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Cabergoline Versus Levodopa Monotherapy: A Decision Analysis

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Abstract: We evaluated the incremental cost-effectiveness of cabergoline compared with levodopa monotherapy in patients with early Parkinson's disease (PD) in the German healthcare system. The study design was based on cost-effectiveness analysis using a Markov model with a 10-year time horizon. Model input data was based on a clinical trial "Early Treatment of PD with Cabergoline" as well as on cost data of a German hospital/office-based PD network. Direct and indirect medical and nonmedical costs were included. Outcomes were costs, disease stage, cumulative complication incidence, and mortality. An annual discount rate of 5% was applied and the societal perspective was chosen. The target population included patients in Hoehn and Yahr Stages I to III. It was found that the occurrence of motor complications was significantly lower in patients on cabergoline monotherapy. For patients aged ≥60 years of age, cabergoline monotherapy was cost effective when considering costs per decreased UPDRS score. Each point decrease in the UPDRS (I-IV) resulted in costs of €1,031. Incremental costs per additional motor complication-free patient were €104,400 for patients <60 years of age and €57,900 for patients ≥60 years of age. In conclusion, this decision-analytic model calculation for PD was based almost entirely on clinical and observed data with a limited number of assumptions. Although costs were higher in patients on cabergoline, the corresponding cost-effectiveness ratio for cabergoline was at least as favourable as the ratios for many commonly accepted therapies.

Key words: Markov; Parkinson's disease; cost; cabergoline; decision analysis; levodopa

Levodopa (L-dopa) remains the gold standard in the treatment of Parkinson's disease (PD).[1] Response to L-dopa has been established as one of the diagnostic criteria of idiopathic PD and almost all patients with PD respond to its administration. Long-term use of L-dopa, however, is associated with a gradual decline in efficacy and the development of motor and nonmotor complications.[2] After L-dopa treatment for 4 to 6 years, motor complications occur in approximately 40% of patients, and after 9 to 15 years, in >70% of patients. Motor complications are more likely to occur in individuals with disease onset at a younger age.[3] Motor complications constitute a major source of disability, decline in the activities of daily living, and a decrease in the health-related quality of life in PD patients.[4] In addition, major increases in the cost and use of healthcare resources have been associated with the treatment of these late-stage complications.[5–7]

Recently, a number of prospective drug trials indicated that PD patients who started on dopamine agonists for PD symptoms exhibited a much lower frequency of motor complications than patients who started on L-dopa.[8–11] Factors contributing to the development of mo-

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tor complications include a higher dose of L-dopa and greater severity of the underlying disease, among others.[12,13] Recent evidence suggests that abnormal pulsatile stimulation of dopamine receptors as a result of the short elimination half-life of L-dopa seems to be the key event in a cascade, which finally results in disabling motor complications.[14,15]

Cabergoline, an ergolinic dopamine agonist, has a longer elimination half-life than L-dopa (~65 hours compared with 1.5–2 hours, respectively) and therefore, other than being suitable for a once-daily use, it may provide fairly steady dopaminergic stimulation. It has been studied in both early and advanced PD patients.[16] Although, there remains considerable debate about when and how to use dopamine agonists, they are now established firmly in treatment guidelines for PD[1]; however, from an economic point of view, these drugs cause considerably higher daily treatment costs. The costs in Germany for the daily defined dose (DDD) are €2.65 for L-dopa compared with €10.85 for cabergoline.[17] This price difference is comparable to other newer dopamine agonists, such as pramipexole (€9.05 per DDD), pergolide (€11.41), and ropinirole (€7.52). Therefore, an evaluation of the cost effectiveness of dopamine agonists for the treatment of PD is necessary. The aim of this study was to evaluate cost effectiveness of cabergoline monotherapy compared with L-dopa monotherapy, with respect to the development of motor complications, using a Markov model.

