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Costs of Parkinson's Disease and Antiparkinsonian Pharmacotherapy: An Italian Cohort Study

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Key Words
Costs · Economics · Parkinson's disease · Antiparkinsonian drugs

Abstract
Objective: Antiparkinsonian pharmacotherapy is costly and the determinants of drug costs in Parkinson's disease (PD) have been poorly investigated. The objective of this study was to investigate the costs of PD and antiparkinsonian drugs in an Italian cohort of patients and identify cost-driving factors of drug therapy. ***Methods:*** Seventy outpatients with idiopathic PD were recruited in the Department of Neurology, Napoli University, Italy. Data on resource utilization were collected for 6 months using a bottom-up approach. Clinical status was evaluated using the Unified Parkinson's Disease Rating Scale. Direct and indirect costs were calculated from the societal perspective (figures of year 2009). Independent determinants of total costs and costs of antiparkinsonian drugs were identified using multivariate regression analysis. ***Results:*** The total costs of PD were EUR 8,640 (95% CI: EUR 6,700–11,240) per patient over a 6-month period. Direct costs accounted for 70% of the total costs. Antiparkinsonian drugs (EUR 1,450; 95% CI: EUR 1,220–1,760) were the primary component of costs paid by the health insurance (39.6%) and one of the most expensive components of the direct costs (24.0%). The highest copayments made by patients were for antiparkinsonian drugs and medical equipment (58%). Independent determinants of the increased costs of antiparkinsonian pharmacotherapy were younger age and occurrence of motor fluctuations. ***Conclusions:*** Antiparkinsonian pharmacotherapy is one of the major cost components of PD-related costs for health insurance. It imposes a considerable economic burden on patients and their families as well.

Introduction

As the global population continues to age, the prevalence of neurodegenerative disorders has continuously increased. According to the World Population Prospects of the United Nations, the number of people aged 60 years will increase nearly 3-fold by the year 2050, reaching 2.1 billion [1]. The World Health Organization estimated

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that there are currently 4 million people with Parkinson's disease (PD) worldwide. PD is a common neurodegenerative disorder. The incidence rates of PD in Europe are 8–18 per 100,000 and its prevalence rates are 66–255 per 100,000 [2–4]. As such, the number of individuals with PD in Italy is estimated to be approximately 112,000 [2].

Dopamine replacement therapy with levodopa combined with agents that improve its bioavailability and the use of synthetic dopamine agonists are the current pharmacological options for treatment of this disease. Pharmacotherapy for PD is purely symptomatic as disease-modifying drugs are not available yet. The disease has a chronic progressive course, with motor complications occurring in 70–80% of patients receiving levodopa therapy.

Both the increasing prevalence of PD and its progressive disabling course have led to it imposing a considerable economic burden on society, individual patients and their families. A number of studies investigating the economic consequences of PD in different European countries have been published in the last decade [5–10]; however, data about Southern Europe are still lacking. Furthermore, data on factors that predict an increased economic burden related to pharmacotherapy are scarce. Antiparkinsonian pharmacotherapy is costly. Drug therapy in most countries is not fully covered by the health insurance and thus copayments by patients for antiparkinsonian drugs are high [10–12]. Only one previous study investigated the determinants of drug costs using multivariate analysis [10].

The objective of this study was to investigate the costs of PD and antiparkinsonian drugs in Italy and to determine independent factors that influence the costs of antiparkinsonian pharmacotherapy.

Methods and Patients

The study was initiated by the EuroPa (European Cooperative Network for Research, Diagnosis and Therapy in Parkinson's Disease) study group (www.EuroParkinson.net) in the context of a larger international health economics project that is investigating the cost of illness in patients with PD [13]. The participants in the study were recruited from the registry of the EuroPa study group, a database of approximately 2,000 patients that has been organized as a research pool for PD. The participants in the EuroPa registry are outpatients with idiopathic PD randomized from the clinical databases of the outpatient departments of large medical centers such as university hospitals. The following countries are participating in this international health economics project: Austria, the Czech Republic, Germany, Italy, Portugal and Russia. Cost data from participating countries will be published separately in order to provide detailed cost analyses [11, 12, 14]. The Italian cohort study concentrated on additional factors that determine the costs of antiparkinsonian drugs. The participants in the Italian cohort study were recruited from the Italian pool of the EuroPa registry and consisted of outpatients (n = 70) with idiopathic PD who visited the neurological department of the Napoli Federico II University between July 1, 2003, and June 30, 2004. The diagnosis was based on the UK Parkinson's Disease Society Brain Bank clinical diagnostic criteria for PD [15]. The study was approved by the local ethics committee and all participants gave informed consent.

