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Impact of complications and comorbidities on treatment costs and health-related quality of life of patients with Parkinson's disease

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ABSTRACT

Background: Data regarding both drug-related and non-drug-related costs in patients with Parkinson's disease (PD) are scarce, mainly due to the difficulties in data acquisition in experimental designs. Likewise, the reported impact of drug costs on total direct costs varies across different studies. In addition, the influence of comorbidities on both treatment costs and health-related quality of life has not been adequately evaluated.
Methods: A sample of office-based neurologists (n = 315) in Germany was asked to examine up to five consecutive patients with PD (n = 1449) on a specified day during the study period. Patients of all ages were eligible and their evaluation was performed using standardized questionnaires.
Results: PD-specific therapy costs increased with the stage of the disease, early onset of the disease and disease duration. The major costs were due to PD-related therapy, whereas other medications only resulted in minor costs. Disease stage mainly influenced direct therapy costs, with an observed increase of total daily costs from €7.3 to €11.3/day. In addition, disease onset at age <65 years resulted in total daily costs of €11.2 compared to late onset of disease (>75 years) with daily therapy costs of €5.3. In this patient group neuropsychiatric comorbidities such as dementia and depression were only insufficiently treated. In addition, these comorbidities severely affected health-related quality of life.
Conclusion: Therapy costs were influenced by disease stage, disease onset as well as present comorbidities. Furthermore, comorbidities such as depression and dementia were diagnosed but were not adequately treated.

1. Introduction

During the past century life expectancy has substantially increased in industrialized nations. While this is certainly gratifying, the ongoing aging of our society means that age-related diseases will have an increasing economic impact on national healthcare systems. This is especially true for chronic neurodegenerative disorders such as Parkinson's disease (PD). PD affects 1 to 2 out of 100 people aged 65 years and nearly 10% of people older than 80 years [1]. Recent projections suggest that the number of individuals with PD over the age of 50 will probably double by the year 2030 [2,39]. Moreover, the course of illness in PD can be aggravated by motor complications, such as motor fluctuations and dyskinesias, and by a number of non-motor complications, including psychiatric comorbidities, gastrointestinal symptoms and sleep disorders, which require additional demanding intervention strategies [3,4]. All of these complications can have a considerable impact on the economic burden of the disease, especially through the requirements of additional and complex therapeutic interventions (e.g., for motor complications and depression, and deep brain stimulation), additional in-patient stays (e.g., for patients suffering hallucinations) or premature nursing home placement (e.g., psychosis) [5].

Although a number of studies have already evaluated the cost of illness in different countries [6], studies dealing with therapy costs in an office-based setting are relatively scarce and partly inconclusive [7]. Regarding the share of drug costs in the total cost, previous results from different studies varied from 20% in European investigations to up to more than 65% in a Chinese study [8]. Most reports suggest a strong association between the severity of PD and the expenses for disease-related medications, i.e., with disease progression, the drug costs increase by up to twice as much in advanced patients compared to patients in the early stages of the disease [9]. Similar associations have been found for motor complications, with their occurrence considerably increasing the cost of treating PD.

Although PD patients frequently develop non-motor comorbidities, which influence quality of life [10], the economic impact of

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concomitant dementia and behavioral and psychological symptoms in PD outpatients has not been systematically investigated to date. This study, which was based on an epidemiological survey involving office-based neurologists, focuses on the daily costs of PD treatment and the economic burden as well as the impact of non-motor complications such as dementia and depression.

2. Methods

2.1. Study design and recruitment procedure

The study design and recruitment procedure of the German Study on the Epidemiology of Parkinson's Disease with Dementia (GEPAD) have previously been reported in detail [11,12]. Briefly, the primary goal of GEPAD was to estimate the prevalence of dementia and cognitive impairment among PD patients treated in the outpatient care-sector. Data were derived from a random sample of PD outpatients (n = 1449) who attended a representative sample of office-based neurologists (n = 315) in Germany on a specified day during the study period of September to October 2005. Patients of all ages and PD severity stages were eligible. Primary exclusion criteria were the patient's inability to read or write, severe cognitive impairment that precluded the application of the assessment or further logistical reasons preventing the examination (e.g., acute severe pain or medical emergencies).

Eligible PD patients visited the respective neurologists (n = 1749 in total) on the study day; 300 patients were excluded from assessment by the physicians (89 for lack of consent, 39 for too severe impairment, 139 for logistical problems, and 33 for other reasons, for example language problems or sensory deficits). No clinical data were available for these patients. Thus, 1449 patients were included and examined according to the study protocol (overall participation rate: 82.3%). All patients included fulfilled the NINDS criteria for possible PD [13]. Moreover, n = 873 of these patients also met the UK Brain Bank criteria for PD [14]. As previously reported by Riedel et al., the subgroups of patients did not differ in terms of age ($p = 0.140$), gender distribution ($p = 0.196$) or the primary study outcome variables, as described in the next section (i.e. frequency of dementia ($p = 0.761$), MMSE score ($p = 0.409$) or MADRS score ($p = 0.761$)) [15]. Therefore, we included the entire sample in the analysis of this paper. All PD patients were rated in the "on" stage. The local ethics committee reviewed and approved the study protocol (EK No. 140082005). Written informed consent was obtained from all participating patients or their caregivers.

