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Cost and Efficacy of Therapies for Advanced Parkinson's Disease

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1. Introduction

The economic burden of Parkinson's disease (PD) has become a very important health topic. From the perspective of a general neurologist, health economics can appear as not prioritary; however, it is a growing topic in most modern healthcare systems; consequently health professionals should have at least a minimal understanding of how health economic information is derived. It has become important that payers and providers consider the significant impact the disease has on quality of life and how resource utilisation is directed to improve PD related clinical problems. Such measures are determinant in assessing the value of drug therapy, particularly for chronic conditions such as PD, and in determining the appropriate placement of medications on plan formularies. In the past, a comprehensive examination of a clinical condition would focus almost exclusively on areas considered relevant to patient management, such as diagnosis, etiology, treatment, and prognosis. Now, however, additional demands are being made by health policy decision makers, who can influence medical decisions through coverage and reimbursement policies. Physicians and other professional caregivers increasingly must consider the economic implications of their decisions, which has led to increased demand for disease-specific cost information.

2. Economic burden of Parkinson disease

PD is a progressive neurodegenerative disorder of the central nervous system with motor, cognitive, behavioural and autonomic symptoms. PD has a significant economic burden from all perspectives: society, health system, and individual patient and relatives. This is due to the high prevalence of the disease, 6.3 million people around the world (European Parkinson's disease Association [EPDA], 2008), the nature of the symptoms and the fact that no cure exists and treatments are only aimed at relieving the effects of the disease and to improve patients' quality of life.

In Spain, taking into account a population of around 47 million people (Spanish National Institute of Statistics, 2010), and considering the different incidence and prevalence rates published (Abasolo-Osionaga et al., 2006; Benito-León et al., 2003; Bergareche et al., 2004; Claveria et al., 2002), the average incidence has been estimated at around 6,400 new cases per year, and the average prevalence at 150,000 people (European Parkinson's Disease Association [EPDA], 2008) with PD. It is estimated that 30% of these patients are in an advanced stage of the disease (Kulisevsky, 2005). The economic impact of PD is mainly

driven by in-patient care and nursing home costs caused by motor and non-motor symptoms that lead patients of PD to progressive disability. In addition, the cost of illness increases dramatically with severity as patients at the advanced stages are bedridden, wheelchair bound or institutionalized.

According to the most recent version of the World Health Organisation (WHO) report on Global Burden of Disease, published in 2008 (Mathers et al., 2008), neuropsychiatric conditions are responsible for 22% of global disability adjusted life years (DALYs) for women aged 15–59 years, the largest cause group in all regions outside Africa. The DALY is used as a measure to quantify the burden of the disease and consists on the years of life lived in less than full health or lost from premature death. It is also important to consider that these costs will increase along with the prevalence of these diseases due to the aging of the population in Europe.

Several studies have been performed to date in different countries to analyze the economic and social burden of PD. According to this literature, the main drivers of the total direct cost of PD are hospitalization and drug costs (Keranen et al., 2003; O'Brien et al., 2009) and the main drivers of total indirect cost are nursing care and productivity loss (Dengler et al., 2006; Hagell et al., 2002; O'Brien et al., 2009).

In the United States, the annual economic impact of PD was estimated in 2007 at $10.78 billion, being 58% of this amount related to direct medical costs ($6.22 billion) (O'Brien et al., 2009). Nursing home care ($2.6 billion) and PD-related medications ($1.47 billion) accounted for 63% of direct medical costs. Regarding indirect costs, annual lost productivity for persons with PD was estimated at $1 billion and caregivers cost at $2.36 billion. When considering the individual economic data, annual cost per patient was $21,626 (direct cost: $12,491).

Another study published in the United States (Huse et al., 2005) in 2005 quantified direct medical care costs for individual patients with PD and compared them with the costs obtained in a control group of persons without PD. Total annual direct cots were $23,101 per patient with PD versus $11,247 for controls. According to the study and based on annual data, PD patients spent approximately 2 more days in the hospital, 43 more days in long-term care institutions, and required more than 20 additional prescriptions than controls. These differences led to an increment of total annual health care costs of approximately $12,000 in PD patients. Around 50% of this excess cost was for long-term care, 24% for outpatient services, 15% for hospitalization and 14% for pharmacological treatment. The study projected the total cost of PD for the United States to be around $23 billion annually.

In an Australian study (Cordato et al., 2006) the total direct health-care cost of PD for patients with Hoehn and Yahr stage 3 was found to be four times higher than that of an age- and sex-matched control group of patients without PD. The estimated annual cost was Australian $7,020 per patient. Medication was the most costly component for both groups, being significantly higher for PD patients. Within the PD group, the health care costs attributable to PD were significantly higher than health care costs not related to PD (for a 3 month period, A$1,202 versus A$553).

As concerns European data, no Pan-European survey of the economic cost of PD has been performed to date. However, several studies from different countries are available in the literature. Some of the most representative ones have been considered for this chapter.

A review of the literature on the economic impact of PD in UK (Findley, 2007) reported an estimated total cost of PD in the UK between £449 million and £3.3 billion annually, depending on the methodology and prevalence rate considered in each individual analysis.

In another study in 2003, service use and costs for PD patients in the UK (McCrone et al., 2007) were measured. The annual costs were £13,804 per patient. Formal care costs accounted for 20% of this amount, while informal care was related to the 80% of the burden. Predictors of higher costs were identified, being male gender, level of disability and depression the more significant ones.

