Social and Economic Benefits of Early Optimised Treatment for Parkinson's Disease Patients – Improved Quality of Life and Greater Productivity

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Abstract

From a broad societal perspective, the economic burden of Parkinson's disease ranges from direct medication expenses to costs associated with home help and lost production. The last two generally arise in the more advanced stages of the disease. Savings are nevertheless possible and the two main ways of attaining this are by slowing down disease progression and reducing the time patients spend in off-periods. Earlier onset of optimised treatment, both in the initial and later disease stages, has the potential to achieve both. We highlight examples of advanced therapies that alleviate severe motor symptoms and thereby prolong the time patients can remain in their own homes and at their places of work. Health economic calculations for two forms of advanced therapy, continuous dopaminergic stimulation via pumps and deep brain stimulation, are also shown.

Keywords

Parkinson's disease, quality of life, advanced therapies, onset of treatment, socioeconomic burden, cost-utility

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Like other chronic neurodegenerative diseases, Parkinson's disease (PD) is associated with an impaired quality of life (QoL) for patients and costs to society. In Sweden at 2011 prices, the overall average cost per patient and year has been estimated at SEK (Swedish crowns) 148,000 or €16,500.[1] In 2005 in Europe, the direct cost was estimated as €10.7 billion per year, but it was considered that the total costs may be around 40 % more.[2] Significantly, future costs in developed countries were predicted to double by 2030.

Most of the costs associated with PD fall outside of the healthcare system, e.g. they are due to home care or lost productivity. A growing body of expertise believes that allocating more resources to early, optimised therapy can offset direct medication costs by raising patient QoL. This should reduce their need for home care and prolong the time they spend at work. We provide support for this view and show how economic simulation modelling can help generate meaningful cost-utility data.

Socioeconomic Experiences of Focused Treatment in Haemophilia

In developing countries with a per capita gross national product (GNP) of less than US$2,000, few citizens with haemophilia live beyond the age of nineteen. Many do not survive childhood. However, survival to adulthood and beyond increases approximately fivefold if these people have access to a specific haemophilia treatment centre (HTC).

Data collected by the World Federation of Haemophilia (WFH)[3] clearly show that even minimal level treatment at a HTC boosted recovery from bleeding episodes and increased survival to adulthood. This resulted in a quicker return to school or work, as well as preserved functional independence. Absenteeism decreased, productivity improved and the burden on caregivers was reduced.

A relatively modest investment in the health of haemophilia sufferers thus benefits both government and society since as adults they are able to work and contribute to the community. The long-term financial consequences of higher morbidity are avoided.

This simple yet dramatic example has parallels with the treatment of PD in western countries. Although the costs of treating PD may be higher than the expenses of running a basic HTC, the economic resources of industrialised nations are correspondingly greater. So just as it makes economic sense for countries with even limited resources to provide organised haemophilia care, developed countries should evaluate the cost benefits of the therapeutic options available for PD. Expenses associated with providing optimised treatment as early as possible could be more than offset by improved outcome.

Symptoms of Parkinson's Disease

PD is still primarily regarded as a movement disorder caused by the depleted production of the neurotransmitter substance dopamine (DA).[4] It is characterised by motor symptoms (MS) such

as slowness of movement, rigidity, tremors and balance problems.[5] This focus on MS has largely dictated the development of therapeutic options for treating PD and the administration of levodopa (the precursor of DA) and/or dopamine agonists has met with much success in combating the major visible motor complications of PD, especially when given orally.

Recent years have also seen an increased awareness of non-motor symptoms (NMS) as a cause of concern for PD patients.[6] Many NMS are considered to be as troublesome as MS or even more so. Typical NMS include depression, stress incontinence, sleep disorders, concentration difficulties, impaired memory, apathy and daytime sleepiness.

Current Treatment Approaches to Parkinson's Disease – The Potential of Early Treatment

The treatment of PD continues to make good progress and several recent advances now complement more traditional therapies.[7] Levodopa remains the most potent drug for controlling PD symptoms and is often given orally in the first years of the disease. It is nevertheless associated with motor complications and the timing of its therapeutic onset is the subject of some discussion. Various forms of continuous dopaminergic stimulation (CDS) have been advocated as a means of controlling motor fluctuations related to oral levodopa therapy, as has neurosurgical treatment.