2.2. Study material

Each patient was evaluated by the neurologist with a questionnaire that consisted of three parts. Part A documented sociodemographic information. Part B was related to the documented PD status, including the Hoehn and Yahr Scale (HY) [16] and the Unified Parkinson's Disease Rating Scale (UPDRS) [17]. Furthermore, the presence of neurological, neuropsychiatric or somatic symptoms was recorded. Each physician was also asked to list their patients' current intake of PD-related drugs as well as any other medication. All agents were recorded in terms of daily dosage. Part C featured ratings of the cognitive level of functioning and depressive disorders. Cognitive impairment was assessed using the Mini-Mental State Examination (MMSE) and was rated as "none" (scores of 25–30), "mild" (21–24), "moderate" (11–20) or "severe" (0–10) [18]. The diagnosis of dementia was based upon the corresponding DSM-IV criteria, using a structured symptom list [19,20]. Depression was screened with the Montgomery-Asberg Depression Rating Scale (MADRS), using a cut-off score of ≥ 14 as an indicator of depressive symptoms [21]. Each patient was also administered the EQ-5D in order to assess their health-related quality of life [22].

2.3. Drug cost calculation

Daily therapy costs were calculated for each patient based on their documented medication. The dosage and dose per day were documented in the patients' questionnaire. Costs for prescription medications were obtained from the official German drug price list ("Rote Liste", 2006) and included a deduction according to the German social security code [23]. Only PD-specific drugs and drugs used to treat PD complications were included in the calculation. The costs were calculated in Euros (€). The total costs (direct and indirect costs) were calculated from the statutory healthcare perspective.

2.4. Statistical analyses

Statistical analyses were performed using STATA Version 10.1 (StataCorp, 2008). The cost data are presented as median, arithmetic mean, standard deviation and 95% confidence intervals of the mean. The median cost can be interpreted as the typical cost per patient while the mean cost multiplied by the number of patients describes the total cost. Cost data are usually highly skewed and standard, non-parametric or normalizing methods are often not appropriate [24]. The bootstrap technique provides an appropriate and flexible approach for presenting and comparing skewed cost data. Bootstrap confidence intervals of 95% were calculated using the bias-corrected and accelerated percentile method [25]. The number of bootstrap replications B was 1000. Univariate comparisons of cost differences between groups were estimated using a linear regression approach with standard errors estimated by bootstrapping that was defined by potential cost predictors. The total scores of the EQ-5D were calculated using the scoring algorithm for the German population [26]. Differences in predictor variables for quality of life were estimated using a linear regression approach with standard errors estimated by bootstrapping.

3. Results

3.1. Characterization of the study sample

Table 1 provides an overview of the study sample. The mean age of the study population was 70.7 ± 8.4 years and about a third of the patients were female. The mean disease duration was 5.8 ± 5.2 years and, on average, disease onset had occurred when patients were aged 64.8 ± 9.7 years. In 50% of all patients, the age of PD onset occurred before the age of 66, in 37.4% of patients between 66 and 75, and in 12.6% of patients after the age of 75 years. The majority of patients had been suffering from PD for up to 3 years (41.4%), and 4 to 6 years (22%). The disease duration for 36.6% of the patients had been longer than 7 years at the time of the study. The majority of patients were retired (88%, n = 1250), in contrast to 5.5% who were still working; 13.1% claimed that retirement was due to PD and approximately 1% (n = 11) of the patients were unemployed. Furthermore, 72.5% lived in a stable relationship while the remainder were single, widowed or divorced.

3.2. Distribution of different PD medications within the study sample and the distribution of costs

Table 2 shows the distribution of PD medications as stratified by the HY stage. It shows that 75.8% of patients received levodopa. Another 13.6% were receiving levodopa and a COMT inhibitor, so that more than 90% of the patients received levodopa.

Combined levodopa and COMT-inhibitor therapy was also frequently used and increased with advancing disease severity. Among the patients with severe cognitive impairment according to the MMSE (n = 3), all patients received dopamine agonists and levodopa, two were treated with antidepressants, one patient was treated with amantadine and one patient received a neuroleptic drug.

Table 1
Characteristics of the GEPAD study sample (N = 1449).

