Caregiver Burden in Late-Stage Parkinsonism and Its Associations

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Abstract

Background: Patients in the late stages of parkinsonism are highly dependent on others in their self-care and activities of daily living. However, few studies have assessed the physical, psychological and social consequences of caring for a person with late-stage parkinsonism. **Patients and methods:** Five hundred and six patients and their caregivers from the Care of Late Stage Parkinsonism (CLaSP) study were included. Patients' motor and non-motor symptoms were assessed using the UPDRS and Non-motor symptom scale (NMSS), Neuropsychiatric inventory (NPI-12), and caregivers' health status using the EQ-5D-3 L. Caregiver burden was assessed by the Zarit Burden Interview (ZBI). **Results:** The majority of caregivers were the spouse or life partner (71.2%), and were living with the patient at home (67%). Approximately half of caregivers reported anxiety/depression and pain/discomfort (45% and 59% respectively). The factors most strongly associated with caregiver burden were patients' neuropsychiatric features on the total NPI score (r = 0.38, p < 0.0001), total NMSS score (r = 0.28, p < 0.0001), caring for male patients and patients living at home. Being the spouse, the hours per day assisting and supervising the patient as well as caregivers' EQ-5D mood and pain scores were also associated with higher ZBI scores (all p < 0.001). **Conclusion:** The care of patients with late stage parkinsonism is associated with significant caregiver burden, particularly when patients manifest many neuropsychiatric and non-motor features and when caring for a male patient at home.

Keywords

late-stage parkinsonism, caregiver burden, neuropsychiatric, non-motor symptoms

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Introduction

Parkinson's disease (PD) is a common neurodegenerative disorder with motor and non-motor symptoms affecting approximately 1% of the population over 60 years, the prevalence of which increases with age.[1] As the disease progresses, there is an increasing rate and severity of motor features such as postural instability, falls or dysphagia,[2] as well as non-motor problems such as cognitive impairment, depression, anxiety, sleep disorders, apathy and psychosis,[3,4] which increase disability and reduce quality of life in the later disease stages.[5] As a consequence, patients in this late stage are typically highly dependent on caregivers for their activities of daily living.

Caring for a person with a neurodegenerative disease is a demanding process and may result in various negative physical, psychological and social consequences for caregivers,[6] which usually increase as the disease progresses and the patient gradually becomes more dependent on the caregiver.[7] With disease progression, patients' needs become more complex as they require increased assistance for daily activities (mobility, dressing, personal hygiene, eating, handling utensils) and medical requirements (administration of medication, attending medical appointments, therapy coordination) as well as communication.[2] Caregiver burden is a broad, multidimensional term describing the negative psychological state of caregivers induced by the demands of care for a person with chronic illness or disability.[6] Persistent burden may affect the caregiver's well-being and lead to physical (chronic illness) or psychological problems (emotional strain, depression, anxiety).[8,9]

Late-stage parkinsonism patients and their caregivers constitute a complex group of participants that cannot easily be recruited in studies due to the severity of motor and non-motor problems, age, comorbidities as well as the fact that patients tend to withdraw from specialized health care in the late stage.[2] Only a few studies concentrated on the burden of caregivers of patients with advanced PD[10-13] or atypical parkinsonism[14-16] and their satisfaction with support,[17] which had relatively small samples, yielded inconsistent results regarding the contribution of motor, non-motor symptoms and caregiving factors to caregiver burden, and did not include an in-depth assessment. Therefore, aim of this study was to investigate caregivers' burden in late-stage parkinsonism patients and the factors associated with it. Identifying the factors that contribute to caregivers' burden could help develop interventions, in order to improve psychosocial outcomes for caregivers and consequently improve care of patients in these late stages.

