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Health state values during the first year of drug treatment in early-stage Parkinson's disease.

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Abstract:

Background: Parkinson's disease (PD) is a common neurodegenerative disorder in the elderly that may lead to both motor and non-motor symptoms with consequently a severe impairment of the quality of life. PD represents a substantial economic burden on society, both because of a decreased ability to work, an increased need for care and a costly treatment. The evaluation of "quality adjusted life years" (QALYs) is an important tool in cost-effectiveness analyses. But until now there are few data available about the gains or losses in utility due to the disease and its management.

Objective: To evaluate the changes in health state values in patients with newly diagnosed PD during their first year of drug treatment, and to calculate the gain in QALYs and the incremental cost-effectiveness ratio (ICER) for this patient group.

Design: Prospective population-based cohort study.

Method: 199 patients with incident PD and 175 controls were followed over one year. Clinical data, drug use and utility scores using the SF-6D were registered.

Results: Patients with PD had lower utility scores than controls. Patients started on antiparkinsonian drugs had an improvement in utility scores of 0.039 from 0.667 to 0.706. The ICER was EUR 45 259 per QALY, of which two thirds were caused by drugs and one third by costs for clinical consultations.

Conclusion: Drug treatment in patients with early-stage PD increases health state values, but the ICER is high. Further investigations will be necessary to capture the full consequences of the treatment of PD and to evaluate the efficacy of the disease management.

Key words: Parkinson's disease; QALY; cost-effectiveness

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Introduction

“Quality adjusted life years” (QALYs) is a tool for the measurement of utility in health economics, where utility expresses a value based on health states. Utility scores normally rank from zero (= dead) to 1 (= healthy), and the amount of QALYs is computed by multiplying the years of survival by the obtained utility scores^[1]. Thus the use of QALYs as a measure of utility takes both time of survival and health state into consideration. In addition, instead of describing disease specific consequences, it allows for comparison of different medical conditions and different therapeutic regiments.

Parkinson’s disease (PD) is a common neurodegenerative disorder in the elderly^[2, 3]. Its course is progressive and may lead to both motor and non-motor symptoms with consequently a severe impairment of the quality of life^[4, 5]. Until now the disease is not curable and treatment therefore aims at the palliation of the symptoms. There is a common understanding that PD represents a substantial economic burden on society, both because of a decreased ability to work, an increased need for care and a costly treatment^[6, 7]. The state of patients with PD and therapeutic effects are normally measured with disease specific tools, like the Hoehn and Yahr staging^{[8][9]} or the Unified Parkinson disease rating scale (UPDRS)^[10], supplemented by rating scales for the quality of life and neuropsychiatric symptoms. These tools give abundant information about the disease severity of PD, but they do not allow an economic evaluation in the perspective of resource allocation within a health system. A review from 2006 on the health-related quality of life and the economic impact of PD showed that there were few studies evaluating cost-effectiveness by using QALYs as an outcome measurement, and all of them were part of medical trials^[11].

In this study we compared the utility scores for 199 newly diagnosed patients with PD from an incidence study in Western Norway to the scores of 172 controls matched for age and sex at the date of the initial diagnosis. We further evaluated the utility scores one year after the baseline examination and the therapy costs during that period of time, giving an estimate of the incremental cost-effectiveness ratio (ICER) for treatment of newly diagnosed patients with PD.

Methods

Patients and controls

Both patients and controls were drawn from a longitudinal incidence study of PD in Western Norway, the Norwegian ParkWest study. This study includes 212 patients with newly diagnosed probable or possible PD within a population of approximately 1 million inhabitants between 01.11.04 and 31.08.06. A thorough description of the case finding, diagnostic criteria and diagnostic procedures is given by Alves et al^[12]. Four patients dropped out because of death during the observation period and five patients had to be excluded because they were not PD-drug naïve at baseline. In four patients the information about the health status was not complete. The cohort of patients with PD thus included 199 individuals. The patients were examined at baseline and then every six months. In addition, there was an extra consultation four weeks after the start of PD-medication. At each visit clinical data about medical history, drug use and living situation was collected and a physical examination was performed. Disease severity was registered by using the UPDRS part I to IV, the HY staging, and the Schwab and England activities of daily living scale^[13]. Information about health states was collected at baseline and one year later.

A control cohort of 205 individuals was recruited from friends and relatives of patients with PD. We used a subset of the control cohort consisting of 175 individuals, who provided a best possible group match regarding sex, age and education. Three control individuals had to be excluded as data about health states were not complete. The controls were examined at baseline. Data about the health state, living situation and independency in daily life activities (ADL), as measured with the UPDRS part II, were collected.