Variable	Value
Sociodemographics	
Male, N (%)	877 (60.5)
Female, N (%)	572 (39.5)
Age, years (mean ± sd)	70.7 ± 8.4
Marital status, N (%)[a]	
Married	1049 (72.5)
Widowed	269 (18.6)
Single	65 (4.5)
Divorced	64 (4.4)
Occupational status, N (%)[b]	
Retired (total)†	1250 (88.0)
Homemaker	81 (5.7)
Employed	78 (5.5)
Unemployed	11 (0.8)
Clinical characteristics	
Hoehn & Yahr stage, N (%)[c]	
Stage I + II	617 (44.2)
Stage III	540 (38.7)
Stages IV + V	239 (17.1)
Age of PD onset, years (mean ± sd)	64.8 ± 9.7
PD duration, years (mean ± sd)	5.8 ± 5.2
Dyskinesias, N (%)	394 (21.5)
Motor fluctuations, N (%)	494 (34.9)
Gastrointestinal diseases, N (%)[d]	141 (9.9)
Neuropsychiatric characteristics	
Depression (MADRS ≥ 14), N (%)	336 (25.2)
Dementia (DSM-IV criteria), N (%)	407 (28.1)
Cognitive impairment (MMSE ≤ 24), N (%)	224 (15,5)
Hallucinations, N (%)	166 (11.5)
Delusions, N (%)	32 (2.2)

Data missing for [a]N = 2, [b]N = 29, [c]N = 53 patients, [d]N = 18 patients.
†Hereof, N = 139 (15.2%) retired due to PD.

Overall, patients with dementia according to DSM-IV criteria received significantly less frequently dopamine agonists than non-demented patients (55% vs. 71%, p < .001, data not shown), whereas the slightly lower prescription rates in depressed vs. non-depressed patients according to the MADRS did not become significant (63.2% vs. 67.5%, p = .403).

Three patients were subcutaneously treated with apomorphine. Two patients were rated as HY stage III and one was rated as stage IV. None suffered from dementia and all were experiencing motor fluctuations. Daily treatment costs for these patients amounted to a mean of €37.9. When calculating the drug costs for the entire group, these patients were excluded as they would have considerably distorted the data of the other patients.

3.3. Treatment patterns and costs due to psychiatric complications

The drug costs stratified by drug group, comorbidity and disease stage are compiled in Table 3. The main costs were due to PD-related drugs (~86%); only minor costs were contributed by antidementia drugs (4.6%), central nervous system (CNS) drugs (2.3%) or other medications (7.0%). Motor fluctuations, dyskinesias and advanced disease stage (HY stage/PD duration) significantly increased treatment costs. The presence of any of these led to a near doubling of both total and PD-associated daily costs. Young onset of disease was a cost-driving factor in this study, with significantly lower total costs occurring in patients with a disease onset after the age of 76 years (€5.3/day) in contrast to patients with a disease onset at <65 years (€11.2).

Daily PD drug treatment costs decreased in patients with dementia or depression. Only 91 patients (6.3%) received antidementia drugs, although 224 patients (15.5%) suffered from cognitive impairment according to the MMSE (≤24). The distribution of dementia drugs depending on the MMSE is shown in Table 3. The costs of antidementia drugs increased in univariate analyses according to age, disease stage and PD duration; however, the extent of cognitive impairment had a minor influence on costs. In the multivariate

Table 2
Distribution of medication used in the GEPAD study sample (N = 1449).

	Total		Disease status by Hoehn and Yahr[a]						Cognitive impairment (MMSE-score)						Depression (MADRS score)			
			I + II		III		IV + V		None (30–25)		Mild (21–24)		Moderate (20–11)		No (≤13)		Yes (≥14)	
	N = 1449		N = 617		N = 540		N = 239		N = 1068		N = 130		N = 63		N = 1036		N = 345	
	N	%	N	%	N	%	N	%	N	%	N	%	N	%	N	%	N	%
No medication/no response	62	4.3	25	4.1	19	3.5	12	5.0	42	3.9	2	1.5	3	4.8	46	4.4	13	3.8
Amantadine	417	28.8	139	22.5	192	35.6	69	28.9	335	31.4	37	28.5	14	22.2	305	29.4	89	25.8
Anticholinergics	66	4.6	26	4.2	25	4.6	12	5.0	47	4.4	9	6.9	1	1.6	42	4.1	21	6.1
Antidementia drugs[b]	91	6.3	20	3.2	33	6.1	31	13.0	22	2.1	19	14.6	25	39.7	45	4.3	44	12.8
Antidepressants	293	20.2	101	16.4	125	23.2	57	23.9	217	20.3	27	20.8	20	31.8	134	12.9	154	44.6
Antiemetics	8	0.6	1	0.2	7	1.3	0	0.0	6	0.6	2	1.5	0	0.0	5	0.5	2	0.6
Apomorphine	3	0.2	0	0.0	2	0.4	1	0.4	3	0.3	0	0.0	0	0.0	3	0.3	0	0.0
Benzodiazepine	4	0.3	1	0.2	0	0.0	3	1.3	2	0.2	0	0.0	0	0.0	2	0.2	2	0.6
Betablockers	5	0.4	2	0.3	2	0.4	1	0.4	3	0.3	2	1.5	0	0.0	4	0.4	1	0.3
Budipine	14	1.0	7	1.1	6	1.1	0	0.0	9	0.8	3	2.3	0	0.0	8	0.8	4	1.2
COMT-inhibitor	154	10.6	27	4.4	80	14.8	42	17.6	105	9.8	20	15.4	8	12.7	102	9.9	42	12.2
Dopaminagonists	964	66.5	402	65.2	372	68.9	157	65.7	741	69.4	80	61.5	33	52.4	699	67.5	218	63.2
Gingko biloba	16	1.1	7	1.1	7	1.3	2	0.8	9	0.8	2	1.5	2	3.2	8	0.8	7	2.0
Levodopa	1098	75.8	409	66.3	452	83.7	201	84.1	796	74.5	111	85.4	56	88.9	763	73.7	280	81.2
L-Dopa/COMT	197	13.6	54	8.8	76	14.1	60	25.1	145	13.6	13	10.0	8	12.7	134	12.9	54	15.7
Neuroleptics	21	1.5	3	0.5	8	1.5	10	4.2	11	1.0	2	1.5	3	4.8	9	0.9	12	3.5
Nootropics	12	0.8	4	0.7	3	0.6	5	2.1	6	0.6	1	0.8	3	4.8	7	0.7	5	1.5
Rasagiline	13	0.9	4	0.7	7	1.3	2	0.8	10	0.9	2	1.5	0	0.0	9	0.9	4	1.2
Selegiline	117	8.1	58	9.4	44	8.2	14	5.9	91	8.5	10	7.7	4	6.4	90	8.7	22	6.4
Other[c]	4	0.3	1	0.2	1	0.2	2	0.8	3	0.3	0	0.0	1	1.6	1	0.1	3	0.9
L-Dopa alone	126	8.7	71	11.5	42	7.8	9	3.8	95	8.9	8	6.2	5	7.9	107	10.3	11	3.2
Dopamine agonists alone	88	6.1	76	12.3	5	0.9	4	1.7	69	6.5	3	2.3	0	0.0	80	7.7	6	1.7
L-Dopa and dopamine agonists	228	15.7	111	18.0	80	14.8	28	11.7	175	16.4	20	15.4	6	9.5	182	17.6	33	9.6