Patients and Methods

Patients and Caregivers

The Care of Late Stage Parkinsonism (CLaSP) study[18] is a longitudinal, multicenter, prospective cohort study conducted from September 2014 to March 2019 assessing the needs and provision of care for patients with late-stage parkinsonism and their caregivers in 6 European countries. 588 patients in the cross-sectional part of the study had a primary informal caregiver, of whom 506 (86.1%) completed the Zarit Burden Interview (ZBI), while 82 (13.9%) did not. The number of participants and response rate per site were as follows: 91 participants from the United Kingdom (UK) (87.5% responders), 73 from France (97.3%), 112 from Germany (75.2%), 68 from the Netherlands (88.3%), 86 from Portugal (93.5%) and 76 from Sweden (83.5%). Responders were more often the spouse (57.7% vs 18.3%, $p < 0.001$) or child (18.2% vs 7.3%, $p = 0.02$) of the patient compared to non-responders. Additionally, responders less often received assistance from others (45.8% of responders had no assistance from others vs 24.1% of non-responders, $p = 0.04$). There was also a marginal difference regarding living with the patient (67% of responders vs 45.8% of non-responders, $p = 0.06$), while there was no difference regarding employment state. Participants were recruited from outpatient settings (hospital and office-based neurologists, psychiatrists, rehabilitation centers), nursing homes, palliative and primary care settings, adapted to health care arrangements in each country. Inclusion criteria were late-stage parkinsonism i.e. disease duration of at least 7 years and Hoehn and Yahr stage IV or V or significant disability (Schwab and England stage 50% or less) in the "on"-state. Patients with potentially curable parkinsonism such as normal pressure hydrocephalus or drug-induced parkinsonism were excluded. Most of the patients (95%) had idiopathic PD according to the UK PD society Brain Bank clinical diagnostic criteria,[19] but as distinction of different parkinsonian syndromes after longer disease duration is difficult, patients with atypical parkinsonism (Multiple system atrophy-MSA, Progressive Supranuclear Palsy-PSP, Corticobasal Degeneration-CBD, Lewy body dementia-LBD) and vascular parkinsonism were also included if they had a disease duration of longer than 7 years. Patients were selected based on their health record and invited to participate by a letter from their clinician or they were referred by clinicians directly. The study was approved by the local ethics committees of all participating study sites and all participants gave their informed consent.

Assessments

Caregiver's burden was assessed by the ZBI,[20] which is a 22-item questionnaire assessing the physical, emotional, social and financial impact of the disease on the caregiver. Each item is answered on a 5-point scale from 0 (never) to 4 (nearly always). The ZBI ranges from 0-88 with higher scores indicating higher burden. The total score can be categorized as follows: 0–20 (little or no burden), 21–40 (mild to moderate burden), 41–60 (moderate to severe burden), and 61–88 (severe burden).

Patients' disease characteristics included age, gender and residential status; disease severity was assessed using the Unified PD rating scale (UPDRS),[21] disease stage using Hoehn and Yahr scale[22] and disability using the Schwab and England scale.[23] Mini-Mental-state examination (MMSE)[24] was used to assess patients' general cognitive function. Non-motor

symptoms were measured by the Non-Motor Symptom Scale (NMSS),[25] which consists of 30 items grouped in 9 domains: cardiovascular/falls, sleep/fatigue, mood/cognition, perceptual problems/hallucinations, attention/memory, gastrointestinal system, urinary symptoms, sexual function, miscellaneous. The score of each item is a multiple of frequency (1-4) and severity (0-3). Neuropsychiatric symptoms were assessed using the Neuropsychiatric inventory (NPI-12),[26] a caregiver-based instrument assessing 12 neuropsychiatric symptoms (delusions, hallucinations, agitation/aggression, depression/dysphoria, anxiety, euphoria/elation, apathy/indifference, disinhibition, irritability/lability, aberrant motor behavior, nighttime behavior disorders, eating changes) in patients. The frequency and severity of neuropsychiatric symptoms within the last month are rated on a 3-point and 4-point Likert scale respectively, are multiplied and the subscores are then added to give the sum score. Patients' comorbidities were assessed by the Charlson Comorbidity Index (CCI).[27]

Informal caregiver information included their relationship to the patient, whether they lived with the patient, their current employment status and time providing care (hours per day and days per month assisting the patient and supervising the patient). Moreover, it included the proportion of care provided by the caregiver, whether additional assistance was provided and the frequency of contact with the patient if not living together. In addition, we assessed the caregivers' own health status using the EQ-5D-3 L.[28] The EQ-5D-3 L consists of 2 parts, one assessing the 5 dimensions of mobility, self-care, usual activities, pain/discomfort, anxiety/depression on 3 levels, and a visual analog scale (EQ VAS), indicating the current own health status from 0 (worst imaginable health state) to 100 (best imaginable health state).

Data Analysis

The statistical analysis was performed using the IBM SPSS 25.0. Descriptive statistics were used for sociodemographic and clinical variables. The normality of the variables was assessed using graphical methods and the Shapiro-Wilk test of normality. We included variables having <10% missing data, in few variables with >10% missing the number of cases (N) is reported in parenthesis. To analyze the relationship between ZBI and other variables we performed correlation analyses using Pearson or Spearman rank correlations. Correlations were considered weak for r values ≤0.29, moderate from 0.3 to 0.59 and strong for values ≥0.6. Statistical comparisons for non-normally distributed data were performed with the non-parametric Kruskal-Wallis or Mann-Whitney test. Comparisons were done using ANOVA for continuous variables and chi-squared test for categorical variables. Bonferroni and Scheffe correction were applied to adjust for multiple comparisons. A stepwise multiple regression analysis was performed considering the variables that showed significant correlations with ZBI (having <10% missing data), after excluding collinearity between the variables. The level of significance was set at 0.05.