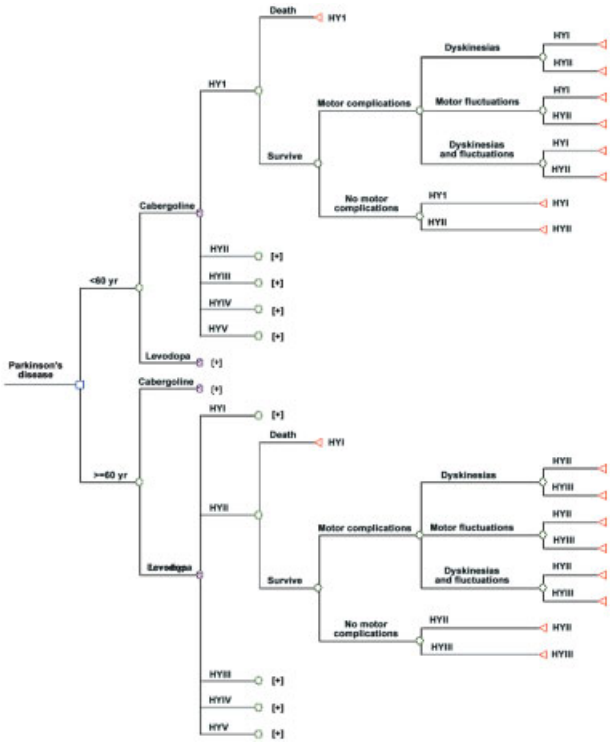

FIG. 1. Markov cycle tree (excerpt). The branches were structured similarly for cabergoline and L-dopa treatment. For different HY stages, branches differ only by the possible progression stages (patients cannot return to a lower HY stage). HY = Hoehn and Yahr stage; (+) = collapsed tree structure.

PATIENTS AND METHODS

Description of the Markov Model Structure

We developed a state-transition, or Markov model,[18] which allows an estimation of costs and effectiveness for patients with PD based on the natural progression of the disease (Fig. 1). The model starts with an initial distribution of patients in assigned states and applies transition probabilities over time to simulate how patients progress through disease stages and settings. In each cycle, patients face several possible transitions among various disease stages and setting combinations. Different sets of transition probabilities are assigned to cohorts receiving L-dopa or cabergoline monotherapy. As the cohorts cycle through the model, costs are accrued and outcome weights are associated with each stage and setting, providing the basis for calculating the incremental cost effectiveness. By varying the transition probabilities associated with a new treatment, one can assess the impact of a new drug.

Markov states are based on age (patients aged <60 years and ≥60 years), drug therapy (cabergoline or L-dopa), Hoehn and Yahr (H&Y) stages, and occurrence of motor complications (Fig. 1). The model was designed to include patients in stages H&Y I to V, but costs and outcomes were calculated only for the target population of this study, i.e., patients in initial stages H&Y I to III. For complications, only motor complications (e.g., dyskinesias, fluctuations, or both) were included, whereas nonmotor complications as well as sleep disturbances were not considered in the model.[2] The model was analyzed as cohort simulation with 10 cycles, each covering 1 year. The basic algorithm is described as Markov chain, using transition probabilities constant over time with a cohort of 100 patients. Model outputs are the cohort distribution at the end of the 10-year time horizon, expected costs and outcome, incremental costs per improved Unified Parkinson's Disease Rating Scale (UPDRS; sum of Part I + II + III + IV; total score), and incremental costs per avoided motor complication.

Data Input

Clinical Trial.