[a] N = 1396 valid assessments on disease status; N = 1414 information about fluctuations; N = 1264 valid assessments on MMSE; N = 1381 valid assessments on MADRS.
[b] Prescription of antidementia drugs, cholinesterase-inhibitor or memantine.
[c] Prescription of antiepileptics, heparin, macrogol or antacids.

Table 3
Distribution of drug treatment costs (€) for Parkinson's disease, dementia, other CNS disease and other medication in the GEPAD total sample (patients on apomorphine treatment were excluded).

		Total costs			PD costs			Dementia costs			CNS costs			Other medication costs		
		M ± sd	95% CI	p	M ± sd	95% CI	p	M ± sd	95% CI	p	M ± sd	95% CI	p	M ± sd	95% CI	p
Total		8.7 ± 12.4	8.2–9.6	–	7.5 ± 6.7	7.2–7.9	–	0.4 ± 6.6	0.2–1.2	–	0.2 ± 1.0	0.2–0.3	–	0.6 ± 8.1	0.4–1.6	–
Hoehn & Yahr stage	I + II	7.3 ± 11.6	6.7–8.7	(Ref)	6.5 ± 6.1	6.0–7.0	(Ref)	0.5 ± 10.0	0.1–2.2	(Ref)	0.1 ± 0.5	0.1–0.2	(Ref)	0.2 ± 0.7	0.2–0.3	(Ref)
	III	9.3 ± 14.1	8.6–11.6	*	8.1 ± 6.9	7.7–8.9	*	0.2 ± 0.8	0.1–0.3	n.s.	0.2 ± 0.9	0.2–0.4	*	0.8 ± 12.4	0.2–3.5	*
	IV + V	11.3 ± 10.4	10.1–12.8	*	8.9 ± 7.3	8.1–9.9	*	0.5 ± 1.2	0.3–0.7	n.s.	0.5 ± 1.7	0.4–0.8	*	1.4 ± 7.2	0.7–2.7	*
Cognitive impairment[a]	None	8.8 ± 10.3	8.4–9.7	(Ref)	7.9 ± 6.7	7.6–8.5	(Ref)	0.3 ± 7.7	0.1–1.5	(Ref)	0.2 ± 1.0	0.2–0.3	(Ref)	0.4 ± 2.0	0.3–0.5	(Ref)
	Mild	9.4 ± 25.5	6.9–18.1	n.s.	6.3 ± 5.5	5.4–7.3	*	0.5 ± 1.3	0.4–0.8	n.s.	0.2 ± 0.5	0.1–0.3	n.s.	2.4 ± 24.9	0.2–13.3	n.s.
	Moderate	8.1 ± 6.3	6.6–9.9	n.s.	5.9 ± 5.5	4.6–7.4	*	1.4 ± 2.0	0.9–2.0	*	0.5 ± 1.1	0.3–0.9	*	0.3 ± 0.6	0.1–0.5	n.s.
	Severe	8.2 ± 3.9	4.9–10.7	n.s.	7.3 ± 3.7	5.1–11.5	n.s.	0.6 ± 1 .0	0.0–1.1	n.s.	0.3 ± 0.5	0.3–0.9	n.s.	0.0 ± 00	–	*
Dementia (DSM-IV)	No	9.3 ± 13.9	8.7–10.5	(Ref)	8.1 ± 6.9	7.8–8.7	(Ref)	0.3 ± 7.8	0.0–1.3	(Ref)	0.2 ± 1.0	0.1–0.3	(Ref)	0.7 ± 9.4	0.4–1.7	(Ref)
	Yes	7.3 ± 7.3	6.6–8.0	*	5.9 ± 5.8	5.4–6.5	*	0.6 ± 1.4	0.5–0.8	n.s.	0.3 ± 0.8	0.3–0.4	*	0.4 ± 3.4	0.2–1.2	n.s.
Age of PD onset (years)	≤65	11.2 ± 13.3	10.6–13.1	(Ref)	10.1 ± 7.3	9.7–11.0	(Ref)	0.1 ± 0.6	0.1–0.2	(Ref)	0.2 ± 1.0	0.2–0.4	(Ref)	0.8 ± 11.2	0.3–2.9	(Ref)