A study published in 2003 (Zecchinelli et al., 2003) assessed health care costs associated with PD in Italy. Patients and results were classified using the Hoehn and Yahr scale. Annual direct health costs were €4,320 for mild stage (1-2), €4,748 for moderate stage (2.5-3) and €6,175 for severe stage (4-5). The average was estimated at €4,808. These results were identified as lower than the real cost, as they didn't consider the societal perspective and neither informal care nor health care costs incurred in the private sector were included.

In Germany a 3-year prospective study of the economic cost of PD (Dengler et al., 2006) was performed in 2006. The average annual cost per patient was estimated at €12,091, of which 55,9% accounted for direct costs. Drugs took up the major share of direct costs, €5,763 per year. Indirect costs accounted for €4,851 per patient per year. Within this, 76% of the costs were related to nursing care and the loss of productivity.

In Sweden resource use and costs in patients with PD were collected from medical records of a cohort of 127 patients (Hagell et al., 2002) in 1996 (year 2000 costs). Direct health care costs averaged approximately €3,200 per patient per year, of which drugs were the most costly component. Non-medical direct costs were higher, €4,800 per patient per year, and costs due to lost productivity were around €5,800 per patient per year. The average total annual cost for PD was therefore estimated at €13,800 per patient.

Costs of PD illness were studied in a Russian Cohort of 100 patients (year 2008 costs) (Winter et al., 2009). From the societal perspective, total annual costs per patient amounted to €5,240 per patient, with direct costs accounting for 67% and indirect costs for 33% of the total. The main drivers of the burden were informal care and drugs. Global costs for the nation were estimated at €1.1 billion per year.

One of the most recent European studies, published in 2010, was performed in a cohort of 100 Czech patients with idiopathic PD to evaluate direct and indirect costs and to identify cost-driving factors (Winter et al., 2010b). Results were assessed for a 6-month period and have been projected to annual costs. Total annual costs for PD were €11,020 per patient. Direct costs accounted for 60% of the total costs and indirect for 40%. Independent cost-driving factors included disease severity, motor complications, psychosis and age.

The degenerative nature of PD leads to an increase of resource consumption in its advance stages. In fact, disease severity has been identified as a strong cost-predictor in several of the studies already mentioned. Motor complications (fluctuations, dyskinesias, dystonia) have been identified as factors increasing PD-related costs (Dowding et al., 2006; McCrone et al., 2007; Winter et al., 2010a; Winter et al., 2010b; Zecchinelli et al., 2003).

In a 6-month observational study of PD in France, Germany and the UK, patients with different degrees of motor complications, measured using the Unified Parkinson Disease Rating Scale (UPDRS), and its effects on health care costs were examined (Péchevis et al., 2005). Dyskinesia (UPDRS part IVa) was associated with significant increases in total health care costs. Each unit increase in dyskinesia score lead to €562 additional costs per patient over a 6-month period.

A 2007 published study developed in the UK (Thanvi et al., 2007) showed that Levodopa induced dyskinesia increased health care costs. Relationship between increasing cost of care and severity of the disease as measured by Hoehn and Yahr stage was proven to be

statistically significant. A correlation was also found between the severity of the disease, patient's age and the use of Social Services.

If we focus on advanced PD (APD) treatment costs, a systematic review of the available economic evidence of deep brain stimulation (DBS) for APD was performed in 2009 (Puig-Junoy & Puig, 2009). Ten studies were identified, five of them being simple cost analyses and the other five, full economic evaluations.

The cost studies included were: one description of costs of the treatment with DBS (McIntosh et al., 2003) and four comparative analyses (Charles et al., 2004; D'Ausilio et al., 2003; Fraix et al., 2006; Gerzeli et al., 2002) of DBS versus conservative pharmacological treatment. In the comparative analyses, a significant difference was observed when annual average pharmacological cost was compared between conservative treatment and DBS. The independent average cost of the DBS intervention was specified in four of the five cost studies. These results showed some variability from €20.033 (Gerzeli et al., 2002) to -€33.220 (McIntosh et al., 2003), explained mainly by differences in resources utilization, which was highly driven by surgeons' level of experience. The intervention duration and costs decreased along with the increase of professional experience on DBS.

It was also observed that pharmacological treatment costs were lower in patients after DBS intervention than in patients that remained in conservative pharmacological treatment. Regarding costs distribution, the higher resource consumption for DBS was experienced during the first year of the therapy. The comparison of DBS costs to conventional pharmacological alternative is sensitive to the inclusion of non-health related costs. When productivity loss and informal care costs were considered (Gerzeli et al., 2002), the cost of the DBS alternative was lower to the cost of the conventional pharmacological treatment.