Clinical Evaluation

Clinical evaluation was performed at baseline. It included a complete medical and neurological examination and involved documentation of the following clinical data: disease onset and time of diagnosis; clinical status as measured by the Unified Parkinson's Disease Rating Scale (UPDRS) parts II and III [16]; motor complications (motor fluctuations, dyskinesias and dystonia); non-motor signs (mental and sleep disorders, autonomic dysfunction), and use of antiparkinsonian medication.

Cost Evaluation

Cost evaluation was performed during 2 visits (at baseline and 3 months later). During each visit, cost data were collected using a comprehensive questionnaire about the consumption of health care resources during the preceding 3 months. As such, disease-related costs over a 6-month period were collected. The health economics questionnaire used in this study has been applied in previously published studies on neurological diseases [17–21]. If patients had dementia, severe depression or psychosis, the data were obtained from the caregivers. Only PD-related costs were considered in the analysis. Drug costs included only costs of antiparkinsonian medication in order to reduce the influence of non-PD-related costs. Data collection was performed between July 1, 2003, and June 30, 2004. The costs were calculated in Euros (EUR), using 2004 prices, and then inflated to 2009 Euros using the consumer price index. The total costs (direct and indirect costs) were calculated from the societal perspective.

Direct costs consisted of the costs of statutory health insurance and out-of-pocket costs. The costs for health insurance included the following components:

(1) Inpatient care: sources of cost information were the official tariffs of reimbursement for hospitalizations according to the Italian diagnosis-related groups
(2) Outpatient care and ancillary therapy (physiotherapy, occupational therapy): sources of cost information were the official Italian state tariffs called 'Nomenclatore Tariffario'. The fees were multiplied by the number of outpatient visits or diagnostic procedures within the 6-month period [22]
(3) Drug costs: source of cost data was the official Italian price list of drugs [23]
(4) Expenditures on special home equipment: sources of cost data were Italian price lists for special equipment [24]
(5) Formal care (care is provided by healthcare professionals, e.g. nurses and medical social workers): sources of cost information were the price lists of home care agencies [25]

Out-of-pocket costs included the following components:

(1) Informal care (home care provided by family members and friends): the calculation of costs for informal care was performed using the disposable income of primary caregivers,

Table 1. Demographics and clinical parameters of patients stratified by age groups

	<60 years	60–69 years	≥70 years
Total number	18 (25.7)	28 (40.0)	24 (34.3)
Sex			
Male	9 (50.0)	19 (67.9)	13 (54.2)
Female	9 (50.0)	9 (32.1)	11 (45.8)
Motor complications			
No	10 (55.5)	8 (28.6)	13 (54.2)
Yes	8 (44.4)	20 (71.4)	11 (45.8)
Nonmotor complications			
No	5 (27.8)	5 (17.9)	3 (12.5)
Yes	13 (72.2)	23 (82.1)	21 (87.5)
UPDRS II[1]	10/7 (6–13)	11/10 (8–14)	14/13 (11–17)
UPDRS III[1]	15/10 (10–20)	15/11 (11–19)	20/22 (15–24)
Duration of disease[1], years	5.6/4.4 (3.7–7.5)	8.3/6.9 (5.9–10.6)	8.8/7.7 (6.5–11.1)
Marital status			
Married	14 (77.8)	24 (85.7)	17 (70.8)
Divorced	1 (5.6)	2 (7.1)	0 (0.0)
Single	1 (5.6)	1 (3.6)	3 (12.5)
Widowed	2 (11.1)	1 (3.6)	4 (16.7)

Values denote numbers with percentages in parentheses.
[1] Mean/median with 95% CI in parentheses.

with disposable income defined as the net income after mandatory deductions such as income tax and social contributions
(2) Copayments of patients for treatments, drugs and equipment: the amount of copayments was reported by each patient and documented in the questionnaires

Indirect costs (productivity losses) were calculated using the human capital approach [26]. The loss of productivity due to premature retirement was calculated as follows: the calendar days remaining in the study period prior to the official age of retirement (60 years for women, 65 years for men) were divided by the mean number of calendar days per month (30.44), and then multiplied by the mean gross wage per month in 2004 (EUR 2,320) [27]. The loss of productivity among PD patients and their caregivers due to sick leave or reduction in working hours was also calculated using the mean gross wage.