	66–75	6.4 ± 6.8	5.8–7.1	*	5.3 ± 4.9	4.9–5.8	*	0.2 ± 0.7	0.1–0.3	n.s.	0.2 ± 0.9	0.2–0.4	n.s.	0.6 ± 4.3	0.3–1.3	n.s.
	≥76	5.3 ± 19.4	3.7–11.8	n.s.	2.9 ± 3.4	2.5–3.5	*	2.0 ± 19.1	0.4–8.2	*	0.1 ± 0.3	0.1–0.1	*	0.3 ± 0.8	0.2–0.4	*
PD duration (years)	≤3	5.6 ± 5.9	5.2–6.2	(Ref)	4.9 ± 5.0	4.5–5.4	(Ref)	0.2 ± 0.8	0.1–0.3	(Ref)	0.2 ± 1.2	0.1–0.4	(Ref)	0.4 ± 2.8	0.2–1.0	(Ref)
	4–6	9.2 ± 6.7	8.5–10.0	*	8.6 ± 6.6	7.9–9.4	*	0.2 ± 0.7	0.1–0.3	n.s.	0.2 ± 0.5	0.1–0.2	n.s.	0.3 ± 1.1	0.2–0.5	n.s.
	≥7	11.8 ± 18.7	10.8–14.4	*	9.7 ± 7.4	9.2–10.6	*	0.7 ± 11.2	0.2–3.2	*	0.3 ± 0.7	0.2–0.3	n.s.	1.1 ± 13.4	0.4–4.7	*
Motor fluctuations	No	6.9 ± 10.2	6.4–7.8	(Ref)	5.8 ± 5.4	5.5–6.2	(Ref)	0.5 ± 8.3	0.2–1.6	(Ref)	0.2 ± 0.8	0.2–0.3	(Ref)	0.4 ± 2.8	0.3–0.7	(Ref)
	Yes	12.1 ± 15.3	11.4–14.6	*	10.4 ± 7.4	10.0–11.4	*	0.3 ± 0.9	0.2–0.3	n.s.	0.3 ± 1.2	0.2–0.5	*	1.1 ± 13.4	0.4–4.1	*
Dyskinesias	No	7.7 ± 13.0	7.1–9.1	(Ref)	6.5 ± 6.0	6.1–6.8	(Ref)	0.4 ± 7.5	0.2–1.3	(Ref)	0.2 ± 0.8	0.2–0.2	(Ref)	0.6 ± 8.9	0.3–1.7	(Ref)
	Yes	12.5 ± 9.3	11.8–14.1	*	11.0 ± 7.6	10.5–12.3	*	0.3 ± 1.0	0.2–0.4	n.s.	0.4 ± 1.4	0.3–0.7	*	0.8 ± 5.2	0.4–1.6	n.s.
Sleep disturbances	No	8.1 ± 12.7	7.4–9.4	(Ref)	6.8 ± 6.2	6.4–7.3	(Ref)	0.2 ± 0.9	0.2–0.3	(Ref)	0.2 ± 0.9	0.1–0.3	(Ref)	0.9 ± 11.1	0.4–2.5	(Ref)
	Yes	9.0 ± 7.9	8.6–9.8	n.s.	8.1 ± 7.1	7.8–8.9	*	0.2 ± 0.8	0.1–0.3	n.s.	0.3 ± 1.0	0.2–0.4	*	0.4 ± 2.8	0.3–0.9	n.s.
Depression[b]	No	8.3 ± 7.2	7.9–8.9	(Ref)	7.6 ± 6.8	7.3–8.2	(Ref)	0.2 ± 0.7	0.1–0.2	(Ref)	0.1 ± 0.6	0.1–0.2	(Ref)	0.4 ± 2.2	0.3–0.6	(Ref)
	Yes	9.5 ± 21.4	7.8–13.0	n.s.	6.6 ± 5.8	6.0–7.3	*	1.1 ± 13.5	0.3–4.2	*	0.5 ± 1.5	0.4–0.8	*	1.3 ± 15.7	0.3–5.2	n.s.

n.s. = not significant; 95% Ci = 95% confidence interval of the mean costs; PD = Parkinson's disease; (Ref) = reference group; M ± sd = mean ± standard deviation.
Hoehn & Yahr: N = 1396 valid observations; Dementia N = 1264 valid observations; onset of PD/PD duration N = 1372 valid observations; motor fluctuations N = 1414 valid observations; dyskinesias N = 1412 valid observations; depression N = 1381 valid observations.

