design of this trial had limitations which may have affected our findings. Primarily due to lack of ethics approval in two participating countries and many patients already receiving specialist care, we did not reach the targeted study sample size. We extended the study recruitment window and developed several new strategies to boost recruitment, but this population remains difficult to include in clinical trials. As a consequence, we cannot draw any firm conclusions on the impact of our intervention on the primary outcome measure. In addition, we conducted the study in several countries across Europe with different health care provisions and these differences could have concealed a greater effect. Furthermore, we included patients with all types of parkinsonism, not all of whom would respond to antiparkinsonian medication changes. However, only three individuals who completed the trial did not have a diagnosis of PD and the main results were comparable when we only analyzed typical patients. The movement disorder specialist had limited contact with participants, as assessments were done by trained staff, recommendations were standardized, availability and ease of access, and the beliefs on their treatment were not assessed behavior. As discuss above, these are is likely to have affected to the implementation of the recommendations [52]. In addition, movement disorder experts had limited contact with most of participants' healthcare providers, and greater interaction may have improved adherence to the recommendations. Nevertheless, our methodology mirrored typical daily practice in current healthcare systems, where infrequent specialist appointments with recommendation letters for other involved healthcare providers, are typical forms of intervention, and continuity of care by a specialist, good interaction with primary physicians, and sufficient time

in primary care are often not available. Our results suggest that in order to achieve the best results with significant improvement of outcomes for activities of daily living and quality of life, specialist recommendations need to be accompanied by strategies to increase implementation. Close interaction with primary physicians, sufficient time for discussion with patients and their carers on preferences, wishes and beliefs and the benefits of the recommended treatments, and long-term follow-up with continuity of care may be helpful to achieve this. LSP poses particular challenges to provision and participation in care, including cognitive deficits, low mood, apathy or fatigue which can limit participation in some non-pharmacological interventions [53], and there are limitations in ability to attend appointments and high caregiver burden [12, 54, 55]. Novel approaches to providing specialist input for this population, including community-based support, palliative care models with neurological input, online support and other modalities may be required to maximize the benefit from specialist recommendations to improve quality of life and disability [56].

5.6 Conclusion

Whilst there was no improvement of ADL on the UPDRS-ADL part in this study, which was limited by underrecruitment and limited implementation of recommendations, we found that specialist recommendations communicated by letter had a positive impact on quality of life in patients with LSP. Our results also demonstrate the limitations in implementation of treatment recommendations communicated by letter to the primary treating physicians in this complex and vulnerable patient group.

5.6 Supplementary material

Appendix A. Intention-to-treat analysis CLaSP-trial

	Baseline		Follow-up		Difference between groups at follow-up	
	N	Median (IQR)	N	Median (IQR)	Mean (95% CI)	p-value
Primary outcome measure						
Unified Parkinson Disease Rating Scale – Part II						
Intervention	68	26 (22-31)	56	28 (22-31)	-1.2 (-4.2 to 1.8)	0.45
Care as usual	21	29 (26-33)	18	32 (28-33)	ref.	
Secondary outcome measures						
Unified Parkinson Disease Rating Scale – Part I						
Intervention	69	6 (4-8)	56	6 (3-9)	-0.9 (-2.1 to 0.4)	0.17
Care as usual	21	5 (3-8)	18	8 (4-10)	ref.	
Unified Parkinson Disease Rating Scale – Part III						
Intervention	67	45 (33-56)	56	44 (32-60)	-5.1 (-10.7 to 0.6)	0.08
Care as usual	21	47 (40-53)	18	45 (40-60)	ref.	
Unified Parkinson Disease Rating Scale – Part IV						
Intervention	69	4 (2-6)	56	4 (2-6)	-0.1 (-1.4 to 1.3)	0.93
Care as usual	21	5 (3-8)	18	4 (3-6)	ref.	
Unified Parkinson Disease Rating Scale – Total						
Intervention	69	79 (66-96)	56	82 (65-100)	-7.8 (-16.4 to 0.8)	0.07
Care as usual	21	88 (70-98)	18	89 (83-111)	ref.	
Geriatric Depression Scale – 15 items						
Intervention	47	7 (3-10)	43	7 (3-9)	+0.9 (-1.2 to 3.0)	0.39
Care as usual	14	7 (5-10)	12	8 (6-11)	ref.	
Non Motor Symptom scale						
Intervention	67	102 (62-130)	55	106 (77-143)	+0.1 (-21.0 to 21.2)	0.99
Care as usual	19	116 (82-147)	18	119 (99-145)	ref.	
Mini-Mental State Examination *(increase equals better score)*						
Intervention	67	21 (15-25)	52	20 (15-24)	+0.7 (-1.4 to 2.8)	0.51
Care as usual	19	20 (13-26)	16	18 (14-24)	ref.	
Parkinson Disease Questionnaire – 8 items						
Intervention	36	16 (12-19)	32	14 (11-19)	-3.8 (-6.7 to -0.9)	**0.01**
Care as usual	12	14 (12-18)	8	20 (14-23)	ref.	

table continues

	Baseline		Follow-up		Difference between groups at follow-up	
	N	**Median (IQR)**	**N**	**Median (IQR)**	**Mean (95% CI)**	**p-value**
EQ-5D-5L – index score *(increase equals better score)*						
Intervention	54	0.2 (0.1-0.6)	45	0.3 (0.0-0.5)	+0.1 (-0.1 to 0.3)	0.29
Care as usual	18	0.3 (0.2-0.6)	14	0.1 (-0.1-0.4)	ref.	
EQ-5D-5L VAS score *(increase equals better score)*						
Intervention	54	50 (39-60)	43	50 (34-70)	+ 4.8 (-9.4 to 19.0)	0.50
Care as usual	16	50 (25-58)	12	55 (30-60)	ref.	
Levodopa equivalent daily doses						
Intervention	62	700 (525-866)	56	755 (606-999)	+108 (-26 to 242)	0.11
Care as usual	21	798 (525 -1129)	18	887 (400-1171)	ref.	

Group differences were estimated using linear regression models adjusting for baseline measurements and covariates: age, gender, disease duration, residence in nursing home and presence of dementia. For all score increase equals worse score, except if otherwise stated. IQR = Interquartile range; SD = Standard deviation, CI = Confidence Interval

Appendix B. Per protocol analysis CLaSP-trial

	Baseline		Follow-up		Difference between groups at follow-up	
	N	**Median (IQR)**	**N**	**Median (IQR)**	**Mean (95% CI)**	**p-value**
Primary outcome measure						
Unified Parkinson Disease Rating Scale – Part II						
Intervention	37	28 (22-32)	36	28 (23-33)	-1.1 (-3.6 to 1.3)	0.37
Care as usual	36	26 (22-31)	36	30 (24-32)	ref.	
Secondary outcome measures						
Unified Parkinson Disease Rating Scale – Part I						
Intervention	37	5 (4-8)	37	5 (3-9)	-1.1 (-2.2 to -0.4)	**0.04**
Care as usual	36	5 (3-7)	35	8 (4-9)	ref.	
Unified Parkinson Disease Rating Scale – Part III						
Intervention	37	43 (33-54)	37	45 (32-60)	-4.2 (-9.2 to 0.8)	0.10
Care as usual	35	42 (31-51)	35	45 (37-57)	ref.	
Unified Parkinson Disease Rating Scale – Part IV						
Intervention	37	4 (2-7)	37	4 (2-6)	-0.6 (-1.7 to 0.6)	0.32
Care as usual	36	5 (2-7)	35	4 (2-6)	ref.	

table continues

	Baseline		Follow-up		Difference between groups at follow-up	
	N	Median (IQR)	N	Median (IQR)	Mean (95% CI)	p-value
Unified Parkinson Disease Rating Scale – Total						
Intervention	37	82 (66-102)	37	79 (66-96)	-7.4 (-14.6 to -0.2)	**0.04**
Care as usual	36	78 (65-96)	36	87 (72-101)	ref.	
Geriatric Depression Scale – 15 items						
Intervention	24	7 (2-8)	29	6 (4-9)	-0.3 (-2.0 to 1.5)	0.75
Care as usual	29	7 (5-11)	25	8 (6-10)	ref.	
Non Motor Symptom scale						
Intervention	36	106 (62-132)	37	106 (82-145)	+0 (-17.9 to 17.9)	1.00
Care as usual	35	94 (61-128)	34	114 (89-145)	ref.	
Mini-Mental State Examination *(increase equals better score)*						
Intervention	36	21 (16-26)	35	18 (15-26)	+0.7 (-1.2 to 2.5)	0.48
Care as usual	35	21 (16-25)	32	19 (15-23)	ref.	
Parkinson Disease Questionnaire – 8 items						
Intervention	19	15 (12-19)	20	15 (11-19)	-2.7 (-5.1 to -0.3)	**0.03**
Care as usual	24	15 (12-18)	19	17 (13-20)	ref.	
EQ-5D-5L – index score *(increase equals better score)*						
Intervention	30	0.3 (0.1-0.6)	30	0.3 (0.1-0.6)	+0.1 (-0.1 to 0.3)	0.25
Care as usual	31	0.3 (0.2-0.6)	28	0.2 (-0.1-0.4)	ref.	
EQ-5D-5L VAS score *(increase equals better score)*						
Intervention	30	50 (40-61)	29	50 (38-68)	+ 5.9 (-6.2 to 18.0)	0.33
Care as usual	30	50 (30-53)	25	50 (28-65)	ref.	
Levodopa equivalent daily doses						
Intervention	37	798 (600-947)	37	929 (750-1060)	+165 (51 to 279)	**0.01**
Care as usual	36	653 (490-888)	36	658 (400-934)	ref.	

Group differences were estimated using linear regression models adjusting for baseline measurements and covariates: age, gender, disease duration, residence in nursing home and presence of dementia. For all score increase equals worse score, except if otherwise stated. IQR = Interquartile range; SD = Standard deviation, CI = Confidence Interval

Appendix C. Consensus based study treatment guideline.

Problem	Advice directed at..	Further description of problem
Sleep problems		
• nocturnal motor problems and early morning akinesia	Physician	
	Nursing care	The patient has motor fluctuations decreasing the patient ability in self-care, mobility, cognition, speech, mood etc. These fluctuations (on-off periods) can differ from day-to-day and hour-to-hour basis. They can be predictable or unpredictable.
• Restless legs syndrome	Physician	
• REM-sleep behavioral disorder	Physician	
• Nocturia	Physician	
• Insomnia	Physician	
	Nursing care	Patients can have a variety of motor and non-motor problems that can interfere with sleep (e.g. nocturnal dystonia, urinary problems). Nocturia, rem-sleep behavioral disorder and restless legs syndrome are frequent.
Troublesome dystonia		
• Off-time related	Physician	
• Continuous	Physician	
	Nursing care	Dystonia can decrease ability in self-care, mobility.
Troublesome dyskinesia	Physician	
	Nursing care	Dyskinesia can occur as a complication of antiparkinsonian medication. Its occurrence is almost inevitable in late stage Parkinson disease and frequently tolerated well by patients if mild but can be very disabling.

Management suggestion
• Consider adjustment of dopaminergic therapy (e.g. long-acting levodopa, dopamine agonist, rescue levodopa during night-time). • Offer additional help during off-periods: e.g. assist turning in bed, assist ADL-activities. (during off-period more guidance is needed than during ON-period). • Beware of the possibility of nocturia, a frequent symptom in late-stage disease. • Beware of risk of falling during night-time, assist patient when mobilizing. • Use cueing techniques, mainly while assisting patients out of bed and walking (e.g. counting, breaking down a sequence). • Consider appliances (e.g. Lifting pole, light-weight bed sheets)
• Consider dopamine agonist or other RLS treatment
• Consider clonazepam or melatonin • Consider bed rails or other protective measures to safeguard bedroom environment.
• Consider desmopressin
• Review medication • Consider advice on sleep hygiene measure's • Consider hypnotics • Consider referral to sleep center Advice and assist on sleep hygiene measures: • Go to bed and get up at same time each day. • Exercise regularly • Spend some daytime outdoor in natural light • Make bedroom as restful as possible (temperature cool, minimum noise, no/little distractions) • Don't watch TV in bed • Avoid drinking fluids at night • Understand your sleep need (e.g. elderly people sleep shorter and have more frequent day-nap time)
• Adjustment of dopaminergic medication • Consider referring to hospital for botulinum toxin therapy • Consider anticholinergic treatment • Offer additional help during activities involving impaired head/neck/extremity etc. • Once recognized report to clinician • Consider adjustment of pharmacological regime (e.g. fractionating levodopa, adjust levodopa or dopamine agonist, discontinue or reduce dose MAO or COMT inhibitors, start/adjust amantadine slow and low, consider clozapine, consider advanced therapies) • Discuss individual impact of dyskinesia with patient and family • Consider documenting presence of dyskinesia in diary

table continues

Problem	Advice directed at..	Further description of problem
Troublesome motor parkinsonism	Physician	
	Nursing care	The patient has motor fluctuations decreasing the patient ability in self-care, mobility, cognition, speech, mood etc. These fluctuations (on-off periods) can differ on day-to-day and hour-to-hour basis. They can be predictable or unpredictable. Most frequent they are seen prior to and directly after medication intake.
Medication intake	Physician	Treatment with medications potentially associated with exacerbation of PD-related problems are: (a) typical antipsychotics other than quetiapine or clozapine, anticholinergics, benzodiazepines, avoid pills with protein rich meals, antihypertensives in hypotensive patients, valproate, metoclopramide, other medications with side effect exacerbating PD motor or non-motor symptoms.
	Nursing care	Daily functioning of the patient can be highly dependent on adequate and timely intake of levodopa/other antiparkinsonian medications.
Speech problems	Physician	
	Speech and language therapist	The patient has clear hypokinetic dysarthria which can be improved to a certain extent (or which is combined with another form of dysarthria).
		The patient has very severe hypokinetic dysarthria in which little to no improvement is possible.
		The patient suffers primarily from reduced word-finding and communicative problems.
		The patient has severe apathy, meaning that he can speak intelligibly but hardly speaks anymore and prefers to remain silent.
	Nursing care	Speech problems are frequent in PD. Patients can talk with a harsh, breathy, softer, monotonous voice with variable rate and short rushes of speech and imprecise consonants.