Statistical Analysis

The software used in the analysis was Stata (release 10.0; StataCorp, College Station, Tex., USA). The means and 95% CI of the cost data are presented. The standard nonparametric or normalizing methods were not appropriate for a statistical analysis of cost variables because the distribution of these data is usually highly skewed [28]. The statistics were performed using the bootstrapping technique, an appropriate and flexible approach to presenting and comparing skewed cost data [28, 29]. Bivariate comparisons were performed using the bootstrap t test [28, 29]. Multivariate comparisons were performed using linear regression analyses with standard errors estimated using the bootstrapping technique. The level of significance was set at $p < 0.05$.

Results

Demographics and Clinical Features

Among the 70 participants in the study, 41 (58.6%) were male and 29 (41.4%) female. The mean age of the patients was 65.0 ± 8.5 years (range: 41–79 years) and the average duration of disease at the time of enrollment was 7.8 ± 5.5 years (range: 0.1–30.5 years). At onset of symptoms, the patients had a mean age of 57.3 ± 8.6 years (range: 35–72 years). The demographic and clinical parameters stratified by age group are shown in table 1.

Costs from Societal Perspective

The total semiannual costs from the societal perspective amounted to EUR 8,640 (95% CI: EUR 6,700–11,240). The direct costs were EUR 6,030 (95% CI: EUR 4,700–7,970) and accounted for 70% of the total costs. The indirect costs (productivity losses) were lower and amounted to EUR 2,610 (95% CI: EUR 1,630–4,130).

Among the direct costs, the costs of health insurance were EUR 3,660 (95% CI: EUR 2,600–5,730) and the out-of-pocket costs were EUR 2,370 (95% CI: EUR 1,490–3,120). The costs of health insurance calculated per 6 months consisted of the following components: inpatient care (EUR 830; 95% CI: EUR 360–1,810), outpatient care (EUR 90; 95% CI: EUR 80–110), ancillary therapy (EUR

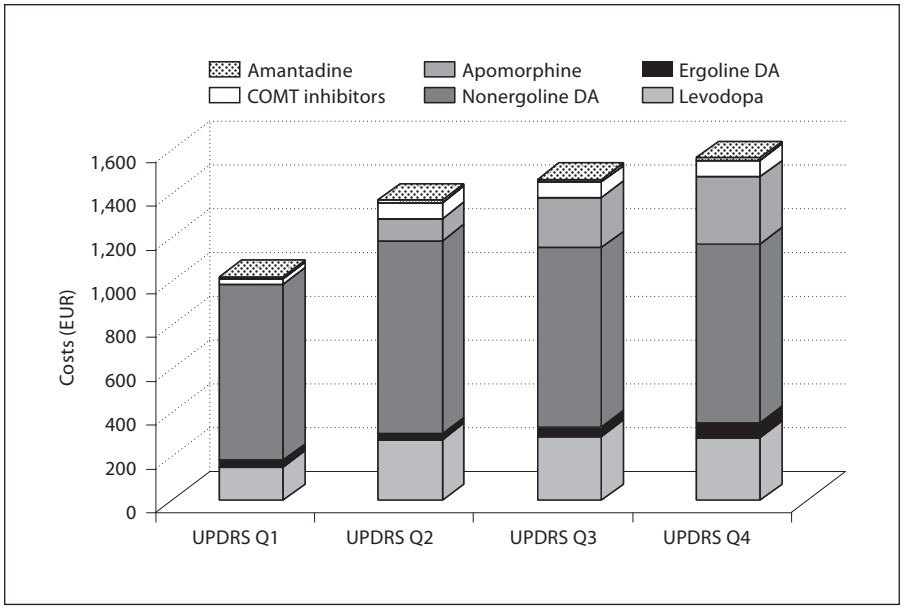

Fig. 1. Costs of antiparkinsonian drugs stratified by disease severity. Cutoff values by UPDRS quartile were 13, 23 and 42. DA = Dopamine agonists.

90; 95% CI: EUR 60–130), special equipment (EUR 90; 95% CI: EUR 40–260), formal care (EUR 1,100; 95% CI: EUR 330–3,580) and antiparkinsonian drugs (EUR 1,450; 95% CI: EUR 1,220–1,760).