[a] Cognitive impairment: none MMSE 25–30; mild MMSE 21–24; moderate MMSE 11–20; severe MMSE 0–10.

[b] Depression: none MADRS ≤ 13; yes MADRS ≥ 14.

* Significant with $p < 0.05$.

analyses, HY and PD duration were not significant predictors of costs, but age and cognitive impairment were.

Further analyses of drug consumption showed that some drugs which lack current evidence of efficacy for cognition deficits, such as gingko biloba and other nootropics, were found to be used by 2% of the total number of patients. These costs totalled approximately €3.7/day (median value) per patient.

Overall, 336 (25.2%) patients suffered from depression (MADRS ≥ 14). However, only 154 (44.6%) of these patients received antidepressant medication. The total costs were €3/patient per day. The presence of depression led to a considerable increase in treatment costs for CNS medication. The CNS costs increased in patients who showed motor fluctuations and dyskinesias. Therapy costs of CNS drugs also increased with the HY stage as well as with the presence of dementia. Nevertheless, the total costs of these drugs were low compared to PD drug costs.

3.4. Treatment patterns and costs of other non-motor complications

Gastrointestinal comorbidities were noted in 9.9% of the patients. Gastrointestinal medications such as antacids, antiemetics and macrogol (polyethylene glycol, used in chronic obstipation) were used by our patient sample. However, their use was infrequent and only 1% of the patients received these medications. Macrogol, in particular, was taken by patients of advanced age and with HY stage V. The use of antacids was negligible as the majority of patients were not taking any.

Sleep disturbance was mentioned by 49% of the patients in our sample. However, drug consumption showed that only a minority of the patients received specific medication for this.

3.5. Health-related quality of life in patients with PD

The EQ-5D was analyzed based on HY stage, disease duration, motor fluctuations, dyskinesias and comorbidities (Table 4). The EQ-5D varied according to the HY stage, with a considerable reduction seen in the advanced stages of the disease. In patients with HY stage V, the utility value dropped to 0.33 (lower scores indicate poorer quality of life). Age, disease duration and the occurrence of motor complications decreased health-related quality of life (HrQoL).

Comorbidities also influenced HrQoL. The patients who were suffering from cognitive impairment showed a decreasing utility value depending on whether the impairment was mild or moderate: patients with mild dementia did not experience much of a decrease in health-related quality of life (0.61) compared to patients without this cognitive impairment (0.66). However, the progression of dementia to the moderate state led to a rapid decrease in the EQ-5D to a value of 0.48.

Moreover, anxiety, depression and hallucinations had a marked and significant influence on self-reported outcomes. An even greater effect on the EQ-5D values was seen when the presence of depression was further classified into mild, moderate or severe (data not shown).

In the multivariate analyses with respect to psychiatric comorbidities, a major impact was found in patients suffering from depression, severe cognitive impairment and the occurrence of paranoid symptoms. The advent of hallucinations was not a predictive factor. Furthermore, gastrointestinal symptoms and advanced PD stage had a significant impact on HrQoL in PD patients.

4. Discussion

The present study is one of the first to evaluate treatment costs in a large and representative PD sample treated by office-based neurologists in Germany and taking non-motor symptoms and neuropsychiatric complications into account.

4.1. Drug therapy and costs

In the GEPAD study, therapy costs for PD increased from Hoehn and Yahr stages I to III, which reflects increasing disease complexity and demonstrates the need for combined therapy strategies in advanced stages of the disease, usually due to motor complications. Our data indicated a decrease in therapy costs in HY stages IV and V, as was also described by Dengler et al. [27]. According to Dengler, this change can be attributed to a switch in medication from expensive drugs in the early stages to levodopa in the later stages of the disease. In contrast, however, other studies described a continuing increase in therapy costs with advancing disease stage [28,29].

The drug treatment of our older patients showed an inconsistent pattern regarding national recommendations [33]. More than 66% of all patients received dopamine agonists, which are actually indicated for patients younger than 70 years of age. However, only 48.6% of our patients belonged to this age group, therefore indicating a deviation from the recommendations for more than 17% of the patients. On the other hand, we observed an overall change in treatment strategy with increasing age in such a way that older patients were less likely to be treated with dopamine agonists, which is in agreement with the national recommendations.