Table 1. Patients' Characteristics.

		Mean ± SD/median (range) or n (%)
Age		76.4 ± 8 years (24-96)
Gender	female	222 (43.9%)
	male	284 (56.1%)
Residential status	Home	374 (73.9%)
	Nursing home or similar	132 (26.1%)
Diagnosis	Parkinson's disease	484 (95.7%)
	Atypical parkinsonism (MSA, PSP, CBD, LBD)	17 (3.4%)
	Vascular parkinsonism	4 (0.8%)
Hoehn & Yahr score		4 (2-5)
Schwab & England scale		30 (0-80)
MMSE (N = 315)		23.3 ± 5.9 (0-30)
UPDRS total		85.5 ± 24.1 (26-158)
UPDRS I		5.9 ± 3.5 (0-15)
UPDRS II		27.7 ± 7.6 (8-47)
UPDRS III		47.3 ± 16.1 (10-89)
UPDRS IV		5 ± 3.4 (0-17)
Dementia	yes 201 (39.8%)	
	no 304 (60.2%)	

Abbreviations: MMSE: Mini-mental status scale, UPDRS: Unified Parkinson's disease rating scale; PDD: Parkinson's disease dementia; MSA: Multiple system atrophy, PSP: Progressive supranuclear palsy, CBD: Corticobasal degeneration; LBD: Lewy body dementia; SD: standard deviation

Results

Patient and Caregiver Characteristics

The sociodemographic and clinical characteristics of patients and their caregivers are shown in Table 1 and 2. The majority of caregivers were the spouse or life partner of the patient (71.2%), and 67% were living with the patient at home. Twenty three percent of caregivers were in employment. The severity of patients' motor and non-motor symptoms is seen in Table 1 and supplementary Table 1. Caregivers' characteristics can be seen in Table 2.

Extend of Caregiving

On average, caregivers reported spending 6.7 (±6.6) hours per day and 23.1 (±10.6) days per month assisting with tasks of daily living (food preparation, housekeeping, shopping, transporting, administering medications, managing financial matters). Caregivers also reported spending 7.6 (±8.2) hours per day supervising the patient, in order to prevent dangerous events. Most caregivers (63.9%) undertook at least 40% of care of the patient and half (46.7%) more than 80% of the care (among all informal and professional care). Approximately half of the caregivers (54.21%) reported that they had assistance from others, mainly another family member or friend. Additionally, almost half of the caregivers (49.2%) reported assistance from professional services such as day or night care, cleaning service, food delivery, care-related transportation. The caregivers, who did not live with the patient (N = 132), reported spending 1.68 (±2.5) hours per day assisting and 1.82 (±4) hours per day supervising the patient. Ninety percent

Table 2. Caregivers' Characteristics.

		Mean ± SD or n (%)
Relationship to patient (N = 410*)	spouse/ life partner	292 (71.2%)
	child	92 (22.4%)
	other family member	19 (4.6%)
	friend/ neighbor	7 (1.7%)
Employment (N = 395*)	active	92 (23.3%)
	housewife	27 (6.8%)
	retired	247 (62.5%)
	unemployed	29 (7.3%)
Living with patient (N = 412*)	yes	276 (67%)
	no	134 (32.5%)
	occasionally	2 (0.5%)
EQ5D3 L		
Problems with mobility	no	353 (76.2%)
	moderate	106 (22.9%)
	severe	4 (0.9%)
Problems with self-care	no	426 (92%)
	moderate	26 (5.6%)
	severe	11 (2.4%)
Problems with usual activities	no	349 (75.7%)
	moderate	94 (20.4%)
	severe	18 (3.9%)
Problems with pain/ discomfort	no	191 (41.4%)
	moderate	237 (51.4%)
	severe	33 (7.2%)
Problems with anxiety/ depression	no	252 (54.5%)
	moderate	189 (40.9%)
	severe	21 (4.6%)
EQ-VAS		73.1 ± 19.5

Abbreviations: EQ5D3 L: measure of health status, EQ-VAS: visual analog scale, SD: standard deviation. *the different N number is due to missing data

of the caregivers (90.7%), who did not live with the patient, visited the patient at least once a week (often several times a day) and 53.5% called them on the phone between once a week and several times a day. The majority of caregivers not living with the patient (70%) were from 5 to more than 24 hours a week in contact with the patient (personally or on the phone). Out of the caregivers who were working (employed or self-employed, N = 92), 36 (39%) were absent from their job at least 1 day in the last month and 6 (6.5%) had to change or reduce their work during the last 3 months because of the patient's care.