The Markov model is based on a multicenter randomly assigned double-blind 5-year phase III trial (PKDS009)

TABLE 1. *Demographic characteristics and clinical data of patients treated with monotherapy*

	L-dopa (n = 110)	Cabergoline (n = 76)
Gender, n (%)		
Male	49 (44.5)	37 (48.7)
Female	61 (55.5)	39 (51.3)
Age (yr)[a], mean	62.5	60.1
Stage[a]		
HY I (%)	33 (30.0)	20 (26.3)
HY II (%)	66 (60.0)	52 (68.4)
HY III (%)	11 (10.0)	4 (5.3)
UPDRS score (mean)[a,b]	24.1	21.8

[a]At baseline visit.
[b]UPDRS part I to IV.
UPDRS, Unified Parkinson's Disease Rating Scale.

designed to assess whether initial therapy with cabergoline alone or in combination with L-dopa prevents or delays the occurrence of motor complications in newly diagnosed PD patients.[9] Initial distribution of patients in the H&Y stages, complication rates, and type of motor complication were used as model parameters. Because the model focuses on patients on monotherapy (either L-dopa or cabergoline) and does not include patients who received combination drug therapy, all data were obtained from a subsample of the clinical trial population. Data on baseline distribution of patients to the different H&Y stages was obtained from the clinical trial[9]: of the newly diagnosed patients, 28.5% were in H&Y I, 63.4% in H&Y II, and 8.1% in H&Y III.

The occurrence of complication events (dyskinesia, fluctuations, or both) was obtained from the clinical trial, where motor complications were reported on using a motor complication checklist. Only confirmed motor complications were considered for modeling.

Disease Progression.

Demographic data of study participants are summarized in Table 1. Data on disease progression were obtained from the literature[19] and the calculated probabilities were assumed to be constant over time. Moreover, the assumption was that after conditioning on H&Y stage disease, progression was not dependent on treatment. The base case transition probabilities are shown in Table 2. The clinical experience, i.e., PD patients cannot return to a lower H&Y stage, was incorporated into the model. Patients can only remain in their present stage, progress toward a higher stage, or die.

Excess mortality due to PD was introduced in the model. Actual data on PD-associated mortality showed a large variation.[20,21] A standardized mortality rate of 2.0 was used for the base case analysis, but lower (1.5) and higher values (2.3) were tested in a sensitivity analysis. Aging of patients over the observed period of 10 years was disregarded in the model.

Cost Data.

Cost data were obtained from a 6-month analysis of a German prospective multicenter study to evaluate the health-related quality of life and healthcare utilization in patients with PD (Kompetenznetz Parkinson-Syndrome, KNP).[22] Data were available for 106 patients in H&Y I to III. H&Y stages for cost calculations were derived when patients were at optimal mobility, defined as being *on*.

To obtain societal costs per patient, the following costs were included: 1) reimbursement costs from for the statutory health insurance (Gesetzliche Krankenversicherung, GKV) for diagnostic and medical services, rehabilitation, hospitalization, transportation, medical devices, social services, and short-term incapacity benefits; 2) costs for long-term care covered by the insurance (Pflegeversicherung); 3) patient's fee for services, e.g., hospitalization, transportation, nondrug treatment, and medical devices; 4) patient's income losses due to the difference between his/her regular income and the short-term benefits paid by the statutory health insurance; and 5) indirect costs due to short- and long-term absence from work or early retirement due to PD in patients and their care givers were calculated as productivity losses and based on the human capital approach (€90/patient/day).

Costs for drug treatment were calculated based on weighted mean dosage as applied in the clinical trial. Patients received 2.9 mg/day of cabergoline or 600 mg/day of L-dopa (in combination with a dopa decarboxylase inhibitor).

The medians for all costs were considered with one exception for the indirect costs where the median of costs was zero. The vast majority of PD patients do not experience productivity losses because they are older than 60 years of age, or if they are in the working age group, they remain at work.[23] Even though most of the patients do

TABLE 2. *Transition probabilities conditional on surviving used in this study*

Transition	Transition probability per year
HY I → II	0.370
HY II → III	0.283
HY III → IV	0.179
HY IV → V	0.386
HY V → V	1.000
Live → death (<60 years)	0.015
Live → death (≥60 years)	0.040

See DiRocco et al., 1996.[19]