We observed that COMT inhibitors were frequently used by our patient sample, which also complies with national recommendations, since 34% of all patients suffered from motor fluctuations [33]. In a comparable publication by Möller et al., the percentage of patients who used COMT inhibitors was 20.4%, which is similar to the rate of use found in the present study [30].

Although behavioral and psychological symptoms have been reported to frequently occur in PD patients and have a considerable impact on the well-being and quality of life of these patients, the prescription of drugs in our study did not reflect this. In our cohort, 28.1% suffered from dementia, 25.2% suffered from clinically relevant depression and 11.5% suffered from hallucinations. Antidepressants were prescribed in 20.2% of the patients. However, antidementia drugs were only prescribed in 6.3% and 1.5%, respectively, resulting in less than 7% of the total drug costs. This could partially reflect an often described difficulty in diagnosing depression in patients with PD as there is a substantial overlap between the symptoms of both disorders [34]. Therefore, it seems possible that depression might not be diagnosed on a regular basis in PD patients. This phenomenon was also described by Shulman et al. [35], who found that office neurologists failed to recognize the presence of depression and anxiety in 50% of the total cases. Interestingly, in our study, the diagnosis of depression was frequently made but treatment was not then initiated. However, we did not investigate the number of patients who were not diagnosed, and it is most likely that the number of depressive patients should have been higher, as seen in the study by Shulman et al. [35]. Another interpretation is that the clinician does not make a diagnosis of depression against a background of a severe underlying neurodegenerative disorder, despite increased MADRS scores. Furthermore, the provision of adequate therapy could be hampered by uncertainty over which drug to use as there are insufficient data regarding optimal antidepressive therapy. Only a few randomized controlled trials have tested the efficacy of antidepressants in patients with PD [36].

Another common neuropsychiatric feature is the occurrence of dementia with increasing disease duration. For patients with PD, there is evidence to show the use of cholinesterase inhibitors for this indication, and rivastigmine is licensed in Germany [37]. German guidelines state that the effect is generally modest, but it is significant in 15% of all patients treated [33,38] and the treatment of patients with PD and mild to moderate dementia is recommended. However, there are side effects that need to be considered, such as a transient increase in tremor intensity during the initial dosing phase, as well as the common side effects of cholinesterase inhibitors. Our data

Table 4
Health-related quality of life (EQ-5D) in the sample.

	N	%[a]	EQ-5D total score						
			Mean ± SD	beta[b,c]	95% CI	p-value	beta[b,d]	95% CI	p-value
Age of PD onset, years									
≤65	688	50.2	0.64 ± 0.19	Ref.			Ref.		
66–75	512	37.3	0.63 ± 0.19	−0.02	−0.04, 0.01	0.144	−0.02	−0.04, 0.00	0.056
≥76	172	12.5	0.62 ± 0.18	−0.03	−0.06, 0.01	0.115	−0.02	−0.05, 0.01	0.216
PD duration, years									
≤3	567	41.3	0.67 ± 0.19	Ref.			Ref.		
4–6	301	21.9	0.62 ± 0.19	−0.05	−0.07, −0.02	0.001	−0.02	−0.04, 0.01	0.218
≥7	504	36.7	0.60 ± 0.20	−0.07	−0.10, −0.05	0.000	0.00	−0.03, 0.03	0.905
PD staging (Hoen and Yahr)									
HY I	201	14.4	0.72 ± 0.18	ref.			ref.		
HY II	416	29.8	0.71 ± 0.17	−0.02	−0.05, 0.01	0.293	−0.02	−0.05, 0.01	0.273
HY-III	540	38.7	0.61 ± 0.16	−0.11	−0.14, −0.08	0.000	−0.08	−0.11, −0.05	0.000
HY IV	211	15.1	0.46 ± 0.16	−0.26	−0.29, −0.23	0.000	−0.18	−0.22, −0.13	0.000
HY V	28	2.0	0.33 ± 0.20	−0.39	−0.47, −0.31	0.000	−0.31	−0.42, −0.20	0.000
Motor fluctuations									
No	920	65.1	0.67 ± 0.18	Ref.			Ref.		
Yes	494	34.9	0.56 ± 0.19	−0.11	−0.13, −0.09	0.000	−0.02	−0.05, 0.01	0.193
Dyskinesias									
No	1108	78.5	0.65 ± 0.19	Ref.			Ref.		
Yes	304	21.5	0.55 ± 0.20	−0.10	−0.13, −0.08	0.000	−0.02	−0.05, 0.01	0.252
Depression (MADRS ≥ 14)									
No	1036	74,8	0.67 ± 0.18	ref.			Ref.		
Yes	336	25.2	0.50 ± 0.17	−0.17	−0.20, −0.15	0.000	−0.10	−0.13, −0.08	0.000
Dementia (DSM-IV)									
No	1028	71.9	0.66 ± 0.19	Ref.			Ref.		
Yes	407	28.1	0.56 ± 0.20	−0.09	−0.12, −0.07	0.000	0.01	−0.02, 0.04	0.550
Cognitive impairment (MMSE)									
None (30–25)	1068	84.5	0.66 ± 0.19	Ref.			Ref.		
Mild (24–21)	130	10.3	0.61 ± 0.18	−0.04	−0.08, −0.01	0.009	0.02	−0.01, 0.06	0.211
Moderate (20–11)	63	5.0	0.48 ± 0.19	−0.18	−0.23, −0.13	0.000	−0.05	−0.10, 0.00	0.054
Severe (10–0)	3	0.2	0.63	−0.03	−0.04, −0.02	0.000	−0.03	−0.06, −0.01	0.010
Anxiety									
No	1159	80.4	0.65 ± 0.19	Ref.			Ref.		
Yes	282	19.6	0.54 ± 0.19	−0.11	−0.14, −0.09	0.000	0.01	−0.03, 0.04	0.683
Hallucinations									
No	1272	88.5	0.65 ± 0.19	Ref.			Ref.		
Yes	166	11.5	0.50 ± 0.20	−0.14	−0.18, −0.11	0.000	0.04	−0.03, 0.10	0.290
Paranoid symptoms									
No	1387	96.2	0.64 ± 0.19	Ref.			Ref.		
Yes	55	3.8	0.47 ± 0.20	−0.17	−0.22, −0.11	0.000	−0.03	−0.06, 0.00	0.024
Gastrointestinal symptoms									
No	1290	90.2	0.64 ± 0.19	Ref.			Ref.		
Yes	141	9.9	0.57 ± 0.17	−0.06	−0.09, −0.03	0.000	0.79	0.76, 0.82	0.000