Regarding care provision across the different countries caregivers spent statistically significantly more hours assisting the patient in Germany (9.39 ± 7.78), the UK (8.23 ± 7.14), and France (7.99 ± 5.37) than in Sweden (3.08 ± 3.27) and the Netherlands (3.02 ± 4.41) ($p < 0.001$). Caregivers in Germany spent statistically significantly more hours supervising the patient (12.07 ± 9.17) than in the other countries ($p < 0.001$), while there was no statistically significant difference with regard to the years of caregiving across countries. Caregivers in France, Sweden and the Netherlands received statistical significantly more professional care (78%, 64%, 56.5% of caregivers respectively) compared to the United Kingdom and Germany (42.7% and 34.6% respectively) (χ^2

= 38.380, $p < 0.001$). Moreover, in all countries except for the Netherlands most caregivers were retired ($\chi^2 = 58.098$, $p < 0.001$). In the UK, Germany, Portugal and France caregivers were living more frequently with the patient (85.4%, 81.1%, 77.8%, 65.8% of caregivers respectively) compared to the Netherlands (32.3%) and Sweden (55.6%) ($\chi^2 = 62.627$, $p < 0.001$), where the patients' residential status was more often a nursing home than own home (66.2% and 35.5% of patients in Netherlands and Sweden respectively were living in nursing homes versus 11% in the UK, 6.3% in Germany, 26.7% in Portugal and 27.4% in France)($\chi^2 = 93.891$, $p < 0.001$).

Caregiver's Health Status

On the EQ-5D-3 l, 58.7% reported pain/discomfort, 45.5% anxiety/depression, 23.8% problems with mobility themselves, 24.3% problems with usual activities and 8% with self-care. Their mean health state score on the visual analog scale was 73.1 ± 19.5 (Table 2).

Burden of Caregiving

Five hundred and six caregivers completed the ZBI with a mean score 31.3 ± 16. There was no significant difference of ZBI score among the 6 European countries, except for a marginally higher caregiver burden in France compared to the Netherlands (mean ZBI score 35.11 vs 26.31, $p = 0.06$). For those still living with the patient at home (374 caregivers), the mean ZBI score was 32.47 ± 15.76. Among the most frequently endorsed statements at least some of the time were:felt feeling that the patient depends on them (93.8%), being afraid what the future holds for the patient (90.3%), feeling burdened in caring for the patient (81.8%) and not having enough time for themselves (80.5%). More than 70% (77%) felt stressed between caring for the patient and trying to meet other responsibilities for family or work, that their relative expects them to take care of them as the only one they could depend on (71%) and that their social life and own health suffered because of their involvement with the patient's care (71.4% and 67.1% respectively). At least some of the time many (65.5%) also felt uncertain about what to do about the patient, that the patient asks for more help than they needed (61.8%) and felt strained or angry when they were around the patient (63.5% and 61.3% respectively). Approximately 60% (61.5%) felt at least some of the time that they don't have as much privacy as they would like because of the patient, 61.2% felt at least sometimes that they should be doing more for the patient and 52.3% wished at least sometimes that they could leave the care of the patient to someone else. Moreover, half (51%) reported having at least sometimes felt embarrassed over the patient's behavior, 41.3% that the patient currently affects their relationships with other family members or friends in a negative way but only 27.5% ever felt uncomfortable about inviting friends at home because of the patient. Lastly, 47.9% felt at least sometimes they don't have enough money to take care of the patient. The caregivers'

Table 3. Associations of Zarit Burden Interview Score With Patients' Characteristics.