Management suggestion
• Adjustment of dopaminergic medication (e.g. Increase levodopa dose/number of doses, start/increase dopamine agonist, start/increase COMT inhibitor, start/increase MAO-inhibitor, consider advanced therapies) • Referral to OT/PT for cueing-strategies or environmental adjustments • Offer additional help during off-periods. • Use cueing techniques (e.g. counting, breaking down in sequence). • Consider document presence of motor parkinsonism in a diary • Monitor and beware of risk of falling
• Adjust medication to expert advice. • Schedule medication not to overlap with protein-rich/heavy meal
• Distribute levodopa precisely on set times and make sure no protein-rich/heavy meal is consumed within 30 minutes prior or 60 min afterwards. • Monitor medication side-effects: dyskinesia, hallucinations/psychosis, day-time sleepiness. • If no fluctuations occur and patient suffers for the larger part of the day from off-phenomena (e.g. slowness, rigidity, tremor): consider the possibility of undertreatment. Discuss observation with primary care physician, elderly care specialist, geriatrician or neurologist. • Inform patient and family about the effect of levodopa and heavy meals and support them to have an active role in medication management.
• Consider referral trained speech and language therapist • Attempt intensive treatment, but also supervise and instruct conversational partners.
Focus on supervising and instructing conversational partners or – when the patient has sufficient indicating ability and cognitive skills – on teaching the use of a communication aid. Suggest and discuss compensations, together with the caregiver(s). Explain and help with acceptance.
• Adjust tempo of talking to patient's pace. • Consider consulting SLT and enforce patient's exercises. • Several don't-s: do not talk for them, do not interrupt them, do not insist to pronounce each word perfectly, do not get irritated when patients cannot communicate, do not ignore or isolate them. • If indicated by SLT use communication aids: voice amplifiers, pacing boards, pen and paper, word chart, portable keyboard with speech output

table continues

Problem	Advice directed at..	Further description of problem
Hypersalivation	Physician	
	Speech and language therapist	The patient only has a feeling of having accumulation of saliva. The patient has a history of drooling or the drooling is visible.
	Nursing care	
Dysphagia	Physician	
	Speech and language therapist	The patient has a minor dysphagia, effected by double tasking or inadequate head position.
	Speech and language therapist	Moderate to severe dysphagia, including slow eating and/or aspiration risk.
	Dietician	Problems with dietary intake as well as weight loss can result from chewing and swallowing.
	Nursing care	Signs of dysphagia can be: excessive drooling, weight loss, fear of swallowing, a 'gurgly' voice, coughing before, during or after meal and pneumonia.
Cognitive problems	Physician	The patient has problems with memory function, attention, visuospatial ability and a decreased ability to plan. This can be up to the point of dementia.
	Nursing care	

Management suggestion
• Consider referral trained speech and language therapist • Consider non-pharmacologic intervention: chewing gum, tea. • Consider pharmacological treatment: atropine drops (e.g. 0.5-2%), glycopyrrolate, hyoscine patches, botulinum toxin injection, scopolamine s.c. Explain the importance of swallowing in time. Try out modifications and cues, such as a cue for closing the mouth, swallowing before standing up and so on. When results are insufficient, refer to the neurologist.
• Discuss impact of hypersalivation with patient. • Help patient to attain an upright posture or sit straight in chair. • Monitor mouth hygiene. • Monitor perioral skin problems
• Consider referral to trained speech and language therapist • Consider advanced directives and invasive therapy: Feeding tube? Gastrostomy? Teach compensation strategies (e.g. posture, meal volume) and cues to limit or prevent choking and difficulty with swallowing pills, etc. Modify food consistencies or provide more assistance or cues to maintain an acceptable speed and limit fatigue, if necessary, in consultation with a dietician and occupational therapist.
• Detect nutritional inadequacies due to in-depth dietary history: • Current weight, height, BMI, weight history to determine trend in weight over 3-12 months). • Detailed dietary intake over last days to establish eating patterns and habits. • Dental and oral health • swallowing and chewing difficulties • medications • level of disability, activity and resting patterns • Instigate measures to correct deficiencies or nutrition-related problems. • texture-modified food • supplements • Identify ways to minimize practical difficulties with swallowing and chewing.
• Modify food consistencies. • Use compensations strategies, e.g. upright posture, smaller portions (use dessertspoon, no bolus, no cup with spout). • Offer guidance, but avoid patient having to multitask (e.g. eating and talking). • Monitor weight
• Eliminate triggering factors: infection, metabolic disorder, rectify fluid/electrolyte balance, treat sleep disorder. • Discuss impact of symptoms with patients and family. • Consider to reduce polypharmacy: anticholinergics, benzodiazepines, tricyclic antidepressants, tolterodine • Consider referral to memory clinic • -If patient fulfils criteria consider rivastigmine.
• Patients can be slow in processing information. When given enough time they may be able to communicate better • Enable patient in using memory aids, e.g. calendar or agenda. • Enable patient in following a clear and consistent structure in the day. • In early stages of dementia patients can benefit from explicit information on time, location and persons surrounding them (reality orientation). • In later stage of dementia patients can benefit from an approach in which patients aren't confronted which their impairment and nurses can focus on the emotional content of the communication with patients (validation)

table continues

Problem	Advice directed at..	Further description of problem
Psychotic symptoms	Physician	The patient is confused and has a disturbed sense of reality with hallucinations and psychosis.
	Nursing care	
Depression	Physician	
	Psychologist/ psychiatrist	The patient has fluctuations in mood. Depression is common in patients with Parkinson disease.
	Nursing care	
Daytime sleepiness	Physician	
	Nursing care	Daytime sleepiness can be a consequence of somatic disease, a complication of medication or can be an arousal problem.
Pain	Physician	Pain can be: RLS, dystonia, sensory-type pain like paresthesia's, burning, coldness, numbness. Pain related to motor fluctuations. Musculoskeletal pain.
	Physiotherapy	The intervention, will address pain education, including explaining the influence of fear, and the importance of staying physical active. However, none of these have been evaluated in PD patients
	Nursing care	

Management suggestion
• Control triggering factor: infection, metabolic disorder, rectify fluid/electrolyte balance, treat sleep disorder. • Discuss impact of symptoms with patients and family. • Evaluate cognition: Psychotic symptoms are more frequent in patients with cognitive problems; patient may need to be reviewed for developing dementia. • Consider reducing polypharmacy: anticholinergics, anxiolytics/sedatives. • Consider phasing out and stop antiparkinsonian drugs: anti cholinergic, MAO inhibitors, amantadine, dopamine agonists, COMT inhibitors, lastly levodopa. Balance with costs of motor symptoms. • Consider adding atypical antipsychotics. Evidence only for clozapine. Alternative Quetiapine. • Consider adding rivastigmine (in patients with cognitive impairment).
• Actively inform and discuss the impact of hallucinations and delusions with patients and family. • Consider that the occurrence of hallucinations is more frequent at night. • Make sure patient residence is adequately lit. • Give family instructions on how to cope with hallucinations and delusions.
• Consider optimizing antiparkinsonian therapy • Consider dopamine agonist, antidepressant agent (e.g. desipramine, nortriptyline, venlafaxine) • Consider referral to psychiatrist.
• Consider dopamine agonist, antidepressant agent (first choice SSRI) or referral psychiatrist. • Cognitive Behavioral therapy
• Does mood fluctuate; i.e. is it nonmotor fluctuation? • Discuss impact of disease with patient and family.
• Optimize night-time sleep, see" sleep problems" • Evaluate drugs (consider reducing dopamine agonist, or other sedatives mediation).
• Observe circadian rhythm • Offer day-time activities • Explain and assist in sleep hygiene measures. • Consult general care physician, movement disorder specialist or occupational therapist.
• Treat according to cause with medication
• Exercising including range of motion exercises and postural adjustments for musculoskeletal and neuropathic pain; graded increase of activity; time-dependent exercising, instead of pain-dependent: agree upon steps on forehand • Pain relieve through TENS and manual therapy • Relaxation • Peripheral desensitization techniques • Motor imagery and mirror therapy • Cognitive strategies • A Visual Analogue Scale for pain may be used for evaluation
• Distraction • VAS-score

table continues

Problem	Advice directed at..	Further description of problem
Constipation	Physician	Autonomic dysfunction is common in Parkinson disease. Symptoms include urinary dysfunction, constipation, erectile dysfunction, orthostatic hypotension, weight loss, dysphagia, excessive sweating, excessive saliva.
	Dietician	Constipation is frequent in patients affecting over 50 %
	Nursing care	
Urinary symptoms	Physician	Autonomic dysfunction is common in Parkinson disease. Symptoms include urinary dysfunction, constipation, erectile dysfunction, orthostatic hypotension, weight loss, dysphagia, excessive sweating, excessive saliva.
	Nursing care	
Orthostatic hypotension	Physician	Autonomic dysfunction is common in Parkinson disease. Symptoms include urinary dysfunction, constipation, erectile dysfunction, orthostatic hypotension, weight loss, dysphagia, excessive sweating, excessive saliva.
	Physiotherapy	Orthostatic hypotension is frequent in patients.
	Nursing care	

Management suggestion
• Exclude other causes of constipation. • Advice on fiber intake, fluid intake and exercise. • Reduce anticholinergics • Consider macrogol, other laxatives
• Detailed history on fiber and fluid intake. • Advice on fiber intake. • Advice on exercise
• Advice and assist adequate fluid intake (at least 8 glasses a day). • Make sure patients has adequate fiber intake. • Offer help in accessing toilets • Offer help with exercise. • Help with good posture while sitting on the toilet. • Help patients with setting time to go to the toilet and not putting of the urge.
• Assess autonomic dysfunction. • Exclude urinary tract infection, polyuria due to diabetes. • Pre- and post-void bladder scan to exclude urinary retention. • Consider reducing intake of fluid after 6 pm. • Consider referral to (neuro)urologist of continence advisor • For urge complaints peripheral acting anticholinergic medication could be considered • For nocturia, desmopressin could be considered.
• Observe urinary symptoms • Advice and assist adequate fluid intake (concentrated urine can irritate the bladder). • Help access toilet • Continence material • If indicated by GP/urologist: • Bladder training (with support of specialist continence expert) • Intermittent catheterization.
• Consider documenting blood pressure (supine, 1-minute upright, 3 minutes upright) • Consider increasing salt and fluid intake • Consider fludrocortisone or midodrine • Consider phasing out and stop anti cholinergic, MAO inhibitors, amantadine, dopamine agonists • Consider stopping antihypertensives, tricyclic antidepressants, nitrates, alpha-blockers used to treat urinary disturbances. See advice “increased fall risk”.
• Measure orthostatic hypotension regularly. • Advice and assist patient in avoiding aggravating factors like alcohol, warm environment. • Assist in adequate fluid intake (8 glasses a day). • Assist in adequate salt intake (e.g. bouillon) • Assist patient in adequately performing hypotension inducing maneuvers. • Head-up tilt of the bed at night (or add extra pillows) • Wear elastic stockings • Highlight postprandial affects

table continues

Problem	Advice directed at..	Further description of problem
Mobility and contractures Patient is unable to mobilize independently/ safely (indoors and outdoors) / Risk of contractures or patient has inadequate positioning during activities or rest	Physician Physio-therapy/ nursing care/ occupational therapist	 External cueing and attentional strategies are used to replace internal control of automated and repetitive movements.
Falls	Physician Physio-therapist	Consider as causes of falling freezing, orthostatic hypotension, comorbidity (including sensory impairment), medication, instability, dystonia, dyskinesia.
	Nursing care	Nurses and nurse assistance can take practical measures to reduce risk of falling.