The out-of-pocket costs consisted of costs for informal care (EUR 2,030; 95% CI: EUR 1,320–2,860 per 6 months) and copayments of patients (EUR 340; 95% CI: EUR 240–480 per 6 months). The mean net annual income of the study participants was EUR 19,820 (95% CI: EUR 18,980–21,510). The economic burden imposed on the patients by PD-related out-of-pocket costs amounted to approximately 24% of their mean net income (EUR 19,820; 95% CI: EUR 18,980–21,510 per year). The main burden of home care fell on patient family members and friends. The amount of home care per patient per week included 4 h of professional care and 12 h of informal care. The highest copayments were for antiparkinsonian drugs and medical equipment. These constituted 58% (EUR 200; 95% CI: EUR 110–370) of the total copayments.

Costs of Antiparkinsonian Drugs

The costs of antiparkinsonian drugs (EUR 1,450; 95% CI: EUR 1,220–1,760) were the primary component of the costs paid by the health insurance (39.6%) and one of the most expensive components of the direct costs (24.0%). The costs of nonantiparkinsonian drugs (gastrointestinal drugs, cardiovascular drugs, metabolic drugs, etc.) were substantially lower (EUR 190; 95% CI: EUR 100–310). The study participants were treated with the following antiparkinsonian drugs: levodopa (65 patients; 92.9%), dopamine agonists (54 patients; 77.1%), catechol-*O*-methyl transferase (COMT) inhibitors (12 patients; 17.1%) and amantadine (6 patients; 8.6%). None of the patients received monoamine oxidase B inhibitors or anticholinergics. Dopaminergic medication accounted for 89.7% of the costs of antiparkinsonian drugs. The costs of antiparkinsonian drugs were as follows: EUR 1,040 (95% CI: EUR 850–1,410) for dopamine agonists, EUR 260 (95% CI: EUR 200–340) for levodopa, EUR 240 (95% CI: EUR 60–180), EUR 10 (95% CI: EUR 0–10) for amantadine. Among the dopamine agonists, the highest expenditures were on pramipexole (EUR 790; 95% CI: EUR 710–930) and apomorphine (EUR 170; 95% CI: EUR 100–320).

The costs of antiparkinsonian pharmacotherapy increased with disease progression. Their distribution in quartiles (Q) of UPDRS is shown in table 2. The costs of levodopa nearly doubled from UPDRS Q1 to UPDRS Q2 (EUR 150, 95% CI: EUR 110–230 vs. EUR 280, 95% CI: EUR 220–237; p = 0.11), but they did not change between UPDRS Q2, Q3 and Q4. The costs of COMT inhibitors increased between UPDRS Q1 and Q2 by a factor of 3 (EUR 25, 95% CI: EUR 10–50 vs. EUR 75, 95% CI: EUR 60–120; p = 0.02) and remained unchanged in UPDRS Q2, Q3 and Q4. The expenditures on apomorphine increased with disease progression (fig. 1), whereas the costs of other dopamine agonists were comparable at all stages. The amount of prescriptions and costs of noner-

Table 2. Costs of antiparkinsonian drugs stratified by potential cost-driving factors

	n	Mean costs EUR[1]	95% CI[2]	Costs (min) EUR[1]	Costs (max) EUR[1]	p
Age group						0.04
<60 years	18	1,680	1,300–2,190	70	5,110	
60–69 years	28	1,510	1,140–1,900	50	3,230	
≥70 years	24	1,060	740–1,430	40	2,660	
Sex						0.50
Female	29	1,360	990–1,790	40	4,320	
Male (m = 0)	41	1,470	1,190–1,820	60	5,110	
UPDRS[3]						0.18
UPDRS Q1	15	1,020	910–1,250	50	2,600	
UPDRS Q2	19	1,370	1,220–1,510	100	3,310	
UPDRS Q3	17	1,470	1,380–1,620	100	4,320	
UPDRS Q4	19	1,570	1,400–1,790	40	5,110	
Motor fluctuations						0.02
No	38	1,050	820–1,290	40	2,420	
Yes	32	1,870	1,510–2,280	120	5,110	
Dyskinesias						0.04
No	49	1,160	910–1,400	40	2,870	
Yes	21	2,050	1,620–2,610	150	5,110	
Dystonia						0.19
No	53	1,370	1,100–1,640	40	4,320	
Yes	17	1,590	1,210–2,270	170	5,110	
Freezing						0.11
No	43	1,210	960–1,510	40	4,320	
Yes	27	1,760	1,390–2,240	60	5,110	
Psychosis						0.18
No	63	1,220	570–2,000	40	5,110	
Yes	7	1,450	1,220–1,740	150	2,870	
Dementia						0.19
No	65	710	200–1,570	40	5,110	
Yes	5	1,480	1,240–1,740	150	1,760	
Depression						0.03
No	31	1,130	840–1,450	50	2,660	
Yes	39	1,650	1,340–2,060	40	5,110	