TABLE 3. *UPDRS score data (UPDRS I + II + III + IV)*

	Median score points, change in case of complication, respectively								
	HY I (−)	HY I (+)	Change	HY II (−)	HY II (+)	Change	HY III (−)	HY III (+)	Change
<60 yr									
Cab	13.75	NA	0.00	21.60	32.40	+10.80	44.40	NA	0.00
Levo	13.20	11.00	−2.20	20.80	26.25	+5.45	39.10	NA	0.00
≥60 yr									
Cab	12.30	17.30	+5.00	24.55	29.30	+4.75	31.70	NA	0.00
Levo	16.05	NA	0.00	26.70	33.85	+7.15	32.05	26.00	−6.05

Cab, cabergoline; Levo, levodopa; (−), without motor complications; (+), with motor complications.

not experience productivity losses, a minority of patients do. Within the KNP, indirect costs reached a maximum of about €21,150 per patient per year. The influence of this minority should be considered in the model, and therefore, mean values were used for indirect costs.

Cost-Effectiveness Analysis.

For each cycle, cohort distribution in the different stages of disease and the occurrence of complications were calculated. Calculated data were summarized for the entire modeling period of 10 years. Costs were determined by multiplying the number of stage years (H&Y I, II, III) and the number of events (complications) with their corresponding costs. The effectiveness was determined by multiplying the total number of stages with their corresponding UPDRS scores. The incremental cost-effectiveness analysis was carried out by calculating the difference for costs and effectiveness between one treatment scenario and its comparable scenario (cabergoline vs. L-dopa). Cost effectiveness was defined as additional costs per decreased UPDRS score point, and as additional costs per avoided motor complication.

A discount rate of 5% per year was used as recommended for Germany.[24] Effectiveness data were not discounted. All costs are expressed in 2002 Euros (€).

Sensitivity Analysis

Sensitivity analyses were carried out to allow for uncertainty, by testing if changes in key variables or assumptions affect the results of the analysis. Sensitivity analysis was carried out for the applied discount rate (0, 3, and 10%), for mortality data (relative risk: 1.5, 2.3) and for the cost data (±5%). Drug costs were not varied in the sensitivity analysis. All analyses were carried out on PC-based software systems. For decision-analytic modeling, *DATA v. 3.0.17* (Treeage) and *Microsoft Excel v. 5.0a* (Microsoft, Redmond, WA) were used.

RESULTS

The Markov cycle tree is shown in Figure 1, the annual transition probabilities conditional on surviving are summarized in Table 2, and the UPDRS input data are listed in Table 3.

Complication Events

Complication probabilities were 0.010 per year for cabergoline monotherapy (4/76 patients during 5 years), and 0.030 for L-dopa (17/110 patients during 5 years). Due to the small number of observations, no time-dependent or H&Y stage-specific complication rates could be calculated. Complication rates were assumed constant over time and equal across all H&Y stages. Motor complications were stratified by the type of occurring complication: dyskinesia, motor fluctuations, or both.

The occurrences of motor complications during the 10-year modeling period are summarized in Table 4. Depending on the observed treatment situation, the total number of motor complications to be expected in a 100-patient cohort at ages <60 years is 2.91 for the cabergoline treatment group and 10.91 for the L-dopa

TABLE 4. *Expected number of complication events, by type of complication*

		Complications			
Age group (yr)	Treatment	Dyskinesia	Fluctuations	Dyskinesia and fluctuations	Sum
<60	Cabergoline	0.00	2.91	0.00	2.91
<60	Levodopa	2.11	6.68	2.11	10.91
≥60	Cabergoline	0.00	2.12	1.32	3.44
≥60	Levodopa	6.68	1.92	7.67	16.28

TABLE 5. *Cost summary (discounted at 5% per year)*

Age group (yr)	Treatment	Costs per patient per year (€)	
		Total	Incremental
<60	Levodopa	5,389	—
<60	Cabergoline	6,224	835
≥60	Levodopa	4,815	—
≥60	Cabergoline	5,558	743

treatment group. In a 100-patient cohort at ages ≥60 years, the expected number of complications would be 3.44 for the cabergoline treatment group and 16.28 for the L-dopa treatment group.