3. Cost-effectiveness of bilateral subthalamic stimulation in advanced Parkinson's disease

Levodopa combined with adjunct medical therapy is the standard medical treatment for individuals with PD. However, prolonged use of levodopa can cause disabling motor fluctuations and dyskinesias. When medication is no longer effective or produces unacceptable side effects, surgical treatments may be a possible alternative. Ablative surgery and DBS are the main surgical treatments for advanced refractory PD. Ablative surgery includes pallidotomy, thalamotomy and subthalamotomy, which destroy the globus pallidus (GPi), thalamic nucleus and subthalamic nucleus (STN), respectively. Once the suitable target tissue has been located, it is destroyed by a radio frequency or thermocoagulation method. Expert opinion suggests nowadays that ablative procedures are rarely performed in Western countries although such procedures are still available as a treatment option for individuals in developing countries. Ablative surgery has largely been replaced by DBS, in part because DBS is potentially reversible and is perceived to be associated with improved safety and effectiveness and, in part, because ablative surgery is irreversible and regarded as having limited effectiveness and significant safety concerns. In patients with inadequate control of parkinsonian symptoms by medical treatments, bilateral subthalamic nucleus deep brain stimulation (STN-DBS) has emerged as a surgical choice for APD and has been shown to improve motor function, motor fluctuations, and health related quality of life (HRQoL) and to reduce medication usage and drug induced dyskinesia (Deuschl et al., 2006; Krack et al., 2003; Martínez-Martín et al., 2002; Rodríguez-Oroz et al., 2005; Siderowf et al., 2006; Schupbach et al., 2005; Valldeoriola et al., 2002). DBS was

approved by the Food and Drug Administration (FDA) and the European Agency for the Evaluation of Medical Products (EMEA) for the treatment of APD, but it is still considered a relatively expensive therapy. Authorities are concerned because of the increased health expenses and are taking containment measures based on the principle that the distribution of resources must be supported by the efficiency and not exclusively by the direct clinical benefit (Greenberg et al., 1999; Weinstein et al., 2001).

The DBS procedure is generally performed in two separate steps, implantation of leads followed by implantation of the neurostimulator to which the leads are connected. Patients need to be tested initially for their responsiveness to therapy. This is accomplished by implanting a lead at the relevant site using a combination of stereotactic techniques such as image-guided stereotactic localisation and physiological techniques such as microelectrode mapping or macrostimulation. The implantation procedure is generally performed under local anaesthetic. The placement of the electrode at a particular site is determined by the patient's response to stimulation, involving physical evaluation of the lower limbs and face muscles, and interpretation of the microelectrode recording data. Once the target that elicits the best response has been localised, the testing electrodes are removed and replaced with permanent leads.

Although DBS is non-ablative, the procedure may give rise to complications and side effects, some of which are neither reversible nor adaptable. The complications from DBS can arise before surgery, during surgery, in the immediate post-operative period, and after surgery. Data available on adverse events are derived from case series. Findings from these studies indicated the risk associated with DBS but did not allow quantisation of those risks compared with the Best Medical Treatment (BMT). A systematic review of case series to assess the safety and effectiveness of bilateral STN-DBS for the symptoms of PD in a total of 537 individuals has been performed (Amani et al., 2005). The authors reported the mortality rate, adverse events related to stimulation, general neurological and surgical complications and hardware-related complications. Mortality occurred at a rate of 0.4 per cent.

The adverse events related to stimulation (and rates of occurrence) were: hypophonia (5.8%), eyelid apraxia (4.6%), increased libido (0.8%), sialorrhea (0.9%) and decreased memory (1.1%). Other stimulation-related adverse events included dystonia, paraesthesias, diplopia, dyskinesias and dysarthria; however these events were not reported in the studies or were underestimated. The adverse events related to general neurological and surgical complications (and rates of occurrence) were: depression (4.7%), mania/hypomania (2.0%), peri-operative confusion (13.7%), cerebrospinal fluid leak (0.1%), meningitis (0.1%), venous phlebitis (0.7%), pneumonia (0.4%), urinary tract infections (0.3%), pulmonary embolism (0.5%), seizures (0.9%), haemorrhage (2.8%). Weight gain was also considered to fall into this category, but was reported to be under-quantified in the studies. The adverse events from hardware-related complications (and rates of occurrence) were: lead problems including lead migration, breakage and repositioning (4.5%), and infections of the hardware (3.4%).

The results shown n the literature review indicated that DBS allowed the maintenance of abilities to perform activities and increased motor function in the absence of effective medical treatment. In the absence of a comparator group, it is not possible to quantify the effect attributable to DBS; however, the worsening of akinesia, speech, postural stability, freezing of gait and cognitive function is consistent with the natural history of PD over time (Krack et al., 2003).

The effectiveness of DBS for the treatment of symptoms of PD has been assessed from one double-blind crossover and three case-control studies. DBS appears to be effective for the treatment of PD symptoms, with statistically significant changes observed between case and control participants in UPDRS and PDQ-39SI scores. These results therefore show that DBS can ameliorate the symptoms of PD (as measured by the UPDRS ADL and Motor sections) and reduce the antiparkinsonian medication required to maintain control of the symptoms of PD. Patients experienced up to a 90 per cent reduction at 24 months following surgery in the daily OFF rate. However, the assessment of the effectiveness of DBS for the treatment of symptoms is generally limited by the number of individuals analysed; significant losses to follow-up in some studies; and follow-up of the participants to a maximum of only 48 months.

The reduction in antiparkinsonian medication after DBS may also significantly reduce some of the side effects of high-dose levodopa treatment over a long time (Charles et al., 2004; Mínguez-Castellanos et al., 2005; Molinuevo et al., 2000).

Most of the studies on cost-effectiveness in STN-DBS have been designed in the absence of a control group of similar characteristics receiving conventional oral medication supposed to be the BMT possible. In some of the studies, the costs of expensive therapies such as apomorphine pump infusions were also considered within the concept of BMT.