	ZBI	p-value
age	r = -0.09	p = 0.05*
gender	U = 24057 (male)	p < 0.0001*
residential status	U = 20466.5 (home)	p = 0.003*
disease duration	r = 0.002	p = 0.96
age of onset	r = -0.06	P = 0.21
UPDRS total	r = 0.16	p < 0.0001*
UPDRS I	r = 0.25	p < 0.0001*
UPDRS II	r = 0.21	p < 0.0001*
UPDRS III	r = 0.08	p = 0.08
UPDRS IV	r = 0.05	p = 0.3
Hoehn and Yahr score	r = 0.02	P = 0.73
Schwab and England scale	r = -0.17	p < 0.0001*
MMSE	r = -0.16	p = 0.005*
Charlson index	r = 0.05	p = 0.35
NMS total score	r = 0.28	p < 0.0001*
Domain 1 (cardiovascular, falls)	r = 0.15	p = 0.001*
Domain 2 (sleep/fatigue)	r = 0.18	p < 0.0001*
Domain 3 (mood/cognition)	r = 0.22	p < 0.0001*
Domain 4 (hallucinations)	r = 0.18	p < 0.0001*
Domain 5 (attention, memory)	r = 0.26	p < 0.0001*
Domain 6 (gastrointestinal system)	r = 0.14	p = 0.003*
Domain 7 (urinary symptoms)	r = 0.14	p = 0.002*
Domain 8 (sexual function)	r = 0.05	p = 0.33
Domain 9 (miscellaneous)	r = 0.09	p = 0.04
NPI total score	r = 0.38	p < 0.0001*
NPI A (delusions)	r = 0.15	p < 0.0001*
NPI B (hallucinations)	r = 0.19	p < 0.0001*
NPI C (agitation/aggression)	r = 0.23	p < 0.0001*
NPI D (depression/dysphoria)	r = 0.17	p < 0.0001*
NPI E (anxiety)	r = 0.17	p < 0.0001*
NPI F (elation/euphoria)	r = 0.07	p = 0.10
NPI G (apathy/indifference)	r = 0.23	p < 0.0001*
NPI H (disinhibition)	r = 0.22	p < 0.0001*
NPI I (irritability/lability)	r = 0.21	p < 0.0001*
NPI J (aberrant motor behavior)	r = 0.15	p = 0.001*
NPI K (sleep and nighttime behavior disorders)	r = 0.09	p = 0.047*
NPI L (appetite, eating changes)	r = 0.08	p = 0.08

Abbreviations: NMSS: non-motor symptom scale, NPI: neuropsychiatric inventory; Pearson or spearman correlations (r) depending on normality of variables, U: Mann-Whitney test, χ^2: Kruskal-Wallis test, *p < 0.05

Table 4. Associations of Zarit Burden Interview Score With Caregivers' Characteristics and Care Provided.

	ZBI	p-value
Relationship with patient	$\chi^2_{(3)}$ = 24.6 (spouse/life partner)	p < 0.0001*
Hours per day assisting the patient	r = 0.33	p < 0.0001*
Days per month assisting the patient	r = 0.21	p < 0.0001*
Hours per day supervising the patient	r = 0.37	p < 0.0001*
Assistance from others	U = 18802.5	p = 0.21
EQ5D3 L mobility	r = 0.03	p = 0.6
EQ5D3 L self-care	r = - 0.11	p = 0.81
EQ5D3 L usual activities	r = 0.18	p < 0.0001*
EQ5D3 L pain/discomfort	r = 0.21	p < 0.0001*
EQ5D3 L anxiety/depression	r = 0.37	p < 0.0001*
EQ-VAS	r = - 0.27	p < 0.0001*

Abbreviations: Pearson or spearman correlations (r) depending on normality of variables, U: Mann-Whitney test, χ^2: Kruskal-Wallis test, *p < 0.05

strongest correlations with caregiver burden were seen for agitation/aggression (r = 0.23, p < 0.0001), followed by apathy/indifference (r = 0.23, p < 0.0001), disinhibition (r = 0.22, p < 0.0001) and irritability/lability (r = 0.21, p < 0.0001). With regard to NMSS domains, we found significant correlations of ZBI score with all domains except for sexual function, with the strongest correlations for attention/memory (r = 0.26, p < 0.0001) and mood/cognition (r = 0.22, p < 0.0001). ZBI scores also correlated weakly with MMSE, Schwab and England score and with both UPDRS I (Mentation, Behavior and Mood) and II (Activities of Daily Living) (r = 0.25, p < 0.0001 and r = 0.21, p < 0.0001 respectively) scores. However, there was no correlation with Hoehn and Yahr stage, UPDRS III (Motor Examination), UPDRS IV (dyskinesias and motor fluctuations) scores, disease duration or the Charlson comorbidity index. Caring for a male patient was associated with higher ZBI (U = 24057, p < 0.0001, with median ZBI scores 34 for male patients versus 26 for female), but there was no ZBI difference between the patient groups with different diagnoses (PD, atypical parkinsonism, vascular parkinsonism). Caregivers of patients living at home had increased burden compared to those living at nursing home (U = 20466.5, median ZBI score 32 versus 25, p = 0.003).

Among caregiver-related variables, being the spouse as caregiver was associated with higher ZBI scores (median ZBI 34.5) as compared to being the child (median ZBI 26), other family member (median ZBI 18) or friend/neighbor (median ZBI 17) (Kruskal-Wallis test = $\chi^2_{(3)}$ = 24.64, p < 0.0001, N = 410). ZBI score also increased with hours per day (r = 0.35, p < 0.0001, N = 367) and days per month assisting the patient (r = 0.21, p < 0.0001, N = 378) as well as hours per day supervising the patient (r = 0.37, p < 0.0001, N = 360). ZBI score correlated moderately with caregiver's EQ-5D-3 L subscores for depression/anxiety (r = 0.37, p < 0.0001) and

answers to the ZBI questions can be seen in supplementary Table 2.