[1] In EUR, 2009 values.
[2] 95% CI = 95% bootstrap confidence interval using the bias-corrected and accelerated method.
[3] UPDRS parts II and III. Cutoff values by UPDRS quartile were 13, 23 and 42.

goline drugs was substantially higher than the prescriptions and costs of ergoline drugs ($p < 0.01$).

Cost-Driving Factors

The results of bivariate analysis are displayed in table 2. Increasing age was associated with decreases in the costs of antiparkinsonian drugs. The presence of motor fluctuations or dyskinesias increased drug costs by a factor of 1.7. The patients with depression had 50% higher costs of drugs (table 3), and age was inversely correlated with costs (in Euro).

Independent cost-driving factors were identified by multivariate analysis (table 3). Dyskinesia and depression were found to be independent factors that increased the total costs (in Euro). These variables were able to explain 36.7% (R^2) of the variance in total costs (table 3). Younger age and occurrence of motor fluctuations were independent determinants of the increased costs of antiparkinsonian drugs and were able to explain 37.2% of the cost variance.

Table 3. Multivariate analysis of cost-driving factors

	Total costs (R^2 = 0.367)			Costs of antiparkinsonian drugs (R^2 = 0.372)		
	B	95% CI	p	B	95% CI	p
Constant	5,998	–11,296; 23,292	0.50	2,240	731; 3,749	0.004
Gender	2,954	–1,809; 7,718	0.22	–224	–679; 230	0.33
Age	–39	–319; 241	0.79	–21	–46; –3	0.04
UPDRS II–III	6	–184; 241	0.75	8	–10; 27	0.37
Fluctuations	–414	–5,296; 4,468	0.87	581	43; 1,205	0.04
Dyskinesia	3,651	2,426; 9,728	0.03	438	–270; 1,147	0.23
Dystonia	1,853	–1,918; 3,212	0.47	16	–769; 336	0.44
Freezing	6,131	–624; 11,637	0.23	38	–585; 661	0.91
Depression	2,410	1,954; 6,773	0.04	284	–176; 746	0.23
Dementia	–2,834	–12,364; 6,696	0.56	1,009	–493; 2,474	0.18
Psychosis	1,269	–5,018; 7,556	0.69	–224	–1,223; 775	0.66

B = Regression coefficient; 95% CI = 95% bootstrap confidence interval using the bias-corrected and accelerated method.

Discussion

This study evaluated the costs of PD and antiparkinsonian drugs in a cohort of patients in Italy. To the best of our knowledge, other cost-of-illness studies of PD in Italy are not currently available. As calculated in our study, the costs of PD from the societal perspective amounted to EUR 17,280 per patient when extrapolated to a 12-month period, with annual direct costs of EUR 12,060. We used a bottom-up approach (i.e. data collection was performed directly via individuals). The European Brain Council estimated costs of PD in Italy by means of a top-down approach, i.e. splitting highly aggregated statistical data such as national statistics, and calculated similar direct costs to be EUR 10,105 per patient per year [30]. Among the other countries in Southern Europe, the costs of PD were only estimated in Spain [31]. Cubo et al. [31] reported direct costs of EUR 10,524 per PD patient per year, which was similar to our findings. The annual direct costs of PD in our study were comparable to those reported from other Western European countries (EUR 7,920 in Sweden [5], EUR 8,160 in Germany [10], EUR 9,500 in the UK [32]) but higher than those from countries in Eastern Europe (EUR 6,700 in the Czech Republic [11], EUR 3,520 in Russia [12]) or Asia (EUR 630 in India [33], EUR 820 in China [34]).