A cost-effectiveness study has been published with the aim of assessing the long term cost-effectiveness of DBS versus BMT (Tomaszewski & Holloway, 2001) using modelling techniques to predict long term clinical and economical consequences of using DBS and BMT in advanced PD patients, showing that DBS may be an efficient therapy to treat PD patients. Such mathematical models can be useful to predict long-term cost-effectiveness, considering that long-term studies are difficult to perform in clinical practice. It is likely that such positive cost-effectiveness results would extend at least to the next two or three years after the intervention. This possibility was suggested in a survey which showed a 32% increase in total costs during the first year after surgery but a reduction of 54% for the second year, when compared to preoperative values (Charles et al., 2004). Other studies have shown similar results: a retrospective cost-effectiveness study of DBS in Germany in 46 parkinsonian patients (Meissner et al., 2005) showed an estimated Incremental Cost Effectiveness Ratio (ICER) of €979 for one point improvement of the UPDRS-III in one year; in this survey the annual pharmacological expenses were of €11,230 one year before the implantation while of only €4,449 two years after surgery. A multicentric French survey (Fraix et al., 2006) observed similar improvement of UPDRS scores and decrement of PD costs. In another survey, a prospective analysis, the incremental cost per total UPDRS unit improvement turned out to be €920 (Spottke et al., 2002). Some studies have included the cost of the battery replacement after five years of use (D'Ausilio et al., 2003; McIntosh et al., 2003; Tomaszewski & Holloway, 2001).

Only a few studies considered a social perspective by showing costs derived from the losses and gains of productivity of both the patient and the caregiver before and after the intervention. Most of studies, however, are based in a retrospective design, with a short number of patients and follow-up and the absence of a control group of patients of similar clinical characteristics.

Due to the absence of prospective studies comparing cost-efficacy of STN-DBS with control patients, we designed an open, prospective longitudinal study comparative of the cost, effectiveness and HRQoL between the treatment with STN-DBS and BMT in patients with

APD (Valldeoriola et al., 2007). Twenty-nine patients were enrolled in the study. All were included in a waiting list for STN-DBS at our centre. All participating patients signed an informed consent form. Among the patients in the waiting list for STN-DBS, the first consecutive fourteen patients were enrolled in the treatment group and the last consecutive fifteen patients were enrolled in the control group. The treatment group was assigned to STN-DBS; the control group was assigned to BMT. Both groups (STN-DBS and BMT) were largely comparable in their clinical and demographic variables including mean levodopa equivalent doses. The study estimated only direct costs. We divided them into two categories: direct medical costs, related to costs for goods and services used in the prevention, diagnosis, treatment and rehabilitation of the illness (for example costs for medical visits, hospitalization and pharmaceuticals); and direct non-medical costs, generally assumed by the patient, including expenses related to the disease (for example transportation, social services, adaptation of accommodation and any kind of special equipment, facilities or orthopaedic material). Our results showed that the ICER needed to obtain an additional improvement of one unit in the total UPDRS score was €239.8. Current management of APD includes combinations of expensive drugs and therefore savings after STN-DBS were mainly attributable to the reduction of pharmacological expenses. The incremental cost-effectiveness was of €34,389 per QALY. The quality-adjusted life year (QALY) is a measure of disease burden, including both the quality and the quantity of life lived. It is used in assessing the value for money of a medical intervention. The QALY model requires utility independent, risk neutral, and constant proportional trade-off behaviour. The QALY is based on the number of years of life that would be added by the intervention. Each year in perfect health is assigned the value of 1.0 down to a value of 0.0 for death.

We also performed sensitivity analyses under different situations. When we excluded the BMT patient group patient who had a prolonged hospitalisation from the analysis, the incremental cost per QALY was of €44,078 (X1.3). In this study, two patients in the BMT group were treated with Continuous Subcutaneous Infusion of Apomorphine (CSIA), a therapy that is also considered to be expensive. Consequently we also calculated the cost-effectiveness of STN-DBS when excluding these patients, obtaining a result of €62,148 per QALY (X1.8). This study showed STN-DBS anti-parkinsonian clinical efficacy and that cost-effectiveness is directly related to clinical improvement in parkinsonism and to the reduction of pharmacological expenses after the intervention. As shown by others (Charles et al., 2004; Fraix et al., 2006; Meissner et al., 2005; Spottke et al., 2002), this survey in the Spanish setting showed that STN-DBS is within the adequate limits to be considered as an efficient therapy. Considering the published data available in the literature assessing DBS for APD, it can be considered safe, effective and cost-effective compared with BMT. There is sufficient evidence of safety and effectiveness, and robust information on cost-effectiveness is unlikely to emerge but the total cost is acceptable for patients in whom other therapies are insufficient.

The insertion of a DBS system incurs upfront costs but may result in cost savings from its effect of controlling the motor symptoms of PD as disease progresses, allowing patients to live in more functional health states for longer periods of time with improved QoL. To date, there appears to be no evidence that DBS delays the progression of PD or affects the mortality rate, although it may be argued that mortality due to falling, for example, may

decrease with improvements in motor skills. These savings could be realised through a reduced demand for services or a lower expenditure on certain examinations.

4. Cost analysis of DBS, CSIA and CDLCI in advanced Parkinson's disease: The SCOPE Study

For physicians in general and for neurologists in special, it becomes quite challenging to achieve an antiparkinsonian medication regimen that keeps the patient mobile while at the same time does not create side effects that outweigh the benefits of treatment, impacting patient's quality of life (Adler, 2002). In these APD patients, refractory to pharmacological treatment, three treatments may be recommended such as DBS, Continuous Duodenal Levodopa–Carbidopa Infusion (CDLCI), and CSIA. These therapies are not recommended for all patients with APD and an adequate patient selection allows the optimization of results obtained with the three therapeutic options.