Catechol-o-methyl-transferase (COMT) inhibitors, dopamine agonists and non-dopaminergic therapy are alternative modalities that have been investigated. These may be used concomitantly with levodopa or combined with one another. When optimised, COMT-inhibitor therapy or treatment based on monoamine oxidase type-B (MAO-B) inhibitors may help alleviate symptoms and prolong the QoL of PD patients.

A recent clinical trial, Attenuation of disease progression with azilect given once daily (ADAGIO) has demonstrated the potential of such an approach.[8] Results showed that people who received early treatment with rasagiline, a MAO-B inhibitor, showed slower progression of their disease as measured on the Unified Parkinson's Disease Rating Scale (UPDRS) than those who were diagnosed at the same time but started the same treatment nine months later.

As the ADAGIO study had a large trial population and a rigorous design, it is regarded as one of the most important studies of recent years. Its evidence that early intervention with rasagiline slows the course of PD reinforces the belief that starting treatment as early as possible benefits patient QoL and society in general.

Advanced Parkinson's Disease – Effects on Patients, Care-givers and Society

With advancing disease, the effect of prescribed oral medication, even when optimised, becomes shorter and more irregular. Gaps in the beneficial effect appear and patients spend less and less time in the so-called 'on' period. Fluctuations between 'on' and 'off' increase in intensity and both MS (e.g. involuntary movements) and NMS are affected.

The rapid fluctuations that characterise the advanced disease make life extra difficult for PD patients. The unpredictability of their symptoms means that it is hard to plan daily activities. At work, for example, colleagues may have to take over when the patient is unable to physically manage a task. Even NMS problems such as apathy or concentration difficulties can hinder PD patients from performing as they and their employer would wish. This can lead to considerable irritation and negative feelings. As a result, many PD patients consider part-time working or even early retirement.

Similar problems are likely to arise at home. Patients will find it increasingly difficult to participate in family activities. Their need for active help will become greater and they may eventually be regarded as a burden for a well-functioning family life.[9]

The QoL for all involved seems certain to suffer. Having to engage an outside care-giver or pay for a place in a nursing home may be an option that the family is forced to consider. All in all, advanced PD is a significant burden for society to bear.

Therapeutic Alternatives for Advanced-stage Disease

As noted above, optimising tablet treatment and/or adding MAO-B-inhibitors, dopamine agonists or COMT-inhibitors may provide some temporary respite, as would use of a transdermal patch such as Neupro®, which contains the dopamine agonist rotigotine.[10]

However, when oral or patch therapies no longer provide sufficient effect, the only viable long-term alternative lies in one of several more advanced solutions. Briefly, these comprise alternate ways of providing CDS or neurosurgical treatment. CDS can be achieved via small medicinal pumps carried by the patient that administer a steady flow of levodopa (usually in the form of a levodopa/carbidopa gel known as Duodopa®) directly into the small intestine, or Apomorphine (a dopamine agonist) injected under the skin via a needle. The neurosurgical approach involves implanting thin electrodes into the brain to continuously stimulate deeply located brain regions with high-frequency current. Known as deep brain stimulation (DBS), its effect resembles that of levodopa.

The main advantage of these advanced therapies is that they overcome the rapid fluctuations associated with conventional oral medication. Almost without exception, they dramatically improve the patients' MS. Reported treatment effects of CDS delivered into the small intestine have been positive. For example, an 89 % initial reduction in the time spent in the 'off' state has been observed.[11] It has also been shown that DBS has an excellent effect on MS for up to 10 years in advanced PD.[12] Dyskinesias and motor fluctuations were greatly reduced and most patients required only half the amount of conventional medication. Compared with best medical treatment (BMT), DBS improved patient QoL. Moreover, results from several studies show that even NMS benefit from such advanced treatments.[13] When combined with specific therapies for NMS, e.g., anti-depressants or urological therapy, the overall result can be a significant improvement in patient QoL and capability for productive work.