Utility scores

The Short form-6D (SF-6D) was used to compute utility scores. The SF-6D is based on the health state questionnaire Short form 36 questionnaire (SF-36) which was completed by both patients and controls at baseline and after one year. The SF-6D contains the 6 dimensions physical functioning, role limitations, social functioning, bodily pain, mental health, and vitality, each with four to six levels. The scoring model for the SF-6D was developed based on standard gamble utility measurements on a random sample of 836 individuals from the general population in the UK. Next to death the worst state in the SF-6D system has a utility of 0.30^[14, 15].

ICER

We included costs for anti-parkinsonian drugs, as these were unequivocally related to the treatment of PD. Drugs prescribed for non-motor symptoms of PD or other diseases than PD were not included. We further included the costs for four consultations at the outpatient clinics of Neurology as this corresponds to clinical practice in the catchment area of the ParkWest study. Costs deriving from physiotherapy and transport were not included as these data were not collected. Drug costs were determined by using the price list in the drug compendium *Felleskatalogen 2007* or the pharmacists' price quotes. The costs for consultations in the outpatient clinics were calculated according to the refunding rates as stated by the Norwegian Labour and Welfare Administration. The ICER was calculated by the ratio of the costs and the gain in QALYs.

Statistical analysis

The software program SPSS 15.0 (SPSS Inc; Chicago, USA) was used for statistical analysis. Independent-samples and paired-samples t-test was used to compare means for continuous

parametric variables. The Mann-Whitney-U test was used to test for differences between independent and the Wilcoxon signed rank test for paired non-parametric variables. The Chi-square test was used for testing differences in proportions for categorical variables. Two-sided *p*-values less than 0.05 were considered statistically significant. The confidence interval (CI) for the mean of the PD-drug costs was calculated by bootstrap analysis. The exchange rate was EUR 1 = NOK 8.12 (02.01.2007).

Results

Patients and controls

Table I shows demographics and clinical information for patients with newly diagnosed PD and controls, while table II shows health status by the physical functioning (PF) and mental health (MH) scales of the SF-36 and health state values derived by the SF-6D. Table III shows the use of anti-parkinsonian drugs during the observation period.

A total of 371 individuals were included in the study, 199 patients and 172 controls. Of the 199 patients 165 (83%) started on PD-drugs during the observation period; 163 at baseline and two patients after six months. Thirty four patients (17%) were still PD-drug naïve after one year. Drug naïve patients had a shorter interval between disease onset and baseline examination with 1.7 years (SD 1.1) versus 2.4 years (SD 1.9) and less severe PD-symptoms. Of the patients using anti-parkinsonian drugs, eight received formal home care and one patient lived in an adjusted accommodation, while there was one PD-drug naïve patient receiving formal home care and none of the controls. These data were unchanged during the year of follow-up.

Utility scores

As shown in table II, there was a statistically significant improvement in utility scores in patients treated with PD-drugs during the one year of follow up of a mean of 0.039 points (95% CI 0.022 – 0.056; $p < 0.01$), from 0.667 to 0.706. There was no significant difference in the patient group that remained drug naïve. Control individuals had significantly higher utility scores than patients with PD (mean 0.810).

ICER

Patients using PD-medication caused at average costs of NOK 9552 (EUR 1176) for PD-drugs during their first year of treatment with a 95% CI ranging from NOK 8271 (EUR 1019) to NOK 11 012 (EUR 1356). Costs for consultations in the outpatient clinic for movement disorders were NOK 4784 (EUR 589). Mean treatment costs were thus NOK 14 330 (EUR 1765) during the first year of drug treatment for PD. As the gain in QALYs was calculated to be 0.039, the ICER was NOK 367 500 (EUR 45 259) per QALY.

Sensitivity analysis

The 95% CI of drug costs ranged from NOK 8271 (EUR 1019) to NOK 11 012 (EUR 1356), resulting in an ICER ranging from NOK 334 744 (EUR 41 224) to 405 026 (EUR 49 880).

There are few private neurologists in Norway who are not refunded by the Norwegian Labour and Welfare Administration. However, as all costs for these consultations are borne by the patients themselves, rates may be lower with lowest rates around NOK 800 (EUR 99) per consultation. Consultation cost would thus be decreased to NOK 3200 (EUR 396) per year and patient and the ICER to NOK 326 974 (EUR 40 268).

The 95% CI for the improvement in utility scores was ranging from 0.022 to 0.056, resulting in an ICER ranging from NOK 255 893 (EUR 31 514) to NOK 651 364 (EUR 80 217).