Additionally, the three treatments have no clear positioning in the treatment pathway of APD patients, which leaves the decision about the eligibility of APD patients for one therapy or another to neurologists. Such decision can therefore be subjective and largely depends on the patient's clinical status, patients' and physicians' preferences, as well as previous hospital experience, availability of these treatments or economic constraints.

To date, as it has been described, no economic evaluation has been published comparing the costs-effectiveness profile of these three therapeutic options that exist for APD. The main reason could be the lack of published direct clinical evidence comparing at least two of the three therapies. In these cases, a modelling method can be done as a simulation of the cost-effectiveness results (Stahl , 2008).

A healthcare costs compqarison considering all the costs in the medium and long term (not only the acquisition costs) associated with the treatments and their consequences of chronic diseases management like PD is a valuable tool both for payers and physicians, offering useful information to support their decision making in the treatment of this patient population (Mycka et al., 2010).

In order to address this evidence gap, the first cost study worldwide has already been submitted (Valldeoriola et al., 2011). The SCOPE study[1] is a descriptive, quantitative and economic analysis that tried to compare the healthcare costs associated with these three alternative treatments for a 5-years, period in patients with APD in the perspective of the Spanish Healthcare System.

One DBS battery replacement was included in the analysis, as the average battery life of a non-rechargeable neurostimulator has seem to oscillate between four to five years (Bin-Mahfoodh et al., 2003; Krack et al., 2003). The costs of the devices and components of CDLCI and CSIA (infusion pump, catheters, etc.) were not included; thus it was assumed that they were provided free of charge by the supplier, and therefore their cost to the healthcare system was zero. Once all the health resources associated with the therapies were identified and quantified, its cost per unit or 'price` was obtained from the Spanish health resources database (Spanish Cost Database, e-salud (Spanish Cost Database, e-salud, 2010). Finally,

[1] SCOPE: eStudio COstes Parkinson Enfermedad. The SCOPE Study was evaluated and approved by the Ethics Committee of Clinical Research of the Hospital Clinic i Provincial, Barcelona.

the average total cost for each of the three therapies per patient was then obtained for the 5-years, period. In order to test the statistical differences of mean costs, the data analysis was carried out with the SPSS 15.0 software package for Windows and comparisons among the three therapies (non-parametric Kruskal–Wallis one-way analysis of variance by ranks multiple comparisons) and between the two therapies with the lower average total costs, DBS vs CSIA (Hollander & Wolf, 1999).

Due to the higher APD costs in the first six months, when patients consume more health resources (extra visits, hospitalization, dose adjustments, etc.) (D'Ausilio at al., 2003; McIntosh et al., 2003; Tomaszewski & Holloway, 2001), it was decided to divide the HQR in four sections, or phases.

In Table 1, the average cost per patient associated with the three alternative therapies in the baseline scenario for different phases are shown.

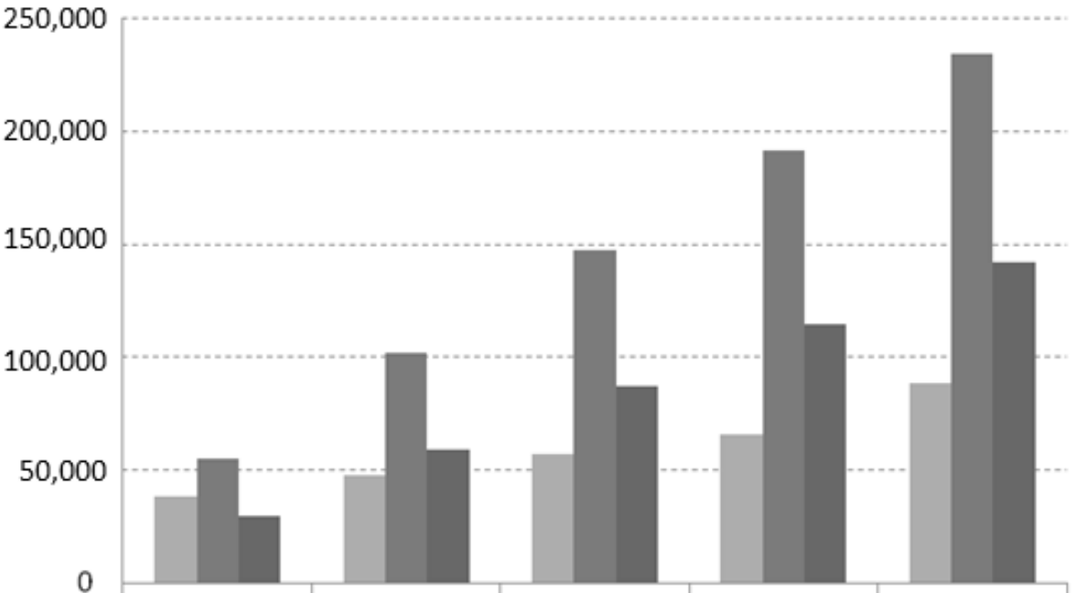
Phases	**Average Costs**		
	DBS	**CDLCI**	**CSIA**
1. Pre-treatment period to hospitalization	1,141 ± 411	1,705 ± 357	1,231 ± 267
2. Hospitalization period to discharge (includes Procedure or Treatment Administration)	27,236 ± 3,105 *	3,165 ± 501 *	785 ± 197 *
3. Discharge from hospital to 6 months post-op	4,768 ± 918 * #	25,521 ± 2,381 *	12,094 ± 2,158 * #
4. From month 6 to year 5	54,869 ± 4,190 * #	203,596 ± 8,737 *	127,284 ± 9,184 * #
Total cost per 5 years	88,014 ± 2,580 * #	233,986 ± 10,552 *	141,393 ± 9,945 * #
Average Cost per year	17,603±516 * #	46,797 ±2,110 *	28,279 ±1,989 * #

(*) Comparison of the three therapies ($p<0.05$). (#) DBS vs. CSIA comparison ($p<0.05$).