Antiparkinsonian pharmacotherapy was one of the most costly components of direct costs in our study (EUR 2,900 per patient per year). Similar drug costs were reported in cost-of-illness studies from other Southern and Western European countries (EUR 2,680 in Spain [31], EUR 1,420 in Sweden [5], EUR 1,680 in the UK [32] and EUR 3,040 in Germany [10]). The costs of antiparkinsonian drugs in Eastern Europe and Asia were lower (EUR 1,220 in the Czech Republic [11], EUR 980 in Russia [12], EUR 180 in India [33]). One explanation is the difference in drug prices between Western and Eastern countries. Drug prices in Eastern Europe and Asia were on average 30–35% lower. The difference in costs could also be explained by the fact that expensive dopamine agonists are much less often prescribed in Eastern Europe and Asia. The proportion of patients on dopamine agonists was 55% in Russia [12], 52% in the Czech Republic [11] and 30% in India [33] as compared to 72% in Germany [10] and 77% among the patients included in our study. Treatment with dopamine agonists was more expensive as compared to the costs of other antiparkinsonian drugs. Dopamine agonists are effective in the treatment of de novo PD [35] and should be considered in national healthcare programs to improve adequate prescription of these drugs.

Disease progression is associated with increasing costs of antiparkinsonian drugs [36]. One of the factors underlying this trend is that more frequent prescription of dopaminergic drugs occurs in patients with higher UPDRS scores, while another factor is that apomorphine treatment is used in advanced stages of the disease. In an earlier German study, the use of apomorphine increased drug costs in patients with Hoehn and Yahr stage V disease by a factor of 2.3 [36]. In our study, apomorphine

comprised approximately 35% of the expenditures on dopamine agonists in the last quartile of the UPDRS though the costs of other dopamine agonists did not differ substantially between early and advanced disease. Similar to previous studies, motor complications in our study were associated with higher costs of antiparkinsonian pharmacotherapy [10, 36].

Several previous studies have investigated cost-driving factors for PD [8, 10–12, 32, 34]. Disease severity was identified as an independent factor that increased the total costs of PD in most studies [8, 10–12, 32, 34]. In our analysis, the total costs increased with advancing disease progression; however, disease severity was not among the independent predictors of costs. It is possible that there are country-specific differences in cost-driving factors. Motor complications (fluctuations, dyskinesias, dystonia) were among the independent determinants of total costs in previous studies [8, 11]. However, the types of motor complications that were identified as independent cost drivers differed between studies from different countries. Determinants of total costs in France were 'on-off' fluctuations, while in the Czech Republic, dystonia was found to be among the cost predictors. In our Italian cohort of patients with PD, dyskinesias were independent determinants of total costs. Interestingly, depression was identified as a cost-driving factor in our study though the majority of previous studies did not include depression in their multivariate analysis [8, 10, 32, 34]. Future large-scale studies should clarify if depression is a country-specific, cost-driving, independent factor in the Italian PD patient population. Depression is one of the most prevalent non-motor symptoms in PD as it affects approximately 40% of the patients. It is a pivotal factor in reduced health-related quality of life and impaired cognitive function in PD patients [37, 38].

To the best of our knowledge, only one prior study investigated cost-driving factors of antiparkinsonian drugs by multivariate analysis [10]. Similar to the results of this study, we found an inverse association between age and the costs of pharmacotherapy. This could be explained by the preferable administration of costly dopamine agonists to younger patients with PD.

Despite a carefully constructed study design, there are several potential limitations. First, because our study design included only one primary center, there is a limited possibility to extrapolate these results to the national level, and thus this study provides only crude cost estimates. In addition, because this is a cohort study, a selection bias is also possible. An epidemiological approach to patient selection may have provided more precise estimations; however, the collection of detailed economic data at the individual level is time consuming and, as such, the majority of cost-of-illness studies on PD have used a bottom-up approach and were performed as cohort studies [8, 10–12, 32, 34]. The participants in our study were predominately in early or moderate disease stages and, therefore, the costs of advanced disease were not reflected adequately, including the costs for patients living in nursery homes. We also used self-reported questionnaires in our study, and thus patient recall may be incomplete, resulting in an underestimation of costs. Finally, residual confounding by unmeasured variables in the analysis of cost-driving factors cannot be excluded.

Conclusion

PD imposes a substantial health economics burden on both society and patient families in Italy. Antiparkinsonian drugs are one of the major cost factors for health insurance companies in the context of PD treatment. In addition, it imposes a considerable economic burden on patients and their families. Drug treatment is most costly in younger patients and patients with motor fluctuations. Another important finding is the identification of depression among the drivers of total costs. These data should be considered in future disease management programs as a means of improving health care for PD patients.

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