Timely Application of New Therapies Requires Simpler Assessment Methods

Today, advanced therapies are generally first considered when the motor fluctuations have become so severe as to exclude the patient from enjoying a normal family and working life. Additionally, the evaluation process requires a spectrum of experts with considerable experience of PD plus specialist treatment centres. As well as taking

time, this means that many patients with advanced PD never get the chance to be considered for these therapies.[14] Some may not even know about them. One probable outcome is that many PD patients may never receive optimal medication, which can mean that they are forced to give up work and/or move into care much earlier than is otherwise necessary.

As new effective treatments for PD are evolving all the time,[7] it is important that patients seek medical advice as soon as the early signs of PD are detected. Investing in an earlier and simpler means of evaluating their need for newer therapies could thus repay itself in reduced indirect costs for society as well as greater QoL for patients.

Calculating the Economic Cost of Parkinson's Disease on Society

Stabilising patients' medical condition with early, optimised treatment should help them avoid the disruptive effect of the symptoms on their working situation and family life. There could thus be socioeconomic gains to be won by slowing down PD progression at earlier stages than is often the practice today. Furthermore, in an ageing population with increased disease prevalence, the gains for society, patients and care-givers could be considerable.

Allocating increased priorities to earlier treatment of PD nevertheless requires that politicians, healthcare authorities and decision–makers are aware of the economic impact of the disease. Estimating the costs of PD and the cost effectiveness of treatment is thus becoming increasingly important. Unfortunately, healthcare costs in PD are relatively sparsely investigated and knowledge of the economic impact of the disease is limited. However, this situation is now beginning to change and a clearer picture of the costs associated with PD is emerging.

Parkinson's Disease Costs Increase with Disease Severity

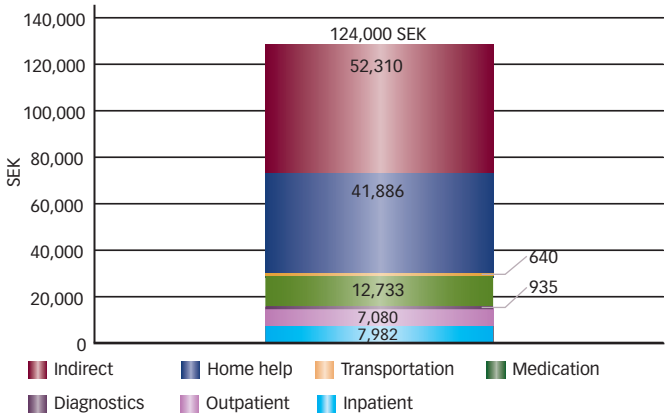
PD costs are generally broken down into direct medical costs, e.g. drugs and hospital care, direct non-medical costs (including home care and special housing) and indirect costs due to sick-leave, early retirement, etc.

Several studies over the past decade have examined this breakdown in more detail. In 2002, a major Swedish cost and resource study of 127 randomly selected PD patients found that direct healthcare costs averaged about SEK 29,000 (approximately US$2,900, €3,200) per patient per year.[15] Drugs were the most costly component. Direct non–medical costs were higher still, averaging about SEK 43,000 (approximately US$4,300, €4,800). Costs due to lost production (i.e. indirect costs) were SEK 52,000 (approximately US$5,200, €5,800). The mean total annual cost for PD thus approximated to SEK 124,000 (approximately US$12,400; €13,800) per patient per year at 2000 prices (see *Figure 1*).

Significantly, the cost per patient increased according to the Hoehn and Yahr (H&Y) stage of disease. In H&Y stage I, the cost was SEK 55,000 (US$5,500, €6,100). By stage V this had risen to SEK 181,000 (US$18,100, €20,100) (see *Figure 2*).

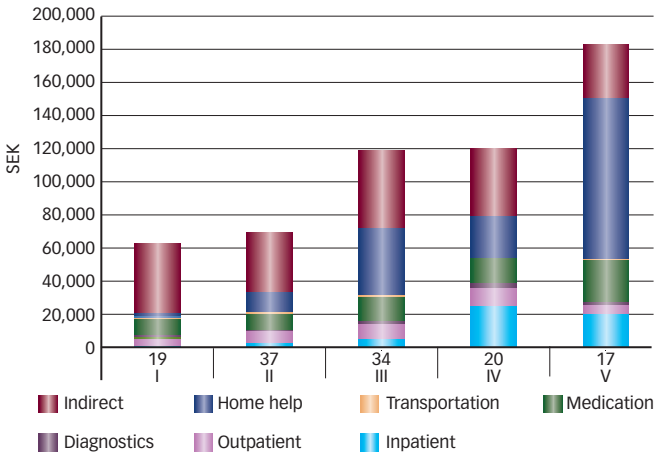
At each H&Y stage, the indirect cost of lost production was the greatest single item, accounting for 42 % of the mean annual cost. In the most severe stage, the costs for home care are extensive.