Management suggestion
• Optimize medication including possibility of advanced treatment • Consider referral physiotherapist
• Support exercise • External cues are defined as temporal or spatial external stimuli associated with the initiation and ongoing facilitation of motor activity (gait). They can be auditory, visual or tactile. • Not all PD-patients benefit from using cues. Yet, there is no insight into which patients benefit and which do not. However, if a patient benefits from cues, this will be visible after one single training session. • Attentional strategies are distinct from cueing as they need to be self-generated and provide an internal focus on the movement. Often, they are used in combination. • Both cueing and attentional strategies can be one-off, merely to initiate movement, or continuous, to prevent freezing of gait. • Prevent complications (e.g. passive movement of severely rigid extremity) • Consider appliances
• Optimize medication • Consider referral physiotherapist
• Improvement of strength and balance, • Reduction of fear (to fall or not being able to get up from the floor), • Practice posture changes • Information regarding (walking) aids • Due to the reduced/absence postural reflexes, learning how to fall is not recommended. However, fall prevention training (e.g. including pushes, pull and increasing confidence) may be effective. • Walking aids, such as a walking-stick and walker, can increase the independence and safety of patient. However, at the same time they can make walking more complex and more difficult, as by using these aids the performance of a dual task is required. Furthermore, inadequate use of, for example, a walker, can worsen the posture. Patient with freezing episodes benefit more from a walker with so-called compression brakes, which are activated when a patient leans on the walker and are advised against using a walking frame. • Ask routinely whether patients have been falling. • Take fall prevention measures depending on cause (identify causes in concert with physiotherapist, physician) • Offer guidance with mobility problems. • Coach patient to use walker. • Assist patients in using glasses and hearing aids.

table continues

Problem	**Advice directed at..**	**Further description of problem**
Inadequate home environment	Physician	Inadequate home environment can increase risk of complications (e.g. falling) and decrease independence
Daytime structure Patient is dissatisfied about day structure/ activity engagement	Occupational therapy	Assistance is required in performing (parts of) some activities: Treatment focus is on optimizing both activity performance and participation.
		Assistance is required in most activities: Treatment focus is on enabling adapted involvement in meaningful activities and prevention of complications due to immobility. Depending on Patient's capacity to change methods or routines, interventions may include all mentioned suggestions.
Caregiver burden Formal or informal caregiver has questions on how and when to assist the patient.	Physician Nursing care	

Management suggestion

- Consider referral for assessing and adjusting home environment according to local facilities

Interventions may include:
- Use of alternative and compensatory strategies to improve task performance: e.g. use of cues, reorganizing complex performance sequences, focused attention, cognitive strategies like problem solving and planning strategies, as well as time pressure management.
- Advice on optimizing daily routines (e.g. fatigue management) and simplifying activities
- Advice on appropriate assistive devices and modification in the home environment to enhance independence, efficiency and safety.
- Specific caregiver interventions:
- information provision (impact of disease on daily functioning of patient, possible care resources, aids and adaptations)
- training skills to support/supervise patient in daily activities, while considering own wellbeing (occupational balance).

Additional attention should be given to:
- Exploring opportunities for engagement in meaningful (leisure) activities
- Appropriate positioning (24 hr.)
- Information, support, advice on appropriate/alternative living arrangements
- Information, support and advice for caregivers (i.e. safety in manual handling, maintaining own wellbeing (occupational balance))

- Refer to local support for informal caregivers

- Have regular contact with informal caregiver and assess impact of disease.

Appendix D. Frequencies of treatment recommendations

	Number of expert recommendations given per guideline-defined recommendation			
Indication	**Type of recommendation**			
	Pharmacological		**Referral**	**General advice**
Overall	93		73	50
Motor symptoms	60		40	18
Motor parkinsonism	Adjustment of dopaminergic treatment		Referral to PT / OT	Tips for nursing care
	38		26	8
Dystonia	Adjustment of dopaminergic treatment		Referral to PT/OT	Tips for nursing care
	8		7	3
Troublesome dyskinesia	Fractioning dopaminergic treatment	Start / adjust amantadine	Referral to PT / OT	Tips for nursing care
	1	0	4	2
Off-time larger than 50 % of the waking day	Adjustment of dopaminergic treatment		Referral to PT / OT	Tips for nursing care
	9		3	4
Error in medication intake	Stop medication potentially associated with PD-exacerbation		-	Tips for nursing care
	4			1
Non-motor symptoms	9		26	24
Speech problems	-		Referral to SLT	Tips for nursing care
			10	8
Hypersalivation	Medication for hypersalivation		Referral to SLT	Tips for nursing care
	5		9	8
Dysphagia	-		Referral to SLT / dietitian	Tips for nursing care
			5	3
Pain	Start/ adjust pain medication		-	Tips for nursing care
	1			1
Constipation	Start/ adjust laxative		-	Tips for nursing care
	1			2
Orthostatic hypotension	Evaluate pharmacological treatment		Referral PT	Tips for nursing care
	2		2	2

table continues

	Number of expert recommendations given per guideline-defined recommendation			
Indication	**Type of recommendation**			
	Pharmacological		**Referral**	**General advice**
Mental health problems	24		7	8
Parkinson disease dementia	Start/ adjust cholinesterase inhibitor		Referral to psychologist/ psychiatrist	Tips for nursing care
	10		4	4
Psychosis	Phase out or stop medication	Start/adjust clozapine or quetiapine	Referral to psychologist/ psychiatrist	Tips for nursing care
	1	2	2	2
Depression	Adjust dopaminergic medication	Start antidepressant	Referral to psychologist/ psychiatrist	Tips for nursing care
	7	4	1	2

PT = Physiotherapy, OT = Occupational therapy, SLT = Speech and language therapy

Appendix E. sensitivity analysis of the outcomes for the per protocol analysis

		Beta, (95% confidence interval lower bound to higher bound), p-value
	Sample size	**Intervention**
Intention-to-treat		
UPDRS-II	89	-1.2 (-4.2 to 1.8) p=0.45
PDQ8	39	-3.9 (-7.1 to -0.7) p=0.02
Per protocol (Intervention: partially or completely followed. Comparison: controls and not followed		
UPDRS-II	73	-1.1 (-3.6 to 1.3) p=0.37
UPDRS-I	73	-1.1 (-2.2 to -0.4) p=0.04
UPDRS-tot	72	-7.4 (-14.6 to -0.2) p=0.04
PDQ-8	38	-2.7 (-5.1 to -0.3) p=0.03
LEDD	73	+165 (51 to 279) p=0.01
Sensitivity analysis		
Per protocol 2 (intervention: completely followed. Comparison: not followed and controls. Not included: partially)		
UPDRS-II	51	-0.1 (-3.5 to 3.3) p=0.96
UPDRS-I	51	-1.0 (-2.1 to 0.1) p=0.08
UPDRS-tot	52	-7.0 (-16.9 to 3.0) p=0.17
PDQ-8	29	-3.0 (-5.9 to -0.1) p=0.04
LEDD	52	+182 (80 to 285) p=0.001
Per protocol 3 (Intervention: partially or completely followed. Comparison: controls. Not included: not followed)		
UPDRS-II	55	-1.5 (-4.6 to 1.6 p=0.33
UPDRS-I	55	-1.1 (-2.5 to 0.3) p=0.13
UPDRS-tot	54	-9.7 (-18.7 to -0.9) p=0.03
PDQ-8	27	-4.0 (-7.1 to -0.9) p=0.01
LEDD	55	+159 (-0.8 to 319) p=0.05

table continues

		Beta, (95% confidence interval lower bound to higher bound), p-value
	Sample size	Intervention
Per protocol 4 (Intervention: completely and partially followed. Comparison: not followed. Not included: controls		
UPDRS-II	53	-0.7 (-3.7 to 2.4) p=0.65
UPDRS-I	54	-1.2 (-2.7 to 0.25) p=0.10
UPDRS-tot	53	-5.3 (-14.4 to 3.8) p=0.25
PDQ-8	30	-2.0 (-4.6 to 0.7) p=0.14
LEDD	55	+148 (-20 to 317) p=0.08
Per protocol 5 (Intervention: partially followed. Comparison: not followed and controls. Not included: completely		
UPDRS-II	51	-1.7 (-4.7 to 1.3) p=0.26
UPDRS-I	51	-1.1 (-2.5 to 0.2) p=0.10
UPDRS-tot	50	-5.9 (-14.2 to 2.4) p=0.16
PDQ-8	29	-1.7 (-5.3 to 1.8) p=0.31
LEDD	52	+154 (14.7 to 293) p=0.03
Per protocol 6 (Intervention: completely followed. Comparison: partially followed, not followed and controls		
UPDRS-II	72	+0.48 (-2.5 to 3.4) p=0.75
UPDRS-I	72	-0.4 (-1.7 to 0.9) p=0.55
UPDRS-tot	73	-4.7 (-13.3 to 4.0) p=0.28
PDQ-8	38	-2.3 (-4.9 to 0.4) p=0.09
LEDD	73	+114 (-26 to 253) p=0.11

UPDRS = Unified Parkinson's Disease Rating scale; PDQ = Parkinson Disease Questionnaire; LEDD = Levodopa Equivalent Daily Dose

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CHAPTER 6. General Discussion

6.1 Introduction

The studies presented in this thesis aimed to improve our understanding of impairments and disability in individuals living with late-stage parkinsonism (LSP). These individuals often manifest considerable impairments, such as motor problems, neuropsychiatric symptoms and autonomic dysfunction. Yet, this specific and highly vulnerable population remains largely understudied, certainly in relation to the earlier stages of Parkinson's disease (PD) or other forms of parkinsonism. Specifically, the prevalence, predictors and effective treatments remain largely unknown. Disability is a defining feature of LSP, but it is basically unclear which impairments contribute most to this disability. Moreover, the treatability of disability in LSP has thus far received little scientific attention. This final chapter summarizes and interprets the findings that are included in this thesis, and discusses the implications for clinical practice, health care organization, education and future research.

6.2 Short summary

In **Chapter 2** we present the characteristics of the persons participating in the Care of Late-Stage Parkinsonism study (CLaSP). This multinational cohort study included 692 persons who met the inclusion criteria of having a duration of Parkinson's disease (PD) of ≥7 years and having either Hoehn and Yahr stage ≥4 or a Schwab and England score of ≤50%. Many of them had multiple motor signs, including severe bradykinesia (77%), gait difficulties (67%), postural instability (56%), speech impairment (43%) and, to a lesser extent, swallowing problems (19%). More than 50% of participants experienced non-motor symptoms, such as concentration and memory problems, fatigue, constipation, or urinary symptoms such as nocturia. Participants almost always experienced a combination of motor and non-motor symptoms. Disability, as measured with the Schwab and England score, correlated most with motor symptoms and cognitive impairment, measured with the Mini-Mental State Examination.

In **Chapter 3** we present the prevalence and determinants of neuropsychiatric symptoms in the CLaSP-study cohort. Neuropsychiatric symptoms, such as depression, psychosis, anxiety and behavioral problems, were assessed through interviews with carers using the Neuropsychiatric Inventory. The results showed that 92% of the 625 included persons with LSP had at least one clinically relevant neuropsychiatric symptom, with an average of three symptoms. The multivariate analysis revealed unique sets of determinants for each symptom, particularly the

presence of other neuropsychiatric features, the inability to undertake personal hygiene tasks, cognitive impairment and daytime sleepiness.

In **Chapter 4** we present the prevalence of orthostatic hypotension, based on data collected in the '*Verpleeghuizen op weg naar integrale Parkinson-zorg*' study (Nursing homes for integrative PD care; VIP). Blood pressure measurements in the supine and in the upright position (after 1 and 3 minutes) were available for 64 nursing home residents, and symptoms were assessed with the cardiovascular-related items of the Non-Motor Symptoms Scale (e.g. fainting and light-headedness). Orthostatic hypotension was considered as 'probably symptomatic' if a resident's frequency score was >1 on the non-motor symptoms scale items, and 'probably asymptomatic' if the frequency score was 0. If orthostatic hypotension was not present, but the frequency score was >1, orthostatic hypotension was considered 'possibly symptomatic'. The prevalence of orthostatic hypotension was 52%, which was almost equally divided into probably symptomatic and probably asymptomatic cases. Another 21% had possibly symptomatic orthostatic hypotension. Importantly, for only two persons with symptomatic orthostatic hypotension an orthostatic hypotension diagnosis had been noted in their medical records and pharmacological treatment was rare: five residents receiving domperidone and one receiving fludrocortisone. None received midodrine.

In the study presented in **Chapter 5** we tested the effectiveness and feasibility of an intervention in persons with LSP, consisting of personalized treatment advice recommended by a movement disorder expert who was not directly involved in the care for the participants. Ninety-one participants were included in this pragmatic multi-center, randomized-controlled trial with six-months follow-up. Those in the intervention group received a letter with treatment recommendations from a movement disorder specialist through their treating physicians, based on a comprehensive clinical assessment by the researchers. Controls received care as usual. Treating physicians followed recommendations at least partially in 37 (64%) participants. The most frequent barriers to compliance with the recommendations were: 1. inability to reconcile patient's preferences with the recommendation (28%); 2. lack of time (22%); and 3. lack of outcome expectancy (19%). The intention-to-treat analysis showed no difference in the primary outcome (i.e., activities of daily living-score) between the two group, but the quality-of-life score in the intervention group had improved more than in the control group. The per-protocol analysis confirmed these findings, and showed less deterioration on the 'mentation, behavior and mood' score, greater improvement on the overall Parkinson symptoms score, and greater increase in dopaminergic medication use in the intervention group.

6.3 Interpretation

The presented studies (CLaSP and VIP) have helped to create a better understanding of the pathway through which impairments contribute to disability in LSP. The most prominent finding from these studies is that disability in LSP has the strongest association with PD-related motor features and cognitive impairments; specifically, both were observed in more than half of persons with LSP (**Chapter 2**). Previous studies, dating back to the work of Hoehn and Yahr, had already identified these features as important predictors of disability in early disease stages [1-5] and in moderate disease stages [5-7]. During the typical evolution of PD, disability starts with problems in motor-oriented tasks, such as performing household duties and walking-related chores, and progresses with problems in cognition-oriented tasks, such as using the telephone, handling finances, and taking medication [1, 8]. Pathologically, postural imbalance and gait difficulties, as well as cognitive impairment, are thought to result from widespread degeneration of non-dopaminergic extra-nigrostriatal systems [9-11]. Recent studies have suggested that these symptoms constitute a more malignant subtype of PD [12, 13], although the biological basis for this subtype is still in dispute [9, 14]. The observation that these features independently induce disability in LSP, is a novel finding from my thesis.

Our findings indicate that motor features and cognitive impairment are central elements in the model of disability in LSP. However, solely addressing motor and cognitive features is an oversimplification, as other features are frequently present as well. For example, we found that most persons with LSP have neuropsychiatric symptoms and orthostatic hypotension (**Chapter 3 and 4**). Previous studies have linked depression, psychosis and apathy to disability [4, 15-18], while psychosis predicts institutionalization [19]. In our analysis, we found some evidence for the interaction of neuropsychiatric symptoms with disability, as the inability to undertake personal hygiene tasks, which is an item of disability, was associated with depression (**Chapter 3**). However, no independent effect on disability was seen when corrected for, among other features, cognition and motor symptoms (**Chapter 2**).