Table 1. Results of the baseline scenario expressed as an average ± standard error. Costs per patient (€, 2010).

As observed, during the pre-treatment phase, costs are similar for the three alternative therapies. In phase 2, DBS is associated with higher costs due to the therapy acquisition cost. However, starting from discharge to 5 years follow-up, DBS is the least costly therapy compared to CDLCI and CSIA. Differences are statistically significant in the comparison of the three therapies ($p<0.0001$) and for the DBS vs. CSIA comparison ($p=0.023$ and $p<0.0001$, respectively for phases 3, discharge from hospital to 6 months and 4, from month 6 to year 5). This suggests that in the long term DBS is a cost-minimizing therapy versus CDLCI and CSIA**.** The yearly average cost of DBS was €17,603 compared to €46,797 ($p=0.001$) for CDLCI and €28,279 for CSIA ($p=0.008$), indicating that for every patient treated during one year with CDLCI, two patients could be treated with DBS (or €29,194 could be saved) and for every patient treated during one year with CSIA, €10,676 could be saved if DBS would be chosen. Figure 1 describes Cumulative annual costs for the three therapies for the 5-year period. Results show that starting from year two, DBS is the therapy associated with the lowest cumulative costs compared with CDLCI and CSIA. All the differences were

statistically significant ($p<0.0001$) for multiple comparisons (among the three therapies) and starting from year two, the difference in costs between DBS and CSIA was statistically significant for the DBS vs. CSIA comparison ($p=0.008$).



	Year 1	Year 2	Year 3	Year 4	Year 5
DBS	37,983*	47,377*	56,498*	65,352*	88,014*
CDLCI	54,530*	101,402*	146,910*	191,092*	233,986*
CSIA	29,201*	58,504*	86,955*	114,576*	141,393*

(*) All differences became statistically significant ($p<0.05$) for multiple comparisons (among the three therapies) and for the DBS vs. CSIA comparison ($p<0.05$).

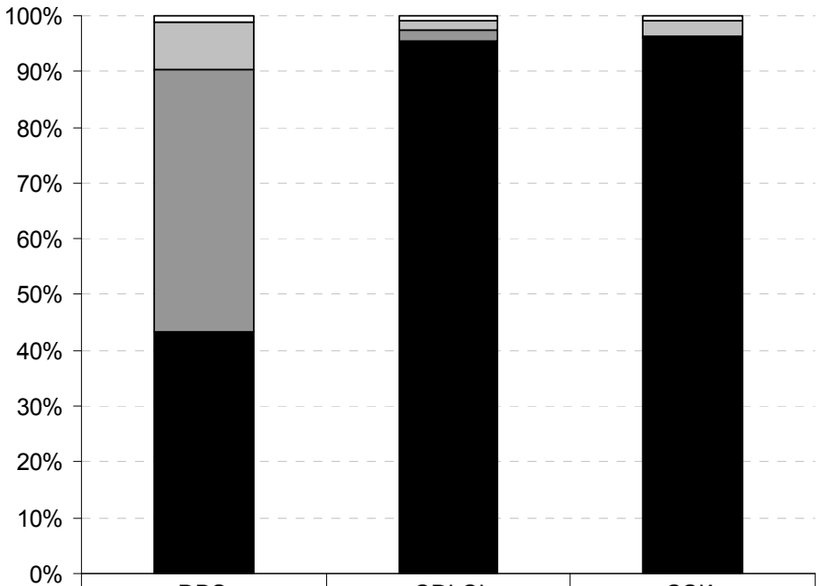
Fig. 1. Cumulative annual costs for DBS, CDLCI and CSIA (€, 2010)

At year 5, mean cumulative costs per patient associated with DBS amount to €88,014±2,580, €141,393±9,945 for CSIA and €233,986±10,552 with CDLCI ($p<0.0001$) (see Figure 1). For DBS, the high initial investment required during the first two phases (pre-treatment period to discharge; 32.2% of the total 5-year cost) is offset by decreases in antiparkinsonian pharmacological treatment and follow-up costs. The majority of the DBS costs are incurred before the initial sixth month. As explained, these results were obtained considering one battery replacement in the 5-years period and without including acquisition costs for CDLCI and CSIA devices and components (infusion pump, catheters, etc; only drug costs): consequently, if these costs were included, results would probably have been more favourable for DBS.

During the total 5-year period, with the amount necessary to treat one patient with CDLCI, two patients could be treated if DBS is chosen (or €145,972 could be saved) and €53,379 could be saved with CSIA.