Figure 1: Parkinson's Disease-related Costs per Patient During One Year in Sweden – Year 2000 Prices



SEK = Swedish crowns. Source: Hagell et al., 2002.[15]

Figure 2: Average Cost per Patient at Different Hoehn and Yahr Stages – Year 2000 Prices



SEK = Swedish crowns. Source: Hagell et al., 2002.[15]

A Finnish study on the economic burden and impaired health-related QoL (HRQoL) made at about the same time as the Swedish study also noted a strong relationship between the severity of PD, decreasing HRQoL and increasing costs.[16]

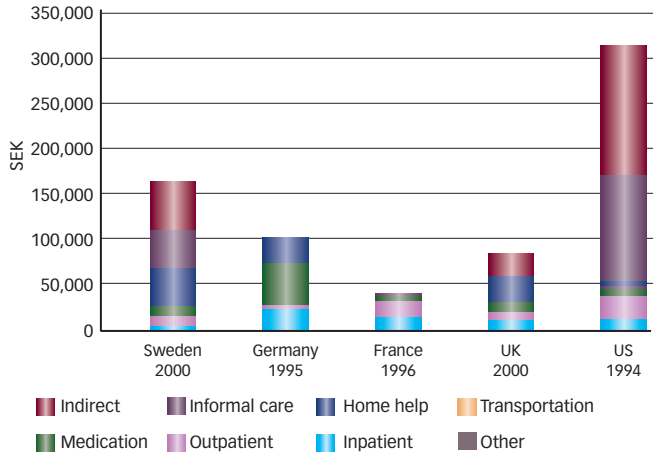
International Comparisons Show Costs per Country Vary

That PD places a financial burden on society, both in direct and indirect costs, has also been noted in other countries, although differences in healthcare organisation, reimbursement policies, etc., make firm cross-national comparisons somewhat uncertain.

When the Swedish study compared its direct healthcare costs with those found in German, French, British and North American investigations, it found that the highest medication costs occurred in Germany. In that country, drugs accounted for 42 % of the total healthcare costs, approximately twice that found in France and the US (see *Figure 3*). In the US, indirect costs and costs for informal care were substantial.

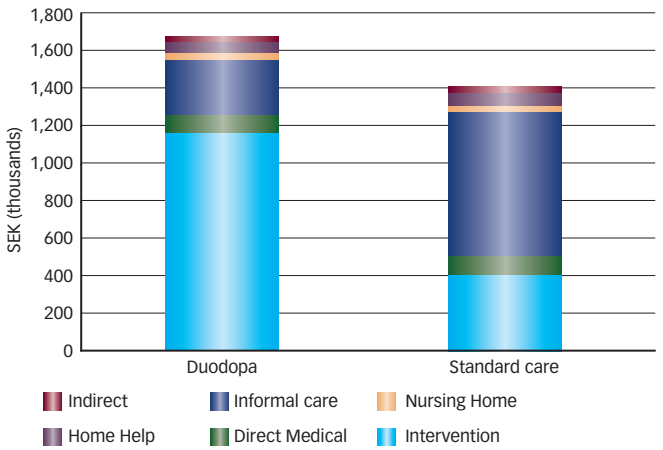
Total annual direct healthcare costs in Sweden appeared to be lower than the other four countries. Swedish home-care costs were higher than direct healthcare costs and also higher than that estimated

Figure 3: Parkinson's Disease Cost per Patient in Some Countries



Compared with Figure 1, *estimates from Sweden and the US also include costs for informal care (eight and 22 hours per week respectively). SEK = Swedish crowns. Source: Hagell et al., 2002.*[15]

Figure 4: Costs per Patient with Advanced Parkinson's Disease Treated with Continuous Intraduodenal Infusion of Duodopa® versus Standard Care – Five Years' Simulation Analysis



SEK = Swedish crowns. Source: Willis and Gradl, 2010.[19]

in the other studies. Swedish estimates of indirect costs due to lost production were between those from the UK and US.