Of the patients using PD-drugs there were eight patients receiving formal home care and one patient living in an adjusted accommodation as an indicator for dependency in daily life activities (ADL). When excluding these patients, the gain in QALYs was 0.044 (95% CI 0.026 – 0.061 and the ICER was NOK 325 681 (EUR 40 109) per QALY.

In the best case scenario with lowest drug costs, lowest consultation costs, patient with no dependency in ADL and an improvement in utility scores in the highest range of the CI of 0.061, the ICER would be as low as NOK 188 049 (EUR 23 158) per QALY. In the worst case scenario with high drug costs, consultation in outpatient clinics and an improvement in utility scores of 0.022, the ICER would amount to NOK 719 936 (EUR 88 591) per QALY.

Discussion:

Patients with PD had significantly lower utility scores as compared to controls. Patients starting on anti-parkinsonian drugs had an improvement in utility scores of 0.039 from 0.667 to 0.706. The ICER was EUR 45 259 per QALY for patients with newly diagnosed PD during their first year of treatment, of which two thirds were caused by drugs and one third by costs for clinical consultations. These findings implicate that treating PD at an early stage improves health state values. At the same time, treatment costs per QALY are rather high. A thorough evaluation of disease management and all its direct and indirect costs and benefits seems therefore important, in order to allocate resources in the most cost-effective way.

Until now, few studies evaluating cost-effectiveness in PD have been performed. This study is part of an ongoing multi centre population-based cohort study of patients with newly diagnosed PD in a catchment area of approximately 1 million inhabitants in Western Norway. All patients were followed by neurologists in the hospitals' outpatient clinics, securing good clinical practice. There are no regulations regarding patient management and no restrictions regarding age or co-morbidity, thus displaying a realistic picture of everyday's clinical life.

Starting drug treatment in PD is normally considered as the "honeymoon" of the disease management, as many patients experience good effect of their treatment and do not show any side effects or long term complications. Nevertheless, the reported improvement in utility scores of 0.039 in our study lies just above minimal important difference of 0.030 that has been evaluated for the SF-6D^[16]. This may be due to co-morbidity in the study cohort. At the same time, there may be a smaller potential to obtain benefits by interventions in early-stage patients with PD with low disease severity and mild symptoms. In a longitudinal study evaluating the cost-effectiveness of pramipexole as compared to levodopa in patients with

incident PD, the gains in QALY during the first year were 0.053 for patients treated with levodopa and 0.067 for those treated with pramipexole^[17]. This difference might be caused by a less aggressive disease management in our study cohort. Patients in the above mentioned drug trial were treated with either levodopa-doses between 300 and 600mg per day or pramipexole doses corresponding to levodopa equivalent doses (LED) of 100 to 300mg per day. If necessary, supplementary doses of levodopa were administered. The patients in our study used a mean of 326 mg levodopa daily, and dopamine agonists corresponding to a LED of 115 mg. In addition, we had a non-selected group of patients, where co-morbidity might prevent optimal treatment of PD. The difference in health state values might as well be due to using the EQ-5D as preference-based measure. It has been shown that utility scores derived by different instruments may result in diverging utility scores^[18, 19]. Utility scores by the SF-6D in our study were 0.667 at baseline and 0.706 after one year, respectively. For comparison, in a cross sectional study in the UK of 2436 non-parkinsonian individuals divided into seven patient groups, a group of women aged 75 years and older had a mean SF-6D score of 0.662, menopausal women 0.716 and patients with lower back pain a score of 0.658^[19].

Norwegian condition may, however, not be applicable in other health systems. Drug prices and drug managements vary^[20]. To evaluate health state values we used the SF-6D as utility instrument, which was validated by an UK study population. By transferring these values to the Norwegian healthcare system we might thus have induced a bias to our calculations, and a gain in utility of 0.039 might be vulnerable to small changes. The ICER was calculated during the first year of treatment. However, cost-effectiveness may improve with a longer time horizon. Treatment benefits may first become evident in later stages of PD as preventing long-term complications or reducing the need for care by retaining independency in daily living. In addition, we included only direct expenses while there might be monetary benefits due to

retained working ability. Thus, the calculated ICER may be too high. At the same time, costs for non-motor symptoms in PD as antidepressants or medication for sleep disorders were not included into the calculations as we had no data confirming that they were directly related to the treatment of PD. Neither did we collect data about physiotherapy, transport, or therapeutic appliances. This may lead to an estimation of the ICER that is too low. All patients were followed by neurologist, while in most countries part of the patients will be followed by general practitioners. It has been shown that follow-up by a specialist causes higher drug costs than follow-up by a general practitioner^[21], but there is no data whether this as well may have an impact on the cost-effectiveness of the treatment. The control cohort was recruited among the patients' relatives and friends. Individuals volunteering to participate in a longitudinal study may constitute a cohort that is healthier and in less need for care than the general population. At the same time it is known that primary caregivers of patients with PD experience a reduced quality of life^[22]. The health state values of the control cohort may thus not reflect mean health state values of the general population.