Correlates of Caregivers' Burden

The correlates of ZBI scores with patient and caregiver variables are shown in Tables 3 and 4. On patient-related variables, ZBI scores correlated most strongly with the total NPI score (r = 0.38, p < 0.0001) followed by the total NMSS (r = 0.28, p < 0.0001). Among the neuropsychiatric symptoms, the

Table 5. Multiple Regression for Determinants of Caregivers' Burden.

Variables	R^2 change*	Unstandardized coefficients	Standard error	Standardized coefficients (beta)	t	p
NPI	0.147	0.353	0.051	0.331	6.903	<0.001
Gender (male)	0.039	5.516	1.350	0.172	4.085	<0.001
Residential status (home)	0.024	6.471	1.560	0.178	4.148	<0.001
NMSS	0.023	0.051	0.014	0.176	3.648	<0.001

Abbreviations: NPI: neuropsychiatric inventory; NMSS: Non motor symptom scale
*R^2 for model comprising NPI total score, patient's gender (male), residential status (living at home) and NMSS score: 0.233

weakly with the subscores for pain/discomfort (r = 0.21, $p < 0.0001$) and for usual activities (r = 0.18, $p < 0.0001$). There was also a negative weak correlation with EQ-VAS scores (r = -0.27, $p < 0.0001$) but no significant correlations with the EQ-5D-3 L subscores for mobility or self-care.

Determinants of Caregivers' Burden

We performed a stepwise multiple regression analysis with ZBI score as dependent variable entering the variables that showed significant associations with ZBI score as independent variables. After excluding collinearity between the variables with both the variance inflation factor (<3) and tolerance (>0.2), we performed a multiple regression analysis within the subset of patients for which data with less than 10% missing data were available (N = 445). The results showed that a model comprising NPI total score, patient's gender (male), residential status (living at home) and NMSS score could explain 23.3% of the total variance of the ZBI score (R^2 = 0.233, $p < 0.0001$; Table 5). The predictor contributing the most to ZBI score was the NPI total score, which explained 14.7% of the variance.

Discussion

In this study, we found that caregivers of patients with late-stage parkinsonism experience considerable burden across physical, emotional and social aspects. High caregiver burden in PD, which increases as the disease progresses, has been reported previously.[8,29-31] The mean ZBI in this sample was higher than in patients with other physical disabilities and mild to moderate dementia[32] and comparable or higher to that in caregivers of patients with more severe cognitive impairment.[32,33] Caregivers, who were in the great majority the spouse or life partner and living with the patient at home, reported spending on average 6.7 hours a day assisting the patient with activities and 7.6 hours supervising them. Only half received other informal or professional assistance for the patient's care. The percentage of caregivers receiving formal care assistance from professional services (49.2% overall, 42.7% in the UK) was higher than in a recent cohort of patients with advancing PD and their caregivers in the UK[34,35] (26.16%), which might be attributed to the different assessment of formal help, which was reported separately for personal care and domestic care in the study by Hand and others.[34] Moreover, caregiving hours were lower in the present study

(6.7 ± 6.6 hours per day, 8.2 ± 7.1 in the UK) than in the study of Hand and others (median 16),[34] which may also be due to discrepancies in definition (for example the study of Hand et al[34] included companionship activities among caregiver's tasks) as well as perception of caregiving by participants. Direct comparisons between these studies are therefore difficult and the different estimates of hours of informal caring and percentage of formal care may be due to differences in assessment. With regard to differences across countries, caregivers of the 6 countries had comparable ZBI scores. It is noteworthy that caregivers in Sweden and the Netherlands were less often living with the patient, spent fewer hours assisting the patient in daily living and received more frequently formal care assistance compared to the other countries. This may reflect differences in recruitment between participating centers but may also suggest different cultural perceptions of caregiving and attitude to nursing homes as well as the increasing development of modern nursing homes with person-centered care in these northern European countries.[36,37]