Cost Calculation

Data from the Kompetenz-Netz Parkinson-Syndromes was analyzed[22] and costs for drug treatment were excluded. Costs were separated for patients without (n = 54) and with motor complications (n = 91). Patients receiving subcutaneous apomorphine (n = 4) were excluded from the analysis. Annual costs per patient without any motor complications were calculated to be €6,123 in H&Y I (n = 19), €4,236 in H&Y II (n = 43), and €14,855 in H&Y III (n = 44). For patients in the death state, zero costs were applied. Additional costs for treatment of motor complications were calculated as a difference in median costs for a patient having or not having this complication.

Table 5 displays total and incremental costs for the modeling period of 10 years. Incremental costs were calculated as difference in costs for the cabergoline group minus the costs for the L-dopa treatment group and were standardized for 1 patient and 1 year.

Effectiveness Calculation

Number of stage-cycles and events were multiplied by their assigned UPDRS scores and all score points were added up for the 100 patients observed for 10 years. Incremental UPDRS score points were +2.04 per patient per year at ages <60 years, and a reduction in the UPDRS score of 0.72 points per patient per year was observed for patients aged ≥60 years (Table 6).

In patients aged <60 years and for a treatment period of 10 years, motor complications could be avoided in 8 additional patients by using cabergoline instead of L-dopa. In patients aged ≥60 years, 12.8 additional patients would be free of motor complication when treated with cabergoline.

Cost-Effectiveness Calculation

Costs per decreased UPDRS score point were calculated only for patients at ages ≥60 years. In general, a CEA cannot be carried out for more expensive therapies unless improved clinical outcomes are also shown.[25] In the age group <60 years there is a dominance in favor of L-dopa. Cost effectiveness was €1,031 per decreased UPDRS score point (sum of UPDRS Part I–V total scores) for patients at ages ≥60 years and treated with cabergoline instead of L-dopa. Costs for each motor complication-free patient reached €104,400 for patients <60 years of age, and €57,900 for patients of age ≥60 years.

Sensitivity Analysis

Sensitivity analysis was carried out for the applied discount rate (0, 3, and 10%), for mortality data (relative risk: 1.5, 2.3) and for the cost data (±5%). No difference was found in the sensitivity analysis when indirect costs were varied (±10%; ±20%). Table 7 demonstrates how changes affect the cost effectiveness results. The model is robust against changes, including changes of discount rate, cost data, and mortality.

DISCUSSION

Treatment with dopamine agonists delays the occurrence of motor complications, however, increase costs in patients with PD.[6] Consequently, economic analyses are necessary to evaluate cost effectiveness. The Markov model presented allows the estimation of costs and outcomes for the treatment of PD patients with cabergoline or L-dopa monotherapy. Treating patients aged ≥60 years with cabergoline monotherapy improved motor performance, as evaluated by the UPDRS total sore. Costs for patients aged ≥60 years treated with cabergoline monotherapy for 10 years would amount to an additional €1,031 per patient per year, but the therapy would create an additional decrease of 1 point in the UPDRS total score.

For patients aged <60 years of age, a comparable improvement in efficacy (UPDRS total score) was not apparent.[9] In patients younger than 60 years, L-dopa is

TABLE 6. *Effectiveness summary (undiscounted)*

Age group (yr)	Treatment	UPDRS score points per patient and year	Incremental UPDRS score points per patient per year
<60	Cabergoline	21.075	—
<60	Levodopa	19.035	2.04
≥60	Cabergoline	15.338	—
≥60	Levodopa	16.059	−0.72

Positive incremental values indicate an increase and negative values a decrease in UPDRS score.