To some degree, cost-effectiveness is a subjective conception, depending on a nation's wealth and willingness to pay. In Norway there are no official numbers, but an unofficial threshold is assumed at around EUR 60 000 per QALY. The ICER of drug management of incident PD during the first year of treatment was EUR 45 000 per QALY, bearing in mind, that we did not catch all direct costs, neither did we consider indirect costs and benefits.

Conclusion:

Drug treatment in early-stage PD improves health state values, but the ICER is high. Further investigations will be necessary to capture the full consequences of the treatment of PD in order to evaluate the efficacy of the disease management.

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Table I: Data about demographics, disease severity and independency in ADL for patients and controls

	Patients on PD-drugs 1 year after baseline (n = 165)		Patients drug naïve 1 year after baseline (n = 34)		Controls (n = 172)
	At baseline	After 1 year	At baseline	After 1 year	At baseline
Men/women (%)	104/61 (63/37)		17/17 (50/50)		103/69 (60/40)
Age at baseline					
Years (SD)	67.3 (9.2)		69.7 (8.7)		67.5 (9.1)
HY stage					
Mean (SD)	1.9 (0.6)	2.0 (0.7)	1.8 (0.7)	1.9 (0.9)	
Median	2.0	2.0	1.8	2.0	
Maximum/minimum	4/1	5/1	4/1	5/0	
Interquartile range	0.8	0.5	1.5	0.5	
UPDRS II score					
Mean (SD)	9.2 (4.5)	8.0* (4.6)	6.9** (5.5)	6.8 (4.0)	0.6** (1.2)
Median	9.0	8.0	5.5	6.0	0
Maximum/minimum	24/1	25/1	29/0	16/0	10/0
Interquartile range	6.0	5.0	6.3	5.0	1.0
UPDRS III score					
Mean (SD)	23.5 (10.5)	18.6* (9.7)	18.3 ** (11.6)	18.5 (11.6)	
Median	21.0	17.0	15.0	16.0	
Maximum/minimum	55/4	57/0	61/5	60/0	
Interquartile range	15.0	12.0	15.3	12.5	
Schwab and England score					
Mean(SD)	88 (8)	89 (10)	91 (11)	90 (12)	
Median	90	90	90	90	
Maximum/minimum	100/50	100/40	100/40	100/40	
Interquartile range	10	0	10	10	
Individuals receiving formal home care	8	8	1	1	0

* Improvement significant with $p < 0.05$

** Significantly different as compared to patients on PD drugs with $p < 0.05$

Table II: Data about health status and health state values for patients and controls

	Patients on PD-drugs 1 year after baseline (n = 165)		Patients drug naïve 1 year after baseline (n = 34)		Controls (n = 172)
	At baseline	After 1 year	At baseline	After 1 year	At baseline
SF-36 Physical functioning (PF) scale score					
Mean	74.2	67.4*	70.3	67.9	73.3
(SD)	(24.5)	(25.0)	(24.7)	(25.1)	(25.0)
SF-36 Mental health (MH) scale score					
Mean	75.7	76.0	77.4	76.2	78.5
(SD)	(18.5)	(15.0)	(19.4)	(16.8)	(17.4)
SF-6D utility score					
Mean	0.667	0.706*	0.694	0.702	0.810**
(SD)	(0.115)	(0.120)	(0.119)	(0.125)	(0.113)

* Decline or improvement significant with $p < 0.05$

** Significantly different as compared to patients on PD drugs with $p < 0.05$

Table III: Data about drug use in patients on PD-medication one year after baseline

	4 weeks after starting on PD-drugs n= 165	after 6 months n= 165	after 1 year N= 165
Monotherapy (%)	149 (90)	128 (78)	125 (76)
Two or more drugs (%)	16 (10)	37 (22)	40 (24)
L-dopa (%)	75 (45)	84 (51)	82 (50)
Mean levodopa dose per day in mg*	291	314	326
Agonist (%)	78 (47)	75 (45)	82 (50)
Mean LED of agonists per day in mg*	82	106	115
MAO-B inhibitor (%)	27 (16)	40 (24)	51 (31)
COMT-inhibitor (%)	0	0	1 (0.6)

* L-Dopa equivalent doses (LED) computed according to Parkin et al.^[23]