Non-motor features can also indirectly impact disability, by complicating the treatment of motor symptoms. For example, dopaminergic medication can worsen orthostatic hypotension, thereby preventing adequate titration and optimal control of motor symptoms [20, 21]. Similar to orthostatic hypotension, other non-motor features such as nausea, psychosis, daytime sleepiness or impulse control disorders can cause problems in titrating dopaminergic medication to levels that

are needed to control the motor signs adequately [22]. This inability to titrate treatments satisfactorily due to non-motor symptoms is one of the elements that contribute to levodopa intolerance, which should not be confused with levodopa unresponsiveness [23]. 'Real' levodopa unresponsiveness is difficult to differentiate from the many forms of pseudo-unresponsiveness (see table 1 for an overview). For this reason, extensive evaluation and elaborate clinical considerations – often necessitating the involvement of experts – are needed to conclude whether persons with LSP still respond to levodopa, and at what cost (in terms of adverse effects). In case of levodopa intolerance, increasing the dopaminergic doses sometimes remains possible when the dose-limiting factors are addressed. For example, domperidone, fludrocortisone and midodrine can alleviate orthostatic hypotension [24-26], and thereby widen the therapeutic window for a possible increase in levodopa dose. However, as reported in **Chapter 4**, these therapeutic interventions are hardly deployed in nursing home practice.

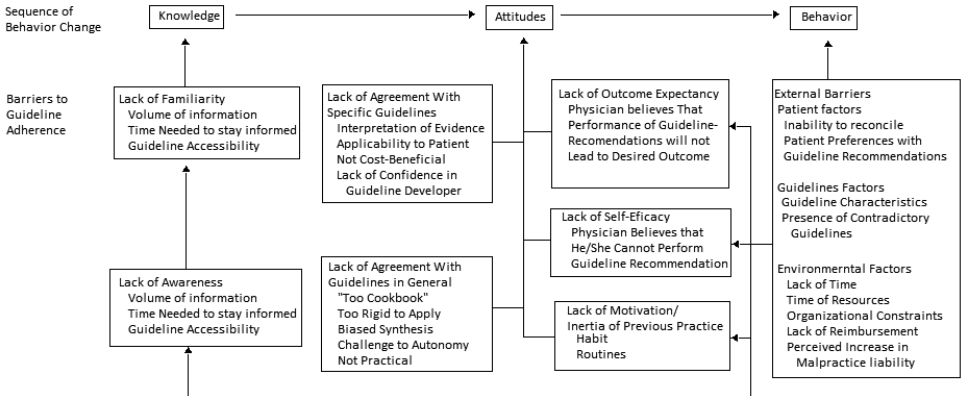
Table 1. Mechanisms underlying pseudo resistance to levodopa.

1.	Differences in pharmacodynamics and pharmacokinetics • between individuals because of: • cotreatment with dopamine receptor blocking agents • a protein containing diet-inducing competition at the transporter level • gastrointestinal dysfunctions inducing delayed absorption
2.	Dose-limiting side effects
3.	Underdosing because of levodopa phobia
4.	Presence of specific motor and nonmotor features of Parkinson's disease that require a relatively higher dosage of levodopa to improve adequately

*Adapted from Nonnekes J, et al. (2016) Mov Disord **31**, 1602-1609.*

For the reasons mentioned above, an elaborate approach that addresses the many symptoms is needed to address the complexity of disability in LSP. The most effective treatment approach for LSP remains unknown. In our pragmatic trial (**Chapter 5**), we formulated recommendations for therapeutic approaches to motor symptoms, mental health issues and other non-motor symptoms. Because of our mixed results and in light of several study limitations (that will be discussed later in this chapter), no undisputable conclusions could be drawn from the trial. However, the data did carefully suggest at least some beneficial effects of taking up expert recommendations for quality of life, mental health and overall Parkinson symptoms. Other, very recent studies indeed show that dopaminergic treatments partly retain their effectivity, even in LSP [27-31]. While the levodopa response is preserved, the treatment effectivity is lower than in earlier disease stages [27].

Perhaps the most important finding of this thesis is the desire to better implement optimal treatments. Increasing the professionals' knowledge about the pros and cons of the various treatments is helpful, but at the same time, this might not be enough in this respect. Treating physicians mentioned that the provided recommendations lacked alignment with patients' preferences, but also indicated that lack of time and lack of outcome expectancy were reasons for not optimizing the treatment accordingly. We are dealing with barriers of 'attitude' and 'behavior' here, which are contrasted with barriers of 'knowledge' (Cabana model; see figure 1) [32]. Therefore, knowledge-based interventions, such as a guideline or a recommendation, seems unsuitable to optimize treatment. Dealing with attitude and behavior barriers requires training of professionals or restructuring of the health care organization, such that specialists become more accessible and inclined to improve treatment. Also, ascertaining that healthcare professionals have adequate time to spend with their patients is also vitally important. I expect that an upfront investment of extra time spent on these very vulnerable persons with LSP will be offset by both a better quality of life, and presumably also fewer disease complications that can be avoided.



*Adapted from Cabana MD, et al. (1999). JAMA **282**, 1458-1465.*

Inspiration for interventions on attitude and behavior can be derived from completely different fields, as these barriers are not unique to LSP [32]. One such example is the struggle to let physicians comply with guidelines on smoking cessation [32, 33]. Counselling is a proven intervention to help people the difficult process of quitting smoking, recognized since the 1980s [34], but, surprisingly, relatively few smokers get counselled [35]. One explanation is that the success rate is still relatively low

and physicians can feel disheartened by the low outcome expectancy [36]. This is a situation comparable to LSP. Interestingly, some physicians are more likely to counsel than others, e.g. those with specialties that treat more smokers and more frequently see the damage that smoking can do (for example, cardiologists and pulmonologists) [34, 37]. By analogy, attitude and behavior will likely improve if physicians have more experience and see a larger variation of persons with LSP. Physicians who are more experienced in LSP – and who treat a higher volume of such patients – are likely more inclined to optimize LSP treatment. Other examples that support the reallocation of care to more specialized professionals in the Netherlands are ParkinsonNet and centers of expertise for Huntington's disease [38-40]. In the ParkinsonNet approach, professionals become specialized in treating people with PD by participating in regional community-based networks that encompass a limited number of dedicated allied health therapists who have been trained specifically according to evidence-based guidelines, and who manage a high caseload because patients are specifically referred to these trained professionals [39, 40]. ParkinsonNet is a largely community-based network, which is possible because of the high prevalence of this disease. But different approaches are needed for chronic conditions that are more rare. For example, for Huntington's disease, seven long-term care institutions collaborate in the delivery of specialized long-term and ambulatory care [38]. Additional efforts to also cluster institutionalized care for persons with LSP to specialized physicians are underway in the Netherlands, as elderly care institutions increasingly create specialized centers and movement disorder experts pay increasing attention to LSP.

6.4 Limitations

Both the VIP-study and the CLaSP-study were targeted to difficult-to-reach populations due to their vulnerability, and we experienced several challenges in study set-up, recruitment and analysis.

First, both studies may well have been prone to selection bias. The VIP study included a small, homogenous population of nursing home residents without dementia, and who had been diagnosed with typical PD. As persons with dementia were excluded, the prevalence of orthostatic hypotension, known to be associated with dementia, may have been underestimated [41]. In contrast, the CLaSP-study was set out to be large and inclusive, including persons with dementia and atypical parkinsonism. This approach raises questions on how subgroups, such as persons with atypical disease, may have influenced the results of this study. Persons with a form of atypical parkinsonism constituted a minority: eighty in the cohort study (12%); and three in

the trial (3%). The results of an additional sub-analysis of persons with a typical disease presentation was in line with the overall findings for all participants. In the CLaSP-study, the proportion of persons with dementia was lower than planned, and lower than that in other cohort studies [42-44], which could indicate a recruitment bias. However, the numbers were still large enough to allow for valid results for both persons with and without dementia. Lastly, as both cohort studies had a naturalistic design, the participants were already treated with a range of different medications. This likely impacted the prevalence of symptoms which, as a result, could have been underestimated. However, since the prevalence numbers were generally already high, underestimation does not change the interpretation and key messages of the work presented in this dissertation.

Second, LSP poses particular challenges to research evaluations, resembling the challenges in provision and participation in care. Participants had problems completing their assessments due to cognitive deficits, low mood, apathy, fatigue, wearing-off, and the absence of caregivers. To mitigate these challenges, we allowed for frequent breaks, and spread the assessments across multiple visits. Moreover, the assessment protocol necessitated several adaptations. For example, an Ewing test battery is the gold standard for the assessment of orthostatic hypotension. However, the Ewing test battery could not be used as participants could not visit the outpatient clinic. Instead, we diagnosed orthostatic hypotension using a validated and clinically widely used measurement technique, tailored to this particular group of people with LSP [45-47]. We believe that these steps contributed to the quality of the data.

Third, both the VIP-study and the pragmatic trial of the CLaSP-study had a relatively small sample size. Though small sample sizes can threaten the representativity of the sample for the total population, the main consequence is that the analyses were under-powered Nevertheless, the CLaSP study did generate valuable insights, such as the responsiveness of several outcome measures (e.g. quality of life) and, importantly, the identification of barriers for implementations. At the least, these insights may aid in the design of future interventions in larger studies with a longer follow-up.

6.5 Future outlook

Implications for clinical practice

To improve clinical practice for people living with LSP, clinicians should reconcile patients' preferences with expert's treatment recommendations, based on a comprehensive assessment of the physical, psychological and social domains. Regarding the trial described in **Chapter 5**, it is unclear why participants and experts did not align on treatment preferences, but I suspect that it is either a matter of participants being ill-informed about the treatment potential, or the expert having poorly assessed the correct treatment potential. To remedy this, inspiration should be drawn from the fields of neurology or elderly care medicine, as both have a tradition of working on person-centered care [48-51]. I will briefly discuss two examples of person-centered care that might be usable for LSP, if adapted to the unique context of LSP. These two examples are shared decision making and collaborative goal planning.

Shared decision making has already been studied within the context of advanced Parkinson's disease, when persons face the choice of invasive treatment – e.g., deep-brain stimulation, continuous infusion of levodopa/carbidopa intestinal gel or subcutaneous apomorphine [50]. Shared decision making consists of: 1. identifying the choice to be made; 2. sharing the information on treatments in an unbiased way; 3. eliciting the person's preference; and 4. reaching a shared decision [48]. In current shared decision making, person's information needs apparently are not completely met, and not all treatment options are fully discussed. In spite of these shortcomings, persons with PD reported this approach as very valuable [50]. In elderly care, collaborative goal-planning is suggested as a tool for person-centered care [51]. Goal planning combines goal-setting and advance care planning and relies on individualized discussions on a health care plan with realistic goals. The feasibility of this approach was demonstrated in a sample of community-dwelling elderly, in that 74% of the goals were attained. Both shared decisions making, and collaborative goal planning align the person's preferences with the expert's expectation and address barriers reported in this thesis, but they demand a person's sufficient cognitive performance. For persons with dementia, my assumption is that more complicated strategies are needed to establish a person-centered care plan. These strategies should focus on reconstructing the will of the person using the collaborative experiences of families and professionals. In long-term care settings, reliable observations of care staff seem like a necessity, and training of observation skills should be included in interventions improving Parkinson' dementia care.

Implications for health care organization

Specific structural changes in health care delivery are thought to facilitate better care for LSP. For the Dutch health care situation, better care can presumably be achieved by either actively involving a neurologist and PD nurse in the treatment of LSP, even when people with LSP are no longer routinely seen in the hospital any more, or by creating a health care infrastructure where care staff and elderly care physicians reach sufficient experience in the treatment of LSP. Recently, ParkinsonNet has started offering more services specifically for people with LSP, such as the training of elderly care physicians, nurse practitioners and physician assistants, and courses on palliative care. Regarding the nursing home setting, Dutch nursing homes have a long-standing tradition of grouping residents who need specialized care, e.g. for Huntington's disease, Korsakoff syndrome or young-onset dementia [52, 53]. In a qualitative study, families of patients reported concerns of increased travelling times if their relative is admitted to a specialized nursing home further away [54]. Presumably, admittance to a specialized nursing home is only advisable if the benefit from residing in a specialized center, outweighs the burden of residing at a greater distance from your relative. It is currently unclear how to accurately make this assessment, however, elderly care organizations have already started grouping people with LSP residing in nursing homes and report positive experiences [55]. As a result, a recent government report recommended grouping people with LSP as a means to increase quality of care [56].

Implications for education

Education of practitioners and carers might be paramount to facilitate better clinical care. First, carers and practitioners should be taught to recognize the complications of LSP. As the prevalence rates of dysarthria and cognitive impairments are high in LSP, people with LSP cannot always accurately communicate symptoms themselves. In addition, symptoms such as orthostatic hypotension and neuropsychiatric symptoms can easily be missed, even by people with LSP themselves. Screening instruments are available, but these have typically not been validated for LSP and may require experience or additional training for correct use. In addition, training programs to help physicians align expert advice with person's preferences is needed (**Chapter 5**). Early evidence suggests that education programs for nursing home staff benefit residents [57].