Ref. = reference; SD = standard deviation.
[a] All percentages refer to number of subjects with existing data.
[b] beta = estimated mean difference in EQ-5D estimated by linear regression analyses.
[c] Univariate analyses.
[d] Multivariate analyses.

showed that only 40% of the patients who suffered from moderate dementia received antidementia treatment. Further analyses are required in order to evaluate the prescription regime of patients with PD and dementia and to evaluate the reasons for the effects observed in our study.

In summary, there is a major gap between current recommendations and the treatment patterns in ambulatory care concerning the adequate handling of neuropsychiatric complications in PD. Further studies are necessary in order to identify obstacles and provide adequate treatment of neuropsychiatric complications as these comorbidities – as already mentioned above – are major contributors to the quality of life of these patients.

4.2. Health-related quality of life

There is evidence to show that the choice of antiparkinsonian medication may affect HrQoL. In a recent article, 14 double-blind, placebo-controlled trials were assessed [31]. Several positive results for both COMT inhibitors and dopamine agonists were shown, but the results were ambiguous. A trial by Noyes compared the impact of pramipexole and levodopa on different domains of HrQoL. They showed that the dopamine agonist supported non-motor-symptom-associated improvements, whereas levodopa improved HrQoL by a direct influence on motor symptoms. However, another study by Stocchi et al. examined the effect of levodopa with and without a COMT inhibitor with respect to the development of dyskinesias [32]. In a sample of more than 700 patients they found that combination therapy using COMT inhibitors did not delay the time of onset of dyskinesias compared to standard levodopa treatment. In contrast, combination therapy decreased the time to dyskinesias compared to levodopa treatment alone.

Regarding neuropsychiatric comorbidities, we found a significant reduction in the HrQoL with increasing disease severity. The presence of dementia was both negatively correlated with, and influenced by, the presence of depression [31]. Therefore, adequate treatment is mandatory when patient-reported outcomes are important in the treatment of PD patients.

4.3. Limitations

This study has several limitations. Only office-based neurologists were included and thus the impact of patients treated in other levels

of the healthcare system was neglected in this study. However, it was our primary aim to evaluate therapy costs in an office-based setting as this is how the majority of PD patients are treated in Germany. Asking neurologists to include patients in the study on a pre-specified day may have introduced the possibility of a bias. Therefore, the patient distribution must be interpreted with caution as this was not a community survey but a survey based on office-based neurologists. Furthermore, PD patients at earlier stages of the disease might initially be seen by their general practitioner rather than an office-based neurologist, thus their participation may have been underestimated in this study.

Another important limitation refers to the calculation of therapy costs, which we restricted to the medications presented in this paper (i.e. anti-Parkinson medications and other CNS medications). We did not collect data on the costs of over-the-counter medications, which are also frequently used by PD patients. In addition, the cost estimates would have been higher if specialized PD centers and hospitals were included, since severe and difficult-to-treat cases are usually referred to these centers. It should also be noted that prior to the study assessment 39 patients were excluded from the study by their physicians due to a degree of impairment that was too severe. Therefore, we lack further information regarding the clinical status and therapy expenses of these patients, whose higher level of comorbidity would have presumably resulted in higher costs compared to the patients who were included. Finally, although the patients were evaluated in the "on" state, we could not be sure that these patients were receiving the "best medical treatment". This may have introduced a bias in the evaluation of patient-reported outcomes.

Conflict of interest

All authors declare that there is no conflict of interest regarding the content of this article.

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