Around 95% of the total 5-years cost of CDLCI and CSIA is related to constant pharmacological costs, mainly driven by Levodopa–Carbidopa intestinal gel cartridges and

Apomorphine ampoules acquisition costs (84.4% for CDLCI and 65.7% for CSIA), while for DBS, antiparkinsonian drugs represent only 43% of the total (see Figure 2).



	DBS	CDLCI	CSIA
Adverse Events	1%	1%	1%
Follow-up	8%	2%	3%
Implant / Admin.	47%	2%	0%
Pharmacological	43%	95%	96%

Fig. 2. Costs Distribution of each therapy in the 5 years (€, 2010)

Several alternative scenarios were tested in the sensitivity analysis: e.g., a second replacement in DBS therapy and a reduction of CDLCI and Apomorphine pharmacological costs. In all different the scenarios DBS remained the lowest costly therapy, even with the most unfavourable assumptions ($p<0.05$).

Due to the complexity and variability in the treatment of APD, the decision was taken to apply the Panel approach. This may be the main limitation of the study described. However, a Panel of Experts can contribute to mapping complex treatment processes, and to provide estimates of health care resources (Simoens, 2006). It is worth mentioning that the eleven experts of the Panel can be considered representative of the clinical practice of APD in Spain, as both neurologists and neurosurgeons from nine centres located in five different Spanish regions were involved, with experience on at least two of the three alternative therapies evaluated in this analysis.

Other published studies that estimated healthcare costs at least with one of the therapies to check if similar results are obtained. Only one Swedish study from 2008 estimated the annual cost of CDLCI (Sydow, 2008). Cost estimates oscillated between €40,000 and €80,000 according to the dosage used. These results corroborated the results of the SCOPE study, as

it was observed an average drug cost of €44,839 per patient per year and the intestinal gel cartridges of CDLCI represented an 84.4% of this total drug costs.
For DBS, as it was described, several published international economic evaluations were conducted in other countries, as presented in the review by Puig-Junoy et al (Puig-Junoy & Puig, 2009). Alike our study, five cost studies and five complete economic evaluations of DBS showed a reduction in medication costs associated with DBS.
From this survey, it can be concluded that despite DBS is perceived as a costly therapy, the initial investment for the implant is offset by a reduction in the consumption of other healthcare resources by patients over the years. For every patient yearly treated with CDLCI, two patients could be treated with DBS (€29,194 saved) and for every patient treated with CSIA; €10,676 could be saved if DBS would be chosen. On the other hand, CDLCI and CSIA are shown to require a constant use of relatively similar health resources, with pharmacological costs being the main source. Based on the results of this study, DBS seems to be the less costly therapy under the Spanish NHS perspective, compared to CDLCI and CSIA when applied to the adequate candidates.

5. Modelling interventions for advanced Parkinson's disease

Parkinson's disease is a complex illness, encompassing many different symptoms and costs, which makes undertaking an economic evaluation challenging. Numerous cost-effectiveness analyses have been published over the last 10-15 years, with significantly different approaches used to represent the progression of the disease, the effect of treatment upon symptoms and other outcomes, and the duration of treatment effect. Furthermore, there is currently an absence of an analysis which directly compares all relevant treatment options for patients with advanced PD. Outlined below are some of the key aspects for consideration in future economic evaluations of interventions for advanced PD.

5.1 Treatment comparisons

There are multiple interventions available for the management of patients with **A**PD. For example, DBS, CDLCI, CSIA and BMT are all options for patients at this stage of thedisease, and although there may be specific reasons for choosing one therapy over another, it is appropriate to consider the full range of interventions available. To date, economic evaluations have focused on comparing a limited number of interventions, rather than addressing the relative cost-effectiveness of each of the interventions listed above.
An analysis which considers a wide range of interventions would be beneficial, both in terms of helping payers to understand the value of each intervention, and in helping clinicians to make informed treatment decisions for their patients.

5.2 Disease indicators

PD is a complex disease which has many different aspects affecting management costs and health outcomes. When attempting to model the disease and the impact of different interventions, it is important to capture both the natural progression of the disease and the changes in disease indicators which occur over time. Previous models have dealt with disease progression in different ways: some have used UPDRS scores as the basis for measuring disease progression, whilst others have used the Hoehn and Yahr scale.
The majority of cost-effectiveness models (across all therapeutic areas) use a Markovian approach, in which patients are categorised into one of a finite number of health states. Data

are then used to estimate the movement of patients between these states over time, to reflect changes in disease status (this could include events such as disease progression and Mortality). In PD, the Hoehn and Yahr scale offers a logical way of splitting patients up into a relatively small number of categories. Trial data could then be used to determine how quickly patients move between these states e.g. from Hoehn and Yahr 2 to Hoehn and Yahr 3, and also to inform how mortality differs between the various stages. The UPDRS scale is less amenable to this approach, since there is no natural way of partitioning patients into categories according to their score. Since the Hoehn and Yahr class in the 'OFF' periods represents the status of the underlying disease, this is the most appropriate way of defining which Hoehn and Yahr class a patient is in at a given point in time.

There are other aspects of advanced PD which are relevant to both costs and health outcomes. For example, the amount of 'OFF' time is a key outcome, whilst outcomes such as non-motor symptoms and dyskinesias are also relevant endpoints to consider within a cost-effectiveness model. Each intervention impacts upon these aspects of the disease in different ways, and representing these differences is key to a comparative assessment of cost-effectiveness.