Palliative care is another field, which is highly relevant for LSP, where knowledge gaps exist. Palliative care takes a holistic treatment approach and treats somatic, psychological, social and existential suffering. It includes discussions on treatment

decisions such as when to start or withhold treatment [58-61]. As a treatment approach, palliative care relies on person-oriented goal setting, and is usually organized in a multidisciplinary team, including specialist in geriatrics and pain management. Dutch health care professionals, who were all member of ParkinsonNet, reported a need for increased knowledge on palliative care, for example on the timing and initiation of palliative care [62]. The importance of palliative care was recently demonstrated by an evaluation of a hospital-based program for palliative care in the USA, that improved quality of life of participants compared to a control group that received standard care [61, 63].

Implications for research

Creating a convincing body of evidence on treatment optimization in LSP likely contributes to a better outcome expectancy in physicians and could help align expert recommendations with persons' preferences. Therefore, interventions and tools for more person-centered care should be studied. The earlier mentioned shared decision making, goal planning and palliative care interventions are promising, but need to be adapted to the specific needs of people with LSP. To maximize the chance of improvement, trials on person-centered interventions should include Parkinson-specific orientated treatment strategies that can be inferred from our studies. Examples are the preferential treatment of motor and cognitive symptoms to improve disability and actively screening for 'masked' neuropsychiatric symptoms. Also, experts in treating levodopa intolerance or pseudo-levodopa resistance should be included in the multidisciplinary team. This likely requires additional training of professionals or ascertaining an easy way of communication to more remote experts who have that knowledge available.

Telemedicine, i.e. the delivery of care at a distance by using technology, could increase access to movement disorder expertise, also for residents with LSP admitted to a nursing home or other forms of institutionalized care. In the United States, as early as in 1993, video visits helped to set up satellite clinics in rural areas [64]. Currently, movement disorder experts across the world use e-mail, video-visits and video-based education as part of their work routines [65]. In addition to residents living at home, some evidence is available that telemedicine also helps to expand access to expert care for nursing home residents [64, 66].Though there is no compelling evidence yet on the benefits of telemedicine, the COVID-pandemic in 2020 prompted a rapid adoption of telemedicine solutions. The potential of telemedicine can be best summarized with 5 C's : expanded Care, increased Convenience, enhanced Comfort, greater Confidentiality and less Contagion [67]. There might

be a 6th C of multidisciplinary Collaboration, as one qualitative study demonstrated easier access to synchronous consultation of community nurses and palliative care experts [68]. However, limitations are also well-known, as telemedicine does not allow for in-person physical examinations. This is a particular problem for persons in whom a new diagnosis needs to be made. But even for persons with an established diagnosis, remote assessments still do not allow for reliable and safe evaluations of issues such as gait, posture instability or rigidity [69]. Also, telemedicine requires a sufficient technological infrastructure, such as broadband internet access in people's homes, and people with LSP or care takers need to be technologically 'literate'. Future research should study and further develop the role of telemedicine for people with LSP.

Among the many topics for future interventional research, creative therapy, such as dance therapy, art therapy or music therapy, is a promising area of development for persons with LSP [70-72]. In the past, non-pharmacological interventions harnessed important progress in the treatment of PD [73]. In our intervention, too, non-pharmacological therapies were an important element in treatment optimization, but participating in therapy can be demanding, especially for people with LSP. Creative therapies are intuitively easy to enjoy (or just plain fun) and therefore might be more suited. One of the key benefits of these therapies is that they can often be enjoyed with the spouse and therefore, in theory, could lower the carer burden. Currently, creative therapists are not yet part of the training programs of the Dutch ParkinsonNet approach, and as such currently still have limited opportunity to develop specific expertise. Future research should try and establish the role of creative therapies in LSP and aim to develop a supporting evidence base.

Lastly, research into care for LSP may need to explore innovative research designs such as mixed methods, action-research and big data analyses. Mixed methods studies allow for qualitative instruments to complement quantitative measurements. Recently, this design has been used to evaluate a Parkinson-specific palliative care intervention [74]. A principal gain of this approach is that the interpretation of quantitative findings is well embedded within a methodologically drafted in-depth framework. Action research relies on the principles of democratic decision making and collaborative learning [75]. Mostly this is done by involvement of stakeholders who play a key role in interpreting findings and developing next steps. A prerequisite of this type of research is that the study protocol has a stepwise design where plans are consecutively drawn. Another recent development is big data research, which studies the efficacy of an intervention based on real-world data. Recently, big data

research showed the effectiveness of ParkinsonNet-physiotherapy based on an analysis of a large nationwide medical claims database [39, 76]. In addition to medical claims databases, data from smart devices are progressively easier to access [77]. People with LSP have, in their environment, multiple carers who maintain registries and, increasingly frequent, smart appliances, like kinetographs, fall detection sensors, medication-delivery systems and smart walkers. Some research questions can be answered using existing registries, claims databases or data from these smart applications. These types of analysis should be explored to improve care of LSP.

6.6 Conclusion

The findings from the studies reported in this thesis lead to a better understanding of disability in LSP. Disability associates strongest with motor symptoms and cognitive impairment, but also 'hidden' non-motor features are prevalent. A simple, multifaceted intervention did not improve daily functioning, but lessons have been learned for the development of future interventions addressing the high care need of people with LSP. Most notable, future intervention should address the barriers of attitude and behavior of treating physicians.

6.7 References

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CHAPTER 7. English Summary

Neurological diseases are the leading cause of disability in the world, and Parkinson's disease (PD) is the fastest growing neurological disease. Parkinson's disease (PD) is the most common form of parkinsonism. However, about 15 percent of people with parkinsonism have one of several conditions that have been jointly termed atypical parkinsonism disorders. These include vascular parkinsonism, multiple system atrophy, progressive supranuclear palsy, cortical basal degeneration and Lewy-body dementia. Understanding disability in parkinsonism is paramount to anticipating the health care needs of future populations and setting the research goals.

Conceptually, disease-specific symptoms can be seen as impairments that cause disability. Regarding the various forms of parkinsonism, these include motor problems, cognitive impairment, neuropsychiatric symptoms and autonomic dysfunctions. Most of these impairments are common in late-stage parkinsonism (LSP). However, with a few good exceptions, relatively few research projects have specifically focused on people with LSP, as many earlier studies typically excluded persons with LSP or failed to recruit or retain them. The data that are available suggests that treatment of people with LSP is suboptimal and can be improved.

The goal of this thesis was to add to the existing knowledge on impairments and disability in people with LSP through the results of two cohort studies (one international and one Dutch) and a pragmatic trial. The study results give insight into the complexity and treatability of disability in LSP.

In **Chapter 2**, I present the results of the Care of late-stage Parkinsonism-study (CLaSP-study). This is a multinational cohort of 692 people with confirmed LSP, defined as having parkinsonism ≥7 years or longer and being dependent upon others in functional mobility (Hoehn and Yahr stage ≥4) or in daily tasks (Schwab and England score ≤ 50). We first studied the prevalence of motor and non-motor complications. Most participants experienced multiple motor problems, most commonly severe bradykinesia (77%), gait difficulties (67%), postural instability (56%), speech impairment (43%) and, to a lesser extent, swallowing problems (19%). Many non-motor symptoms were encountered. More than 50% of people had concentration and memory problems, fatigue, constipation, urinary symptoms like nocturia. People with LSP almost always experienced a combination of motor and non-motor symptoms. Disability, measured with the Schwab and England score, correlated most with motor symptoms and cognitive impairment, measured with the mini-mental state examination.

In **Chapter 3**, I present additional data of the CLaSP-cohort study on the prevalence and determinants of neuropsychiatric symptoms such as depression, psychosis, anxiety and behavioral problems. Six-hundred-and-twenty-five carers of people with LSP were interviewed on neuropsychiatric symptoms using the Neuropsychiatric Inventory. The results showed that 92% of people with LSP had at least one neuropsychiatric symptom, with an average of three symptoms. Clinically relevant symptoms were present in three-quarters of people with LSP. The most frequent neuropsychiatric symptoms were apathy (39%), depression (35%) and anxiety (24%). The multivariate analysis revealed unique sets of determinants for each clinically relevant symptom, particularly the presence of other neuropsychiatric features. Inability to undertake personal hygiene tasks, cognitive impairment and daytime sleepiness were associated with the presence of clinically relevant neuropsychiatric symptoms.

In **Chapter 4**, I report the prevalence of orthostatic hypotension in a sample of Dutch nursing home residents of which the majority had LSP (88%). Data were collected in the '*Verpleeghuizen op weg naar integrale Parkinson-zorg*'-study (Nursing homes on a path to integrative PD care; VIP). Blood pressure measurement in supine and in upright position (after 1 and 3 minutes) were available for 64 nursing home residents. In addition to measurements, we collected data on symptoms of orthostatic hypotension, that were assessed using the cardiovascular-related items of the Non-Motor Symptoms Scale (NMSS; e.g. fainting and light-headedness). An orthostatic blood pressure drop was defined as a difference of ≥ 20 mmHg systolic and ≥ 10 mmHg diastolic between supine and upright measurements. The prevalence of orthostatic hypotension was 52%, almost equally divided into probably symptomatic and probably asymptomatic cases. Another 21% had possibly symptomatic orthostatic hypotension, meaning they had symptoms but no blood pressure drop. Importantly, only two persons with symptomatic orthostatic hypotension had an orthostatic hypotension diagnosis noted in their medical records. Pharmacological treatment was rare: five persons receiving domperidone and one receiving fludrocortisone. None received midodrine.

In **Chapter 5**, I report the effectiveness and feasibility of an intervention consisting of treatment advice from a movement disorder expert. Ninety-one persons with LSP were included in this pragmatic multi-center randomized-controlled trial with six-months follow-up. The primary clinician (i.e., elderly care physician, general practitioner or neurologist) of the persons with LSP allocated to the intervention group received a letter with treatment recommendations from a movement disorder

specialist, based on a comprehensive clinical assessment by the researchers. The primary outcome was an 'activities of daily living'-score (Unified Parkinson Disease Rating Scale – part II). Secondary outcomes related to quality of life, motor symptoms, mentation, behavior and mood, non-motor symptoms and dopaminergic treatments. Participants allocated to the control group received care as usual. Treating physicians followed recommendations at least partially in 37 (64%) people. The most frequent barriers were: 1. inability to reconcile patient's preferences with the recommendations (28%); 2. lack of time (22%); and 3. lack of outcome expectancy (19%). The intention-to-treat analysis showed no difference in the primary outcome between the two groups, but there was greater improvement for the quality-of-life score in the intervention group. The per-protocol analysis confirmed these findings, and showed less deterioration on the 'mentation, behavior and mood'-score, greater improvement on total Parkinson symptoms, and greater increase in dopaminergic medication use in the intervention group.

In **Chapter 6**, I interpret the study findings and discuss the implications for clinical practice, health care organization, education and future research.

In early and moderate disease stages, motor symptoms and cognition are the most important impairments that cause disability. Our findings extend this insight to persons with LSP. However, LSP comes with an additional layer of complexity as non-motor symptoms, such as neuropsychiatric symptoms and orthostatic hypotension, are very common, but any more so than in earlier phases of parkinsonism. These non-motor symptoms contribute to intolerance for levodopa and therefore to more motor impairment. Although movement disorder experts seem well equipped to address this complexity, the study trial results on expert recommendations were mixed. At 6 months follow-up, the primary outcome, i.e. activity of daily living, did not improve, but quality of life, i.e., a secondary outcome, was better in the intervention group compared to the control group. Because of study limitations, no undisputable conclusion can be drawn on this finding. However, it does serve as an encouragement for further work into improving quality of life for people with LSP. In addition, the study gave important clues on how to improve the intervention. Most importantly, future interventions should better align expert recommendations with patient's preferences and address the treatment inertia of physicians resulting from a low outcome expectancy and a perceived lack of time.

With regards to clinical practice, person-centered care tools exist that help align expert recommendations and patient's preferences. Two examples are shared

decision making and collaborative goal planning. Both have already been studied in the fields of neurology and elderly care medicine and may be extended to LSP within an experimental context. As both strategies do not apply to people with dementia, additional strategies might need to be developed for this group.

With regard to health care organizations, restructuring expert care for people with LSP has been ongoing in recent years. Elderly care organizations have started grouping people with LSP residing in nursing homes, as a means to increase expertise of care takers. These expert centers work closely with movement disorder experts working in neighboring hospitals. Although more work needs to be done to establish a detailed care program delivered by these expert centers, the need for organizational changes is supported by the findings of disease complexity and treatment challenges of LSP.

With regard to education, physicians and other practitioners should be trained to recognize and address the complex needs of people with LSP. Recently, a training program in palliative care for persons with PD improved the quality of life of people with PD. Training in palliative care is indirectly supported by the findings of this thesis as palliative care is a person-centered model that deals with issues of complexity and low outcome expectancy.

With regard to future research, we advise additional intervention trials on expert recommendations that involve person-centered care. In addition, telemedicine, e.g. the delivery of health care at a distance using technology, should be studied as it might help bridge the distance between movement disorder experts and people with LSP. As there is a need for less demanding therapies, we advocate for more research into creative therapies for people with LSP, such as dance, music and art therapy. Lastly, because persons with LSP have difficulty participating in traditional research designs, more innovative study design should be explored. We discuss the examples of mixed-methods studies, action research and big data analysis.

In conclusion, the findings from the studies reported in this thesis lead to a better understanding of disability in people with LSP. Disability associates strongest with motor symptoms and cognitive impairment, but also 'hidden' non-motor features are prevalent. The intervention did not improve daily functioning, but lessons are learned for the development of future interventions addressing the high care need of people with LSP.