The majority of caregivers (approximately 80%) felt stressed between caring for the patient and trying to meet other responsibilities, and felt that their social life or own health had suffered because of their involvement with the patient's care. Of note, almost half of the caregivers experienced anxiety and depression, a finding also reported in previous studies.[8,9,38-40] Caregiving for a person with a neurodegenerative disease is a chronic life stressor, causing feelings of isolation and grieve for the disruption of the caregivers' previously active lifestyle and family or relationship dynamic.[41] Additionally, because of the changes that caregivers' experience in their social or professional life, they often encounter feelings of frustration or uncertainty about the future.[42] In this study, these affective symptoms were associated with higher caregiver burden, as in many other previous studies.[40,43-46] They may be a consequence of the burden of caring or, alternatively, depression and anxiety may induce pessimism and burden of caregiving may be experienced as greater.[6] More than half of the caregivers reported pain or discomfort and to a lesser extent problems with mobility or usual activities themselves. It has previously been found that, caregivers report physical symptoms more frequently than non-caregiving individuals.[30,47] Apart from the increasing physical care of the patient in late stages of the disease (requiring feeding, lifting and transferring of the patient), advanced age of most caregivers, comorbidities as well as psychological distress may contribute to poorer physical health.[48,49]

The clinical features of PD most closely associated with increased caregiver burden were the patients' non-motor symptoms but no strong relationship with motor problems was found. This however needs to be considered in the context of a study where all patients were in the late stages of the disease. Nevertheless, non-motor symptoms have also previously been reported to make a greater contribution to caregiver burden with only weak associations with motor scores or complications in early and middle PD stages.[50-52] Particularly, the importance of neuropsychiatric symptoms and their contribution to caregiver burden has also been reported previously.[13,40,50,53-55] Among the neuropsychiatric symptoms, the strongest associations were found with apathy, agitation/aggression, disinhibition and irritability of the patient in our study. Apathy, which includes loss of interests, motivation and empathy, can affect the relationship with the caregiver by reducing the emotional feedback received by the caregiver[6] or being misinterpreted as an act of non-engagement.[41] This can cause negative feelings to the caregiver and strain the spousal dynamic.[41] Disinhibition such as impulsive behavior or hypersexuality as a result of the dopaminergic treatment is another neuropsychiatric feature that has been linked to caregiver burden.[56] Bruno et al[56] reported high rates of both physical and sexual aggression directed against the caregiver in advanced PD. The cause of aggression is likely multifactorial including cognitive decline, depression, anxiety, loss of independence and medication effects. These behaviors apart from the psychological strain, can make the caregiver (spouse or life partner) question the marital relationship or partnership.[41] We also found a correlation of caregiver burden with the attention/memory and mood/cognition domains of the NMSS. Almost 40% of the patients had a concurrent diagnosis of dementia based on clinical diagnostic criteria,[57] which is a common complication of advancing PD.[58] A number of studies[50,54,59,60] have stressed the contribution of patient's cognitive impairment to caregiver's burden. The executive dysfunction of patients can lead to caregivers taking on complex cognitive tasks (such as finances or planning), with increased time demands and distress.[41] Sleep and nighttime behavior disorders are also a common non-motor problem in PD,[61] reported for almost half of the patients in the present study (suppl. Table 1). Caregiver's sleep quality is frequently disturbed due to insomnia, sleep fragmentation, hallucinations or disturbed motor activity such as REM behavior disorder and Restless Leg Syndrome of patients,[61] requiring additional night time care.[41] In keeping with previous reports that PD patients' sleep quality affects caregivers' mood, quality of life and burden.[39,62] we found significant correlations of patients' sleep disturbance as assessed on the NMSS with caregiver burden.

Caring for a male patient was associated with higher burden among caregivers in the present study. This may be due to greater physical demands of care for a male patient but possibly also to the disinhibition such as impulsive behavior or hypersexuality, which is more common in male patients.[58,63] As expected, burden was higher among caregivers of patients still living at home as opposed to caregivers of patients living in a nursing home, as in those living at home the caregiver is the main assistance in daily living. Increased caregiver strain is a strong predictor of patient's institutionalization,[64,65] and the reduced burden of caregivers of PD patients living at nursing homes may reflect the alleviation of caregiver's "burnout."[64] This is supported by the significantly lower number of hours of caregiving reported by caregivers of those living in nursing homes in our study. We found that the hours assisting and supervising the patient were important contributors to caregiver burden. While studies reported inconsistent findings regarding hours of caregiving as predictor for burden ranging from no correlation[45,52] to a weak or moderate correlation,[30,46,66] the meta-analysis of Lau and Au[55] showed that caregiver burden was determined by the intensity of caregiving, measured by the number of caregiving hours and years. In the present study there was no difference of ZBI scores between the patient groups with different diagnoses (PD, atypical parkinsonism, vascular parkinsonism), but the number of patients with atypical parkinsonian disorders was small.