TABLE 7. *Sensitivity analyses*

Age group (yr)	Base case	Applied changes						
		Discount rate (%)			Cost data (%)		SMR in PD	
		0	3	10	−5	+5	1.5	2.3
Incremental costs per decrease in UPDRS score points (€)								
<60	NA	NA	NA	NA	NA	NA	NA	NA
≥60	1,031	1,259	1,113	865	1,033	1,029	1,038	1,027
Costs per motor complication-free patient (€)								
<60	104,393	129,004	113,250	86,618	104,513	104,273	104,725	104,195
≥60	57,909	70,692	62,525	48,573	58,012	57,806	57,226	58,321

NA, dominance in favor of levodopa; SMR, standardized mortality rate; PD, Parkinson's disease.

the dominant strategy, i.e., more effective and less expensive than is cabergoline. Therefore, a cost-effectiveness analysis is not feasible.

Furthermore, we evaluated costs assuming that patients can be treated to achieve complete rescue from motor complications. Due to the small effect on the denominator, the annual costs amounted to €57,900 for PD patients aged ≥60 years and €104,400 for PD patients aged <60 years. Sensitivity analysis indicated that the model was robust against changes concerning discount rate, cost data, and mortality. Unfortunately, no other cost studies are available that would allow for a direct comparison with these results. Recently, a cost-effectiveness analysis calculated costs of US $172,300 to 178,900 per quality adjusted life year (QALY) for the use of dopamine agonists (bromocriptine, pergolide) in the early stages of PD. No additional evaluation, however, was carried out concerning motor complications.

Whether a treatment is universally cost-effective remains a major debate in pharmacoeconomics. Several guidelines have proposed distinct, potentially cost-effective values in regard to QALYs; however, no data are available for most neurological diseases when clinical effects are used as an outcome, in contrast to other diseases, e.g., cardiovascular diseases.[26] More detailed studies in PD patients are therefore essential to provide a meaningful comparison of cost and effectiveness/utilities, which would add to the significance of an evidence-based PD treatment.

The main advantage of the present evaluation is the naturalistic representation of the course of PD and the evidence-based approach using primary clinical data on treatment effects and healthcare utilization. These prerequisites reduce the use of assumptions typical for modeling studies and provide a simple basis for this decision analysis.

Treatment effects were derived directly from the clinical study using original data. We based the effectiveness outcome on UPDRS values because these could be derived directly from the study. In addition, UPDRS score is the current standard evaluation tool for clinical studies, and almost all studies use the UPDRS score as a rating for effectiveness of the treatment in PD. Consequently, the use of UPDRS values in cost-effectiveness studies represents a suitable outcome measurement to evaluate treatment regimens. It allows also a comparison of anti-parkinsonian agents based on costs and efficacy, producing a ratio of cost per UPDRS lowering. This provides a simple, transparent method for the evaluation of cost effectiveness of anti-parkinsonian agents similar to the evaluation of cost effectiveness of antihypertensive agents.[26] It would also allow cost-effectiveness evaluation of different complications associated with PD, including motor and nonmotor complications; however, a major issue is associated with the use of the UPDRS: which score values mark a clinically meaningful outcome? Although some studies use a 30% reduction in the UPDRS as an outcome, there are no evidence-based data for this. Unfortunately, there are only a few cost-effectiveness studies available that evaluate PD treatment options.[27–29,33,34] Although these studies based their calculations on UPDRS values, they did not calculate costs per UPDRS score but used UPDRS score to derive utilities (see below). Recently, we evaluated the cost effectiveness of deep brain stimulation for PD and used UPDRS values as an outcome[30]; however, whether the UPDRS scores may be a valuable and a sound outcome parameter for cost-effectiveness studies (but not cost-utility studies) in PD needs further evaluation.