CHAPTER 8. Nederlandse Samenvatting

Inleiding

Nooit in de geschiedenis van de mensheid leefden we zo lang als in onze tijd. Dit is vooral mogelijk geworden doordat we acute doodsoorzaken konden wegnemen. De keerzijde is dat chronische ziekten vaker aanwezig zijn. Chronische ziekten veroorzaken nogal eens achteruitgang in het functioneren. Dit zijn ofwel problemen in individuele taken of activiteiten, zoals zelfzorg of mobiliteit, ofwel problemen in participatie, zoals deelname aan sociale activiteiten. Van alle ziekten veroorzaken neurologische ziekten het meest problemen in het functioneren en parkinsonismen zijn de snelst groeiende neurologische ziekten. Onder parkinsonismen verstaan we hier de typische ziekte van Parkinson en, in 15% van de gevallen, een atypische parkinsonisme (zoals vasculaire parkinson, multiple systeem atrofie, progressieve supranucleaire parese, cortico-basale degeneratie of dementie op basis van lewy-lichaampjes). Het is belangrijk om bij problemen in het functioneren door parkinsonismen goed te begrijpen welke ziekte-verschijnselen de onderliggende problemen zijn. Dit om gerichte zorg, behandeling en onderzoek mogelijk te maken. Problemen in het functioneren zijn bij parkinsonismen gerelateerd aan ziektebeperkingen als problemen in de motoriek, verstoringen in het autonome zenuwstelsel, cognitieve beperkingen en neuropsychiatrische problemen. In het typische beloop van parkinsonismen komen beperkingen in het functioneren het duidelijkst naar voren in de late-fase van de ziekten. Er is weinig bekend over de late ziekte-fase, omdat deze groep vaak wordt gemist in wetenschappelijke onderzoek. Dit komt omdat mensen met late-fase parkinsonismen door hun beperkingen niet kunnen meedoen aan het onderzoek of omdat het voor onderzoekers te ingewikkeld is om mensen bij het onderzoek te betrekken. Het onderzoek dat wel is gelukt is niet hoopgevend, want er zijn tekortkomingen aangetoond in zowel de zorg als de behandeling. De onderzoeken beschreven in dit proefschrift onderzochten de relatie tussen ziekteverschijnselen en afhankelijkheid in de late-fase van parkinsonismen. Ook onderzochten we of de behandeling gemakkelijk te verbeteren is met een expert-consult en een adviesbrief.

Beperkingen van late-fase parkinsonismen

In **hoofdstuk 2** toonden we de resultaten van de 'Zorg voor de late-fase parkinsonismen'-studie (Care of late-stage Parkinsonism-study; CLaSP-study). In dit internationale onderzoek werden 692 personen in de late-fase van een parkinsonisme geïncludeerd als ze ten minste 7 jaar de ziekte hadden en voldeden aan criteria over beperkingen in het functioneren (Hoehn en Yahr schaal >4 of

Schwab en England schaal van <50%). Bij deze deelnemers waren motorische symptomen vaak aanwezig, zoals ernstige bradykinesie (77%), loopstoornissen (67%), balansproblemen (56%) en spraakproblemen (43%). Ook niet-motorische klachten kwamen vaak voor. Meer dan de helft van de deelnemers had last van concentratie- en geheugenproblemen, vermoeidheid, obstipatie en problemen met plassen, zoals nachtelijk plassen. Problemen in het functioneren, gemeten met de Schwab en England score, correleerden het meest met motorische problemen en verminderd cognitief functioneren (gemeten met de mini-mental state examination; MMSE).

In **hoofdstuk 3** toonden we de prevalentie en bepalende factoren van neuropsychiatrische klachten bij de deelnemers van de CLaSP-studie. Zes-honderd-vijf-en-twintig mantelzorgers van deelnemers werden gevraagd naar neuropsychiatrische klachten, zoals depressie, psychose, angstklachten en gedragsproblemen. Hiervoor werd de 'Neuropsychiatric Inventory'-vragenlijst gebruikt. In totaal hadden 92.2% van de deelnemers last van ten minste één neuropsychiatrische klacht, met een gemiddelde van 3 symptomen per deelnemer. Klinische relevante neuropsychiatrische problemen waren vaak aanwezig, namelijk bij 75.5% van de deelnemers. De bepalende factoren verschilden per klacht, maar terugkerend herkende we als bepalende factoren in de modellen: de aanwezigheid van andere neuropsychiatrische klachten, onvermogen in zelfzorg in persoonlijke hygiëne taken, cognitieve beperkingen en slaperigheid overdag.

In **hoofdstuk 4** werd de prevalentie van orthostatische hypotensie gepresenteerd, gebaseerd of data van de 'Verpleeghuizen op weg naar integrale Parkinson-zorg'-studie (VIP). In 64 verpleeghuisbewoners was een bloeddrukmeting afgenomen volgens een protocol om orthostatische hypotensie vast te stellen (dit bestaat uit 3 metingen: 1. na 15 minuten liggen, 2. na 1 minuut staan, en 3. na 3 minuten staan). Ook was er met hulp van een gestandaardiseerde vragenlijst, uitgevraagd of bewoners last hadden van duizeligheid of flauwvallen. De gemeten prevalentie van orthostatische hypotensie was 51.6%, ongeveer gelijk verdeeld in mensen met en zonder symptomen. Daarnaast had nog eens 20.6% 'mogelijk symptomatische' orthostatische hypotensie, wat betekent dat we de bloeddrukdaling niet gemeten hadden, maar deelnemers wel passende klachten aangaven. Opvallend genoeg, hadden maar 2 mensen met Parkinson een diagnose van orthostatische hypotensie in het medisch dossier en werd medicamenteuze behandeling nauwelijks gegeven: vijf mensen kregen domperidon, één kreeg fludrocortison en niemand kreeg midodrine.

Optimaliseren van behandeling met advies van een bewegingsstoornissen-expert
In **Hoofstuk 5** testten we de effectiviteit en haalbaarheid van een interventie die bestaat uit behandeladvies door een bewegingsstoornissen-expert. Één-en-negentig mensen met een late-fase parkinsonisme werden geïncludeerd en gerandomiseerde naar de interventie of de controlegroep volgens een 3:1 verhouding. Voor de interventiegroep werd een brief met adviezen van een bewegingsstoornissen-expert opgestuurd naar de behandelaar. Deze brief was opgesteld na een uitgebreid assessment door een onderzoeker. De controlegroep kreeg standaardzorg. Na 6 maanden werden mensen opnieuw onderzocht en de uitkomstmaten vastgesteld. Behandelaren volgden de adviezen ten minste gedeeltelijk op in 37 (64%) van de deelnemers. Er werden barrières voor het uitvoeren van de adviezen genoemd door behandelaren. De meest voorkomende barrières waren 1. de behandelvoorkeur van de patiënt kwam niet overeen met het advies (28%), 2. gebrek aan tijd (22%) en 3. geen verwachting op verbetering (19%). De 'intentie-tot-behandeling'-analyse toonde geen verschil in de primaire uitkomstmaat (algemeen dagelijks functioneren) tussen de interventiegroep en de controlegroep. Echter, er was wel een verbetering van de kwaliteit van leven zichtbaar in de interventiegroep. In de per-protocol analyse (waarbij de groepen werden samengesteld op basis van de mate waarin het behandeladvies was opgevolgd) toonde dezelfde bevindingen en aanvullend ook nog een verminderde toename van mentale problemen, grotere verbetering van Parkinson klachten en grotere toename van de dosis van de Parkinson medicatie in de interventiegroep.

Discussie

Door de beschreven onderzoeken is meer inzicht ontstaan in problemen in het functioneren bij late-fase parkinsonismen. Beperkingen in het functioneren hangen het meest samen met problemen in de motoriek en cognitieve problemen. Beide worden vaak gezien in de late fase van deze ziekten, want ze zijn bij meer dan de helft van de mensen met late-fase parkinsonisme in ernstige mate aanwezig. Met deze twee problemen is echter niet het hele verhaal over problemen in het functioneren verteld. In de onderzoeken werd tevens aangetoond dat nagenoeg alle deelnemers neuropsychiatrische problemen hebben en dat orthostatische hypotensie bij de helft van de mensen met Parkinson in het verpleeghuis voorkomt. Hoewel deze verschijnselen geen effect op het functioneren hebben dat onafhankelijk is van motoriek en cognitie, betekent dit niet, dat ze geen effect hebben. Ze kunnen namelijk een indirect effect hebben, doordat orthostatische hypotensie en neuropsychiatrische symptomen problemen in de behandeling van motorische of

cognitieve problemen veroorzaken en daarmee het functioneren belemmeren. Men weet al langer dat maximale controle van de motorische symptomen moeilijker haalbaar is als mensen snel bijwerkingen hebben als orthostatische hypotensie of psychotische klachten. Dat behandeling moeilijker is betekent niet dat het helemaal onmogelijk is. Experts zijn mogelijk beter in staat de behandeling te optimaliseren als er complicerende ziekteverschijnselen zijn.

In onze interventiestudie wordt het veelbelovende resultaat gevonden dat de kwaliteit van leven van mensen verbetert na expertadvies. Helaas werd er geen effect op het functioneren gezien. De voorlopige conclusie is hiermee dat de beste behandeling ter verbetering van het functioneren in de late-fase ziekte onduidelijk blijft. Wel worden er belangrijke aanknopingspunten gevonden voor een werkzame interventie. De belangrijkste les is dat optimalisatie van de behandeling meer vergt dan kennis van behandeling. Barrières op het niveau van attitude en gedrag werden het vaakst gezien, zoals het ervaren van een gebrek aan tijd en het hebben van een lage uitkomstverwachting. Ook betere afstemming met de patiënt lijkt noodzakelijk, aangezien dit de meest voorkomende barrière is.

Net als ieder onderzoek kennen ook deze onderzoeken beperkingen. Zo was er discussie over de selectie van deelnemers. De CLaSP-studie was opgezet om inclusief te zijn en mensen met atypische parkinsonisme konden hierdoor ook deelnemen. Dit roept de vraag op in hoeverre de gevonden resultaten zijn toe te schrijven aan subgroepen met atypische diagnosen. Voor de belangrijkste resultaten is een aanvullende analyse op enkel typische patiënten verricht en werden er geen andere resultaten gezien. De VIP-studie was selectief en liet enkel patiënten met de typische ziekte van Parkinson en een MMSE >18 deelnemen. Hierdoor werden atypische diagnosen en dementie uitgesloten terwijl de literatuur suggereert dat deze samenhangen met het voorkomen van orthostatische hypotensie. De gevonden prevalentie van orthostatische hypotensie zou dus een onderschatting kunnen zijn. In beide studies, CLaSP en VIP, zijn mensen die medicatie gebruikten niet uitgesloten van deelname. Dit zou het gevolg kunnen hebben dat het voorkomen van problemen wordt onderschat doordat klachten reeds adequaat behandeld zijn. Een beperking van beide studies zijn de problemen of volledige informatie te verzamelen. Vanaf het begin is ingezet op een geduldige verzameling van informatie, waarbij werd toegestaan dat deelnemers meerdere keren bezocht werden om een assessment compleet te maken. Desalniettemin kwam het voor dat er informatie miste door ziekteverschijnselen als vermoeidheid, concentratieproblemen en wearing-off. Tenslotte had de trial en de analyse naar orthostatische hypotensie een laag aantal

deelnemers. Dit lage aantal kan het risico op bias vergroten. Ook kan een lage aantal deelnemers het meten van een klein effect beperken en daarmee verklaren dat onze interventie geen effect liet zien op het functioneren van deelnemers. Ondanks het lage aantal deelnemers genereerde beide studies waardevolle inzichten die belangrijk zijn voor toekomstige interventie en onderzoeken.

Toekomstige interventies ter verbetering van de behandeling in de late-fase parkinsonismen moeten beter aansluiten bij de behandelvoorkeur voor de patiënt. Zowel in de ouderengeneeskunde als in die neurologie zijn goede voorbeelden beschikbaar van meer persoon-gerichte behandeling (te weten: shared-decision making, of collaborative goal planning). Als verbeteren van functioneren het doel is van de behandeling, dan kunnen behandelaren zicht richten op het verbeteren van de motoriek en de cognitie. Ook is het belangrijk dat behandelaren alert zijn op de 'verborgen' symptomen, zoals orthostatische hypotensie en neuropsychiatrische symptomen. Aangezien de herkenning van deze klachten moeilijk is en de behandeling vaak gecompliceerd is de rol van experts belangrijk. Maatschappelijk zijn er meerdere gunstige ontwikkelingen gaande ter verbetering van deze expertise. ParkinsonNet heeft een scholing ontwikkeld over palliatieve zorg voor Parkinson en steeds meer specialisten ouderengeneeskunde en verpleegkundig specialisten nemen deel aan ParkinsonNet. Daarnaast worden in de ouderengeneeskunde Parkinson-expertisecentra in de langdurige zorg ontwikkeld. Het opzetten van deze expertisecentra wordt ook aanbevolen in een recent rapport van KPMG in opdracht van het ministerie VWS. Een laatste goede ontwikkeling is ingegeven door de COVID-pandemie en betreft de toegenomen ervaring met zorg op afstand. Mogelijk kan expert-zorg toegankelijker worden door gebruik van telezorg. Toekomstig onderzoek doet er goed aan om aan te sluiten bij deze ontwikkelen.

Toekomstig onderzoek naar de late-fase parkinsonismen zal innovatief moeten zijn om te slagen. Enkele voorbeelden van innovatieve onderzoeksmethoden die verkent kunnen worden voor late-fase parkinsonismen zijn 1. mixed-methods studies, waarbij kwalitatieve instrumenten de kwantitatieve metingen verrijken, 2. action research, waarbij belanghebbenden, zoals mensen met parkinsonisme of behandelaren, actief betrokken worden bij de interpretatie van resultaten en besluitvorming en 3. big data onderzoek, waarbij bestaande registratie databases worden benut om onderzoeksvragen te beantwoorden (en de patiënt niet verder belast hoeft te worden).