5.3 Quality of life

PD is a debilitating condition which can have a significant impact upon patients' quality of life (QoL). Some of the aspects of the disease which influence QoL include:

- The proportion of time the patient spends in the 'OFF' state;
- The severity of the 'OFF' periods;
- The predictability of the 'OFF' stages;
- Disease progression (e.g. in terms of Hoehn and Yahr stage).

Previous cost-effectiveness analyses have focused solely on the impact of motor fluctuations; however, there is a growing view that non-motor symptoms are also important determinants of QoL. Such symptoms may include depression, pain and sleep problems, and whilst the effect of these outcomes may be captured inherently within QoL assessments made routinely during trials, it is important that the effect of interventions upon these outcomes is addressed.

A standard approach to accounting for quality of life is to assign a health state utility to each health state within a model (e.g. one utility for Hoehn and Yahr 3, and a separate utility for Hoehn and Yahr 4). However, given that interventions for PD are focused on symptoms rather than underlying disease progression, such an approach may not be sufficiently sensitive to detect important treatment differences e.g. to represent the impact of an intervention which reduces the amount of 'OFF' time. In order to capture effects such as these, one approach would be to separate patients within each Hoehn and Yahr class into different levels of 'OFF' time, or to evaluate the change in their level of 'OFF' time compared with the baseline level.

Numerous tools have been used to assess patients' QoL during treatment, including generic and disease-specific questionnaires. Typical examples of generic tools include the EQ-5D and the SF-36, which can be readily converted into estimates of utility for the purposes of carrying out cost-utility analysis. The key disease-specific instrument for the measurement of QoL is the PDQ-39. However, to date, no mapping algorithm has been developed to allow the results of this tool to be mapped to health state utilities and so its use in cost-effectiveness modelling is currently limited.

A final issue relating to QoL is the impact of the disease upon patients' carers and families. Whilst this effect has been little-studied, it is a relevant outcome to consider owing to the burden which advanced PD can have upon these individuals. It is, however, a difficult endpoint to quantify, and this probably explains its omission from previous economic evaluations.

5.4 Costs

Advanced PD is associated with a wide range of costs for health systems, patients and their carers. Accurately representing the costs associated with the disease, and the impact of each intervention upon these costs, has a large bearing upon the cost-effectiveness outputs of a model. In general, a disease model which closely reflects the true natural history of the disease and incorporates its key aspects makes the process of assigning costs much simpler. Some examples of costs which should be included in a cost-effectiveness analysis include:

- Device acquisition and implantation;
- Management of device-related adverse events e.g. infections;
- Pump infections (for patients on CDLCI);
- Device explantation;
- Battery replacement;
- Ongoing drug costs;
- Nursing home care for patients with very severe disease;
- Inpatient care;
- Routine follow-up appointments.

This list focuses on costs falling on the health services; however, there are also wider costs associated with PD which are relevant. For example, some patients are forced to take early retirement due to the debilitating nature of the disease, and this has an impact upon society in terms of lost productivity of the workforce. This societal cost impact also extends to patients' families, who sometimes have to give up work.

5.5 Long-term outcomes

The majority of existing economic evaluations in the field of advanced PD have used a relatively short time horizon for assessing cost-effectiveness (between five and ten years), primarily due to the absence of robust trial data to populate long-term outcomes. This is a sensible approach, since any extrapolation of the trial data to predict long-term outcomes is inherently subject to considerable uncertainty. However, given that the impact of interventions may be expected to continue in the long-term, assessing the relative cost-effectiveness of different interventions over a longer time horizon may be beneficial. Many economic models in other fields (e.g. oncology) use a lifetime horizon in which patients are followed until death; such an approach would allow scenarios to be explored under assumptions of different levels of long-term treatment effect.

6. Conclusion

Disease management requires constant evaluation in regard of the quality of treatment as well as of cost-effectiveness. We have reviewed the issue of cost-effectiveness in PD and we think it is demonstrated that there is a need for formal and informal care of patients

suffering from chronic progressive diseases which is major challenge for health and social care systems in the years to come. However, more research is necessary to evaluate the full burden of PD and to explore efficacy and effectiveness of the disease management. At the present moment, giving the scarce evidence that we have found and the lack of direct prospective comparisons, it seems that DBS is the most cost-effective therapy for APD.

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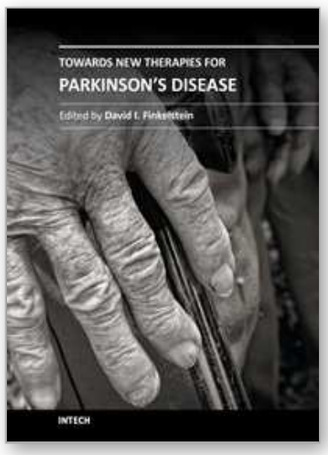
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Parkinson's disease (PD) is characterised clinically by various non-motor and progressive motor symptoms, pathologically by loss of dopamine producing cells and intraneuronal cytoplasmic inclusions composed primarily of ?-synuclein. By the time a patient first presents with symptoms of Parkinson's disease at the clinic, a significant proportion of the cells in the substantia nigra have already been destroyed. This degeneration progresses despite the current therapies until the cell loss is so great that the quality of normal life is compromised. The dopamine precursor levodopa is the most valuable drug currently available for the treatment of PD. However for most PD patients, the optimal clinical benefit from levodopa decreases around five to six years of treatment. The aim of the chapters of this book is to work towards an understanding in the mechanisms of degeneration and to develop disease modifying therapies.

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