As only 23.3% of the total variance of the caregivers' burden was explained from the patient and caregiver characteristics assessed i.e. NPI total score, patient's gender (male), residential status (living at home) and NMSS score, it is likely that other factors—personal, cultural or social—contribute to caregivers' burden such as caregivers' comorbidities and social support, which should be explored in separate studies. Indeed, caregiver burden is a general term that reflects the impact of caregiving on persons from different backgrounds and with different levels of resilience and resources.[6] Goldsworthy and Knowles in their stress-appraisal model[67] acknowledge that apart from disease factors, which act as primary stressors for the caregiver, individuals (caregivers) respond differently to the patient's disease undergoing 2 levels of stress-appraisal i.e. cognitive, emotional, behavioral processes, which help them cope with the stressful event. Perceived positive aspects of caregiving such as the intimacy of the caregiving relationship,[67] the feeling of being useful and able to manage difficult situations,[46,60] the caregiver's personality traits,[68] self-esteem[67] and perceptions in life seem also to be important predictors of caregiver burden. We did not assess these factors which are likely to influence the degree of caregiver strain in addition to the factors that we assessed.

Strengths and Limitations

This is the largest and most comprehensive study of caregiver burden in late-stage PD to our knowledge, providing new information not only on the amount of care provided by informal caregivers, but also on the factors that contribute the most to the caregiver burden. Strengths of the study include the large patient and caregiver sample, the multicenter design protocol and the use of a wide range of standardized validated measures for the assessment of PD and caregivers. One limitation of this study is that caregiver burden was assessed using the ZBI, which although being an established validated caregiver burden measure, is not a PD-specific questionnaire such as the

Parkinson's Disease Caregiver Burden questionnaire (PDCB)[69,70] or an instrument relevant for patients with advanced parkinsonism such as the Parkinsonism Carers Quality of Life (PQoL Carer).[71] It cannot be excluded that some parkinsonism-specific issues were missed through the use of the ZBI, which may account for the discrepancy with other studies.[10,48] Another limitation of the study is that only age and gender of the patient and not age and gender of the caregiver were included in the analysis. However, we used patient age and gender as proxies. Furthermore, some caregivers' variables had missing data (<20%), which is inevitable in such large participants samples. However we feel that this did not affect the overall results as these variables were not entered in the multiple regression model and replaced by equivalent ones (e.g. cognition domain of the NMSS instead of MMSE). Particularly, MMSE could only be completed by 315 patients and it is likely that those patients with worse cognition were more likely not to complete this test. Moreover, there were differences between ZBI responders and non-responders in terms of relationship with the patient and assistance received from others.

This study gives insights into the needs of patients with an advanced neurodegenerative disease and their caregivers, which may inform interventions in clinical practice. Non-motor symptoms should be addressed with focus on those being the most bothersome for both patient and caregiver. Of particular importance are the identification and treatment of neuropsychiatric symptoms, to improve patient but also caregiver burden. Non-pharmacological management of neuropsychiatric symptoms[72] could be implemented by caregivers' interventions, including counseling, demonstration of de-escalation techniques and psychoeducation regarding neurobehavioral changes.[56] The high caregiver burden in the late stages, especially for the spouse or life partner, identifies them as an important group to consider for interventions in their own right. For example, cognitive behavioral therapy for the caregiver focusing on pleasant activity scheduling, relaxation techniques, sleep improvement, identifying and avoiding negative thoughts have been reported to have positive effects on their burden.[73] Goldsworthy and Knowles proposed coping mechanisms such as social support, ameliorating quality of patient-caregiver relationship or breaks in caregiving.[67] The aim of these interventions is to help caregivers adapt their perception and behavior to the changes in their life caused by the patient's disease.

Our findings have implications in organizing targeted management of symptoms in patients with late-stage parkinsonism, in order to improve patients' and caregivers' quality of life. The close links between patients' disease characteristics and caregiver burden suggest a complex physician-patient-caregiver system, so that interventions should involve both patient and caregiver. Patients in the late stages are also increasingly dependent on health systems and caregivers require special education on the associated features and treatment to support the patient and navigate the healthcare and social system. From a societal perspective, effective caregiving not only contributes to the management of the disease-related problems but has also financial benefits by substantially reducing health care costs such as hospital admissions, polypharmacy and delaying institutionalization of the patient.[74] Patients with late-stage parkinsonism have special needs requiring the engagement of multiple specialties (especially neurology, psychiatry, internal medicine, geriatrics) and palliative care services (hospice and nursing service, advanced care such as feeding and airway management, end-of-life planning).[5] Thus, it is essential to have an interdisciplinary network of care to address all their medical issues in a holistic, individual-tailored based concept[75] providing sufficient support for them and their caregivers.

Appendix A

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Supplemental Material

Supplemental material for this article is available online.

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