Conclusie

Dit proefschrift geeft inzicht in de rol van onderliggende ziekteverschijnselen in beperkingen in het functioneren bij mensen met late-fase parkinsonisme. Beperkingen in het functioneren associëren het sterkst met motorische en cognitieve problemen. Ook 'verborgen' niet-motorische verschijnselen komen vaak voor. Een pragmatische interventie verbeterde het functioneren van mensen met parkinsonisme niet, maar belangrijke lessen kunnen geleerd worden van deze interventiestudie om de zorg voor mensen met late-fase parkinsonismen te verbeteren.

CHAPTER 9. Appendices

List of publications

Publications in this thesis:

- Schrag A, Hommel ALAJ, et al. The late stage of Parkinson's –results of a large multinational study on motor and non-motor complications. Parkinsonism and Related Disorders 2020;75:91–96.
- Hommel ALAJ, Meinders MJ, et al. The Prevalence and Determinants of Neuropsychiatric Symptoms in Late-Stage Parkinsonism. Mov Disord Clin Pract. 2020;7(5):531-542.
- Hommel, ALAJ Faber MJ, Weerkamp NJ, van Dijk JG, Bloem BR and Koopmans RT. "Prevalence and prescribed treatments of orthostatic hypotension in institutionalized patients with Parkinson's Disease" Journal of Parkinson's Disease 2016;6:805–810.
- Hommel ALAJ, Meinders MJ, et al. Optimizing treatment in undertreated late-stage parkinsonism: a pragmatic randomized trial. J Parkinsons Dis. 2020;10(3):1171-1184.

Other publications:

- Hommel ALAJ, Plouvier AOA, Krijthe J, Lavrijsen JCM, Koopmans RTCM, Van Erp WS. Complexe neurologische aandoeningen in het verpleeghuis. Tijdschrift voor Ouderengeneeskunde. 2020;5
- Hommel ALAJ, van Gastel S, Koevoets B, de Wit T, van Strien T. De vele gezichten van Geriatrische Parkinson-revalidatie. Tijdschrift voor Ouderengeneeskunde. 2020;4
- Hosking A, Hommel ALAJ, et al. Characteristics of Patients with Late-Stage Parkinsonism who are Nursing Home Residents Compared with those Living at Home. J Am Med Dir Assoc. 2020 Jul 25; Online ahead of print
- Van de Weijer SCF, Hommel ALAJ, Bloem BR, Nonnekes J, de Vries NM. Promising non-pharmacological therapies in PD: Targeting late stage disease and the role of computer based cognitive training. Parkinsonism Relat Disord. 2018;46 Suppl 1:S42-S46.
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- van der Steen J, Lennaerts H, Hommel D, Augustijn B, Groot M, Bloem BR, Koopmans RCTM. Dementia and Parkinson's disease: similar and divergent challenges in providing palliative care. Front Neurol. 2019 ;10:54.

- Hommel D, Weerkamp N. Hora est: de ziekte van Parkinson in het verpleeghuis. Tijdschrift voor Ouderengeneeskunde. 2017;6
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- Meijer A , Overduin P, Hommel D, van Rijnsoever-Greven Y, Haenen A, Veldman-Ariesen M Outbreak of respiratory syncytial virus infections in a nursing home and possible sources of introduction: the Netherlands, winter 2012/2013. J Am Geriatr Soc. 2013;61(12):2230-1.

Curriculum Vitae

Danny Hommel was born on September 26th 1986 in Bergen op Zoom as the youngest son in a family of four children.

Eager to learn, he proceeded to graduate from secondary school in 2004 (Moller Lyceum, Bergen op Zoom) and started studying Applied Physics at the TU Delft. He quickly learned that the human factor (apparently very important to him) was missing in the studies of thermodynamics and quantum mechanics. He therefore switched to studying Medicine at the ErasmusMC, Rotterdam, but not before he made a short but important detour in studying Philosophy also at the Erasmus University, Rotterdam. Philosophical studies interested him the most during his time at the university, but, because Danny is a practical guy, he realized that it is hard to make a living pondering the ancient questions of existence and he set out to become a doctor instead. He did, however, finish his Bachelor in Philosophy of Medicine at the Erasmus University Rotterdam.

At the end of 2011, he graduated in Medicine at ErasmusMC. Internships in genetic epidemiology and neurology awakened an interest in respectively data analysis and diseases of the nervous system. However, much to his surprise, an internships in elderly care medicine brought about the greatest interest and excitement for this young professional. Here, in every-day elderly care many patients were personally pondering real-life philosophical questions on personal identity, the value of existence and the meaning of life.

A career was born; in 2012 Danny started his training in Elderly Care Medicine, which he finished in 2015. His curriculum consisted of internships in psychogeriatrics (Heerma State, Groenhuysen, Roosendaal), somatic diseases (Wiekendael, Groenhuysen, Roosendaal), ambulatory care (GGZ, West-Brabant; and VKO, Groenhuysen, Roosendaal), clinical geriatrics (Amphia ziekenhuis, Breda) and geriatric rehabilitation (Weihoek, Groenhuysen, Roosendaal). During his trainings Danny never lost his interest in data analysis and when the opportunity arose, he started his PhD research project at the department of Neurology, Radboudumc, Nijmegen. He joined the CLaSP-research team studying late-stage Parkinsonism. He was responsible for the set-up, data collection, data-analysis and publication of the CLaSP-study under supervision of dr. Marjan Meinders, dr. Nico Weerkamp, prof. Bas Bloem and prof. Raymond Koopmans.

Simultaneously to his studies, Danny helped Groenhuysen Organisation in their quest to improve regional Parkinson care, by setting up a center of expertise in Parkinson-specific ambulatory care, geriatric rehabilitation and long-term care.

Societally, Danny was involved, on behalf of Verenso, in the development of the 'Kwaliteitsstandaard atypische parkinsonismen' and the revisited 'Multidisciplinaire richtlijn Ziekte van Parkinson'. Danny currently works as an elderly care physician at Kenniscentrum Parkinsonhuys, Groenhuysen, Roosendaal. Also, Danny holds a position as a researcher at the UKON network, Radboudumc, Nijmegen. Danny is married to the wonderful Tessa Hommel and has two children, Tobias and Floor.

Research data management

The studies presented in this thesis are the result of two separate projects: 'Verpleeghuizen op weg naar integrale Parkinsonzorg' (VIP-study) and 'Care of late-stage Parkinsonism' (CLaSP-study). Both studies were human studies, which were conducted in accordance with the principles of the Declaration of Helsinki. The medical and ethical review board Committee on Research Involving Human Subjects Region Arnhem Nijmegen, Nijmegen, the Netherlands has given approval to conduct these studies.

Data collection for the VIP-study was performed using questionnaire booklets. These were stored on site under supervision of the researcher. The results of these booklets were not stored electronically as the study pre-dates additional directives on electronical storage of data. For analysis, data was entered directly into the statistical package SPSS (SPSS Inc., Chicago, Illinois, USA), which was stored on the local Radboudumc server, belonging to the neurology department. The primary and secondary data were stored alongside SPSS-scripts that were used to produce the final result. This project can be found on the Radboudumc, department server: (H:) NEUROdata under ClaSP\VIP-data. Analysis and scripts can be made available upon reasonable request.

The CLaSP study was a multinational project. The Coordinating Centre for Clinical Trials in Marburg in Germany (KKS; http://www.kks.uni-marburg.de) was appointed responsibility for the centralized data collection. Within the KKS, the departments IT-Systems and Data Management were responsible for all IT and data management affairs in this project. The Marburg site collected the computerized data using the data capturing solution MACRO™ (by Infermed; www.infermed.com). All research staff who entered or monitored data were provided with training material and documentation (EDC Manual), before entering data. Also, a test/training database was available for instructional purposes. The primary and secondary data was entered electronically by local researchers via a web-browser and transferred via SSL encryption to the central database. In addition, the Dutch data collection was done using questionnaire booklets, which were stored after entering of the data electronically. The paper data were stored in the department archive.

In both studies the written informed consent was obtained at initiation of the study. The study researcher filled in the research form on paper. For the VIP-study, the consent forms were stored on site under supervision of the principal researcher. The

VIP-study pre-dated additional regulation on electronical storage of consent forms. For the ClaSP-study, the consent forms were stored in the department archive. Additionally, the consent forms were entered into the computer using MACRO™.

Data management and monitoring of the VIP-study were performed upon analysis within the SPSS dataframe. This program does not facilitate an audit trail of the queries performed. For the ClaSP-study, MACRO™ was used an a full audit trail of the queries is available. Queries were coordinated cross-nationally by the KKS. The electronical system MACRO™ implied a wide range of automated checks on plausibility and completeness of data that prompt the research staff upon data entry immediately on appropriate action. Discrepancies which appeared on data management were forwarded to the site directly as Data Query Forms (DQFs).

The files made available for analysis were sent by the KKS to the Radboudumc and stored electronically on the Radboudumc server, belonging to the neurology department. These files contain the published data generated and analyzed for this thesis. For interpretability of the data, a glossary is available containing detailed descriptions of all data variables is available. Analysis was performed using SPSS. The files for analysis includes the SPSS-scripts that were used to produce the final results, and were stored on the Radboudumc, department server: (H:) NEUROdata under ClaSP\Project Uitvoering \ Data. These files are available from the associated corresponding authors upon reasonable request.

In both studies, the privacy of the participants is warranted by use of encrypted and unique individual subject codes. This code correspondents with the code on the patient- and physicians booklets. The code was stored separately from the study data. In hardcopy for the VIP-study and electronically for the ClaSP-study.

The data will be saved for 15 years after termination of the study. Using these patient data in future research is only possible after a renewed permission by the patient as recorded in the informed consent.

PhD Portfolio

Trainingen en cursussen

- ParkinsonNet basisscholing voor specialisten ouderengeneeskunde, ParkinsonNet, 2014.
- Qualitative Research Methods in Health care (introduction), CaRe, Netherlands school in primary research, 2015.
- Basiscursus regelgeving en organisatie van klinisch onderzoek (BROK), NFU BROK academie, 2015.
- Principles of Research in Medicine and Epidemiology (ESP01). Nihes, Erasmus MC Summer School, Rotterdam, 2016.
- Regression Analysis (ESP09). Nihes, Erasmus MC Summer School, Rotterdam, 2016.
- Cohort Studies (ESP39). Nihes, Erasmus MC Summer School, Rotterdam, 2017.
- Scientific writing for PhD candidates course. PON Nijmegen. (8 van de 10 sessies reeds gevolgd). 2018.
- Data analysis with R. Erasmus Graduate School of Social Sciences and Humanities, 2020.

Lezingen en bijeenkomsten

- Late-fase ziekte van Parkinson. Een zorg voor de expert? Verenso congres, 26-11-2015.
- Workshop Parkinson en dementie. Congres moderne dementiezorg, 24-11-2015.
- Innovatie voor de ziekte van Parkinson. Zorgpodium Groenhuysen, 13-10-2015.
- Workshop Parkinson en dementie. PVK/POH congres, 17-9-2015.
- Parkinson en de laatste levensfase. Parkinsoncafé West-Brabant, 3-9-2015.
- Workshop Parkinson en dementie. Congres moderne dementiezorg, 11-11-2014.
- Workshop Palliatieve zorg bij Parkinson, ParkinsonNet congres, Rotterdam, 8-12-2016.
- Workshop Palliatieve zorg bij Parkinson, ParkinsonNet congres, Zwolle, 11-11-2016.
- Workshop Palliatieve zorg bij Parkinson, ParkinsonNet congres, Den Bosch, 7-10-2016.
- Casusbespreking Parkinson. ParkinsonNet scholing VS/SO, 19-02-2016.

- Voorbeelden van multidisciplinaire afstemming. ParkinsonNet scholing VS/SO, 19-02-2016.
- KBS: exploratie: De oudere patiënt met neurologische uitval (Parkinson). Voson (opleiding SO), 30-03-2017.
- Palliative care in Parkinson Disease. A Professionals perspective. Professionals and Public Meeting on Palliative Care. EAN/EFNA congres, Amsterdam, 23-6-2017.
- Kenniscentrum Parkinsonhuys. Ervaring in centralisatie van Parkinson-zorg. Symposium: 2017 A Groenhuysen Odyssey. 11-10-2017.
- KBS: exploratie: De oudere patiënt met neurologische uitval (Parkinson). Voson (opleiding SO), 16-11-2017.
- Presentatie over zorg in de regio. Parkinsoncafé Breda. 25-5-2018.
- Organisatie en dagvoorzitterschap van open dag Kenniscentrum Parkinsonhuys. Groenhuysen. Roosendaal. 11-4-2018.
- Poster JPND congress, November 2019. “Optimizing treatment in undertreated Late-Stage Parkinsonism: a pragmatic randomized controlled trial (CLaSP-study)”

Overige activiteiten

- Kwaliteitsstandaard atypische parkinsonismen, namens Verenso, 2018-2020 .
- Revisie Multidisciplinaire richtlijn ziekte van Parkinson namens Verenso 2018-2020.
- Parkinson Vereniging adviesgroep, sinds 2020.
- Toekenning Verenso beurs 2018.

Acknowledgement / Dankwoord

Allereerst wil ik alle **deelnemers aan de CLaSP en de VIP-studie** bedanken. Ergens las ik de volgende zin die ik erg van toepassing vind: “In een goede samenleving planten oude mensen bomen in wier schaduw ze nooit zullen zitten”. Een groot deel van de deelnemers is niet meer onder ons. Ze hebben kostbare tijd opgeofferd in de verwachting dat ze hiermee goed zouden doen voor toekomstige mensen met de ziekte van Parkinson. Deze inzet is een belangrijke motivator geweest om de onderzoeken zo goed mogelijk te verrichten en ik ben ze erg dankbaar voor het vertrouwen.