The healthcare utilization data were obtained from a multicenter prospective trial, which evaluated prospectively every 6 months the healthcare utilization and health-related quality of life of more than 140 PD patients in Germany.[22] The study recruited the patients from different healthcare providers including general practitioners, office-based neurologists, hospitals and a specialized movement disorder outpatient clinic. Therefore, likelihood for selection bias was low.

Although the model presented here was based on primary data, this study has several limitations.[21] The main limitation is the sample size of the original data set, which limits interpretation of the results for the outcome complication including the probability for the occurrence of motor complications; however, best use was made of the available information. Further trials with larger sample size should be carried out. During the clinical trial, only a subgroup of patients was treated with monotherapy. For cabergoline, 76 of 211 (36%) original patients were on monotherapy; for L-dopa, 110 of 208 (53%) patients were on monotherapy until the study was concluded.

From a statistical point of view, the considered overall complication rates are crucial due to the limitation of confirmed motor complications and the low number of observations during the clinical trial. This is true for both treatment options. In the cabergoline group, 4 of 76 patients had confirmed events, and 17 of 110 patients in the L-dopa group had confirmed motor complication events.

The number of motor complication events was calculated in the model to be between 2.35 and 2.91 in 100 patients on cabergoline monotherapy for 10 years. This was comparatively lower than the number expected based on the 5-year clinical trial, where four confirmed events in 76 patients occurred. Lower complication numbers in the model are caused by "loss of patients" over time toward higher H&Y stages (IV and V) and due to mortality. Motor complication events were separated by type of complication, which is required due to highly variable treatment costs for different types of motor complications. This distribution also suffers from the low number of observations during the clinical trial. For example, in the cabergoline monotherapy therapy group, the distribution was made from four observations mentioned above, which cause uncertainty. These limitations are a disadvantage for the cabergoline treatment.

The second limitation was that we did not extend our study to a calculation of QALYs. Health utility measures combined with the time course of disease generate a quality-of-life adjusted outcome expressed as QALY. QALYs are used as indicators of effectiveness that combine the impact of morbidity and mortality and provide a common metric for expressing effects of different interventions. Generic measures of clinical benefit, which employ individual preferences, such as the QALY, are considered as the most appropriate outcome measure to use in the economic evaluation. Recently, QALYs have been derived from UPDRS scores by regression analysis and used in cost-effectiveness studies.[28] We did not use these transformations because more detailed studies concerning preferences of PD patients are necessary and methodical issues limit their use. Therefore, the calculation of QALYs for PD patients is currently questionable.[31,32]

A further limitation was due to the study design. We included only patients in H&Y stages I to III. No evaluation was carried out for patients in more advanced stages of the disease, which is similar to other recent published studies. An earlier report calculated considerably higher costs for patients in advanced stages of the disease compared with patients in early stages of the disease when a dopamine agonist (pramipexole) was added to the treatment regimen.[28] Costs in 1998 were US $12,294 and US $31,528 per QALY for patients in advanced stages of the disease, when productivity gains were excluded, and US $8,837 (US $34,423) per QALY in the early stages of the disease.

CONCLUSIONS

This study is a model calculation for PD based on evidence from original study data. It considers the natural progression of PD over a 10-year period, treatment effects, and the societal costs in Germany.

In addition to clinical evidence that dopamine agonists such as cabergoline provide a delay in occurrence of motor complications, pharmacoeconomic studies available currently support cost-effective use of dopamine agonist.[27,34] Although we have not evaluated QALYs, which would allow a direct comparison with other treatment strategies, we assume that corresponding incremental cost-effectiveness ratio for cabergoline is at least as favourable as the ratios for many commonly accepted therapies for neurological diseases. For patients aged $\geq$60 years, cabergoline monotherapy was shown to be cost effective. Due to low complication rates in younger patients, no conclusions could be drawn from the limited data. Further large clinical trials are needed to evaluate efficacy and cost effectiveness of treatment options in Parkinson's disease.

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