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Dear **CLaSP-consortium**, it took dedication and adaptability to complete the CLaSP-study. Along the way, we had to adjust, recalculate, rewrite and reschedule, but we achieved our goals and the results are important and unique. I am proud of what we achieved! A special thanks to prof. Schrag who presided the CLaSP-consortium with intelligence, diligence and patience. It was a great opportunity to be able to learn from you all!

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Dissertations of the disorders of movement research group, Nijmegen

Parkinson Center Nijmegen (ParC)

Jasper E. Visser. The basal ganglia and postural control. Radboud University Nijmegen, June 17th 2008.

Maaike Bakker. Supraspinal control of walking: lessons from motor imagery. Radboud University Nijmegen, May 27th 2009.

W. Farid Abdo. Parkinsonism: possible solutions to a diagnostic challenge. Radboud University Nijmegen, October 7th 2009.

Samyra H.J. Keus. Physiotherapy in Parkinson's disease. Towards evidence-based practice. Leiden University, April 29th 2010.

Lars B. Oude Nijhuis. Modulation of human balance reactions. Radboud University Nijmegen, November 29th 2010.

Maarten J. Nijkrake. Improving the quality of allied health care in Parkinson's disease through community-based networks: the ParkinsonNet health care concept. Radboud University Nijmegen, November 29th 2010.

Rick C.G. Helmich. Cerebral reorganization in Parkinson's disease. Radboud University Nijmegen, May 24th 2011.

I.B. Bruinsma. Amyloidogenic proteins in Alzheimer's and Parkinson's disease. Interaction with chaperones and inflammation. Radboud University Nijmegen, September21st 2011.

Charlotte A. Haaxma. New perspectives on preclinical and early stage Parkinson's disease. Radboud University Nijmegen, December 6th 2011.

Johanna G. Kalf. Drooling and dysphagia in Parkinson's disease. Radboud University Nijmegen, December 22nd 2011.

Anke H. Snijders. Tackling freezing of gait in Parkinson's disease. Radboud University Nijmegen, June 4th 2012.

Bart F.L. van Nuenen. Cerebral reorganization in premotor parkinsonism. Radboud University Nijmegen, November 22nd 2012.

Wandana Nanhoe-Mahabier. Freezing of physical activity in Parkinson's disease, the challenge to change behavior. Radboud University Nijmegen, February 13th 2013.

Marlies van Nimwegen. Promotion of physical activity in Parkinson's disease, the challenge to change behavior. Radboud University Nijmegen, March 6th 2013.

Arlène D. Speelman. Promotion of physical activity in Parkinson's disease, feasibility and effectiveness. Radboud University Nijmegen, March 6th 2013.

Tjitske Boonstra. The contribution of each leg to bipedal balance control. University Twente, June 6th 2013.

Marjolein A van der Marck. The Many faces of Parkinson's disease: towards a multifaceted approach? Radboud University Nijmegen, January 20th 2014.

Katrijn Smulders. Cognitive control of gait and balance in patients with chronic stroke and Parkinson's disease. Radboud University Nijmegen, May 21st 2014.

Marjolein B. Aerts. Improving diagnostic accuracy in parkinsonism. Radboud University Nijmegen, June 27th 2014.

Maartje Louter. Sleep in Parkinson's disease. A focus on nocturnal movements. Radboud University Nijmegen, February 13th 2015.

Frederick Anton Meijer. Clinical Application of Brain MRI in Parkinsonism: From Basic to Advanced Imaging, Radboud University Nijmegen, June 23th 2015.

Jorik Nonnekes. Balance and gait in neurodegenerative disease: what startle tells us about motor control, Radboud University Nijmegen, September 25th 2015.

Martijn van der Eijk. Patient-centered care in Parkinson's disease. Radboud University Nijmegen, December 1st 2015.

Ingrid Sturkenboom. Occupational therapy for people with Parkinson's disease: towards evidence-informed care. Radboud University Nijmegen, February 11th 2016.

Merel M. van Gilst. Sleep benefit in Parkinson's disease. Radboud University Nijmegen, April 13th 2016.

Arno M. Janssen. Transcranial magnetic stimulation - measuring and modeling in health and disease. Radboud University Nijmegen, June 2nd 2016.

Annette Plouvier. De ziekte van Parkinson, een gezamenlijke reis van huisarts en patiënt. Radboud University Nijmegen, juni 15th 2017.

Nico Weerkamp. Parkinson's disease in long-term-care facilities. Radboud University Nijmegen, September 1st 2017.

Digna de Kam. Postural instability in people with chronic stroke and Parkinson's disease: dynamic perspectives Radboud University Nijmegen, October 4th 2017.

Freek Nieuwhof. The complexity of walking: Cognitive control of gait in aging and Parkinson's disease Radboud University Nijmegen, October 27th 2017.

Koen Klemann. A molecular window into Parkinson's disease. Radboud University Nijmegen, November 3th 2017.

Claudia Barthel. Moving beyond: freezing of gait in Parkinson's disease. Radboud University Nijmegen, April 4th 2018.

Esther Bekkers. Freezing and postural control in Parkinson's disease. Defense at KU Leuven, May 15th 2018.

Erik te Woerd. Feeling the beat: The neurophysiology of cueing in Parkinson's disease. Radboud University Nijmegen, January 18th 2019.

Ana L. Silva de Lima. Quantifying Parkinson's disease: the use of technology for objective assessment of motor symptoms. Radboud University Nijmegen, March 26th 2019.

Anna Santaella Tortós-Sala. Tackling Parkinson's disease: a proteomic approach to biomarkers and regenerative therapy. Radboud University Nijmegen, October 22nd 2020.

Non-Parkinsonian disorders of movement

Sacha Vermeer. Clinical and genetic characterization of autosomal recessive cerebellarataxias. Radboud University Nijmegen, April 5th 2012.

Susanne T. de Bot. Hereditary spastic paraplegias in the Netherlands. Radboud University Nijmegen, December 20th 2013.

Catherine C.S. Delnooz. Unraveling primary focal dystonia. A treatment update and new pathophysiological insights. Radboud University Nijmegen, January 7th 2014.

Ella M.R. Fonteyn. Falls, physiotherapy, and training in patients with degenerative ataxias. Radboud University Nijmegen, June 29th 2016.

B.S. Hoffland. Investigating the role of the cerebellum in idiopathic focal dystonia. Radboud University Nijmegen, March 22nd 2017.

Vascular disorders of movement – The Radboud Stroke centre

Liselore Snaphaan. Epidemiology of post stroke behavioral consequences. Radboud University Nijmegen, March 12th 2010.

D. de Jong. Anti-inflammatory therapy and cerebrospinal fluid diagnosis in Alzheimer's disease. Radboud University Nijmegen, September 21st 2010

N.M. Timmer. The interaction of heparin sulfate proteoglycans with amyloid β protein. Radboud University Nijmegen, January 13th 2011.

Karlijn F. de Laat. Motor performance in individuals with cerebral small vessel disease: an MRI study. Radboud University Nijmegen, November 29th 2011

Anouk G.W. van Norden. Cognitive function in elderly individuals with cerebral small vessel disease. An MRI study. Radboud University Nijmegen, November 30th 2011.

P.E. Spies. The reflection of Alzheimer disease in CSF. Radboud University Nijmegen, March 15th 2012.

D. Slats. CSF biomarkers of Alzheimer's disease; serial sampling analysis and the study of circadian rhythmicity. Radboud University Nijmegen, September 21st 2012.

Rob Gons. Vascular risk factors in cerebral small vessel disease. A diffusion tensor imaging study. Radboud University Nijmegen, December 10th 2012.

Loes C.A. Rutten-Jacobs. Long-term prognosis after stroke in young adults. Radboud University Nijmegen, April 14th 2014

M.K. Herbert. Facing uncertain diagnosis. The use of CSF biomarkers for the differential diagnosis of neurodegenerative disease. Radboud University Nijmegen July 8th 2014.

Noortje A.M.M. Maaijwee. Long-term neuropsychological and social consequences after stroke in young adults. Radboud University Nijmegen, June 12th 2015.

M. Müller. Footprints of Alzheimer's disease. Exploring proteins and microRNAs as biomarkers for differential diagnosis. Radboud University Nijmegen, April 18th 2016.

K.A. Bruggink. Amyloid-B and amyloid associated proteins in the pathology and diagnosis of Alzheimer's Disease. Radboud University Nijmegen, April 25th 2016.

Anil M. Tuladhar. The disconnected brain: mechanisms of clinical symptoms in small vessel disease. Radboud University Nijmegen, October 4th 2016.

Pauline Schaapsmeerders. Long-term cognitive impairment after first-ever ischemic stroke in young adults: a neuroimaging study. Radboud University Nijmegen, January 24th 2017.

Inge W.M. Van Uden. Behavioral consequences of cerebral small vessel disease. An MRI approach. Radboud University Nijmegen, February 14th 2017.

Renate Arntz. Long-term risk of vascular disease and epilepsy after stroke in young adults. Radboud University Nijmegen, February 16th 2017.

Helena Maria Van Der Holst. Mind the step in cerebral small vessel disease. Brain changes in motor performance. Radboud University Nijmegen, April 5th 2017.

E.M.C. van Leijsen. Unraveling the heterogeneity of cerebral small vessel disease; from local to remote effects. Radboud University Nijmegen, November 19th 2018.

S.J. Ooms. Sleep well, age well. Assessing sleep disruption as a player in Alzheimer's disease. Radboud University Nijmegen, November 30th 2018.

Linda J.C. van Waalwijk van Doorn. Cerebrospinal fluid biomarker assays for Alzheimer's disease: standardization, validation and analysis of confounders. Radboudumc, Nijmegen, August 27th 2020.

Neuromuscular disorders of movement

Mireille van Beekvelt. Quantitative near infrared spectroscopy (NIRS) in human skeletal muscle. Radboud University Nijmegen, April 24th 2002.

Johan Hiel. Ataxia telangiectasia and Nijmegen Breakage syndrome, neurological, immunological and genetic aspects. Radboud University Nijmegen, April 23th 2004.

Gerald JD Hengstman. Myositis specific autoantibodies, specificity and clinical applications. Radboud University Nijmegen, September 21st 2005.

M. Schillings. Fatigue in neuromuscular disorders and chronic fatigue syndrome, a neurophysiological approach. Radboud University Nijmegen, November 23th 2005.

Bert de Swart. Speech therapy in patients with neuromuscular disorders and Parkinson's disease. Diagnosis and treatment of dysarthria and dysphagia. Radboud University Nijmegen, March 24th 2006.

J. Kalkman. From prevalence to predictors of fatigue in neuromuscular disorders. The building of a model. Radboud University Nijmegen, October 31st 2006.

Nens van Alfen. Neuralgicamyotrophy. Radboud University Nijmegen, November 1st 2006.

Gea Drost. High-density surface EMG, pathophysiological insights and clinical applications. Radboud University Nijmegen, March 9th 2007.

Maria Helena van der Linden. Pertubations of gait and balance: a new experimental setup applied to patients with CMT type 1a. Radboud University Nijmegen, October 6th 2009.

Jeroen Trip. Redefining the non-dystrophic myotonic syndromes. Radboud University Nijmegen, January 22nd 2010.

Corinne G.C. Horlings. A weak balance: balance and falls in patients with neuromuscular disorders. Radboud University Nijmegen, April 1st 2010.

Edith Cup. Occupational therapy, physical therapy and speech therapy for persons with neuromuscular diseases, an evidence based orientation. Radboud University Nijmegen, July 5th 2011.

Alide Tieleman. Myotonic dystrophy type 2, a newly diagnosed disease in the Netherlands. Radboud University Nijmegen, July 15th 2011.

Nicol Voermans. Neuromuscular features of Ehlers-Danlos syndrome and Marfan syndrome. Radboud University Nijmegen, September 2nd 2011.

Allan Pieterse. Referral and indication for occupational therapy, physical therapy and speech- language therapy for persons with neuromuscular disorders. Radboud University Nijmegen, February 13th 2012.

Bart Smits. Chronic Progressive External Ophthalmoplegia more than meets the eye. Radboud University Nijmegen, June 5th 2012.

Ilse Arts. Muscle ultrasonography in ALS. Radboud University Nijmegen, October 31st 2012.

M. Minis. Sustainability of work for persons with neuromuscular diseases. Radboud University Nijmegen, 13 November 2013.

Willemijn Leen. Glucose transporter – 1 deficiency syndrome. Radboud University Nijmegen, June 26th 2014.

Femke Seesing. Shared Medical appointments for neuromuscular patients and their partners. Radboud University Nijmegen, September 2nd 2016.

Nicole Voet. Aerobic exercise and cognitive behavioral therapy in fascioscapulohumeral dystrophy: a model based approach. Radboud University Nijmegen , October 14th 2016.

Barbara van der Sluijs. Oculopharyngeal muscular dystrophy (OPMD) in the Netherlands, beyond dysphagia and ptosis. Radboud University Nijmegen, December 11th 2017.

Simone Knuijs. Prevalence of dysarthria and dysphagia in neuromuscular diseases and an assessment tool for dysarthria in adults. Radboud University Nijmegen, July 3th 2018.

Marielle Wohlgemuth. A family based study of Facioscapulohumeral. Radboud University Nijmegen, November 7th 2018.

Karlien Mul. The many faces of FSHD, opportunities and challenges on the road to therapies. Radboud University Nijmegen, 18 January 18th 2019.