Indirect Costs and Loss of Employment are Significant Factors

Further investigations of the economic burden of PD confirm this picture. A 2008 German review demonstrated that the majority of costs are outside the healthcare system and that these increase substantially with disease progression.[17] For example, a health economics study in that country between 2004 and 2006 examined the HRQoL of 145 PD patients with an average age of 67 years in different H&Y stages. The total annual cost was €20,860 per patient. This comprised €3,720 in direct costs (excluding medications) and €3,840 in drug costs, i.e. slightly more than one-third of the total. Indirect costs were quite high (€6,360).

Analysing costs by H&Y stage revealed that the costs of retirement and healthcare insurance payments increase disproportionately in the advanced disease stages. One conclusion drawn by the review authors was that due to the expensive nature of the disorder, the medical community should ensure that enough funding is available for suitable and innovative treatments.

The significance of lost employment on the cost to society of PD, especially in its advanced stages, was indicated by UK studies made at about the same time as the German review.[18] In groups of 151 and 308 PD patients with onset age before 65 years, 52 and 57 % of patients retired early due to PD, while 18 and 5 % of patients were unemployed and 8 and 11 % part-time-employed. Mean age of retirement was 55.8 years compared to an average retirement age of 62 years in the UK population. Forty-six per cent had stopped working after a disease duration of five years and 82 % after 10 years. It was concluded that on average, PD leads to loss of employment in less than 10 years of onset.

Allocating Healthcare Priorities

To provide information and support discussions about future cost allocations and healthcare priorities, an attempt was made to estimate the drug and treatment costs for PD patients during 2009 in Stockholm County as well as in the whole of Sweden.[1]

Total direct healthcare costs per patient averaged SEK 76,000 at 2009 price levels. Drug costs were SEK 15,880 (21 %). In the Swedish study a decade earlier, the direct costs were estimated as SEK 71,200 per patient and year, including the increasing costs of advanced treatments, although that study also included home care.

If the percentage of indirect costs of lost production due to absence from work in the most recent Swedish study was the same as that noted in 2002 (42 %), this would add SEK 63,000 per patient at 2009 prices. The annual total cost per patient would thus be SEK 139,000. Like others before them, the authors observed that the impact of PD places a significant burden on patients and society.

Health Economic Analyses for Advanced Treatments

Health economic analyses will be important when estimating the costs of modern PD treatments and whether these costs are reasonable in relation to the benefits that they bring and what society is prepared to pay for them.

The advanced therapies named above (i.e. CDS via pumps and DBS) represent the only options once oral and patch medication lose their efficacy. Some health economic studies are available for CDS into the small intestine and for DBS. It should nevertheless be noted that these studies are often based on small trials with low patient numbers and that short-term follow-up periods may be unable to provide data for the entire range of benefits. Certain assumptions must therefore be made when evaluating data. Combining clinical trial results with resource utilisation data from other sources should offer a good basis for economic simulation modelling.

Figure 4 illustrates the results of a five-year simulation analysis for CDS with Duodopa®.[19] Base case results showed that total treatment costs per patient increased from SEK 1,410,643 (€147,108) to SEK 1,674,295 (€174,603) compared with standard care. On the other hand, important cost offsets (SEK 461,617) were seen in home help.

In addition, quality-adjusted life-years (QALYs) improved from 0.68 to 1.30, an increase of 0.62 QALYs. Informal care giving contributed

to only 0.02 of this increase (conservatively estimated). The corresponding incremental cost-effectiveness ratio (ICER) was about SEK 420,000 (€43,800) per QALY gained and the ICER for nearly 90 % of the cohorts fell below SEK 655,000 (€68,306), which is the willingness-to-pay threshold often cited for Sweden at 2001 prices.[20]

Table 1 summarises this data. The overall evaluation is considered to provide the necessary evidence that the health benefits conferred represent good value for money for healthcare providers and society in general.

Similar data point to DBS also being cost-effective in the long term. Although a 2009 systematic review[21] of DBS costs and efficiency in advanced PD patients found that some studies estimated the equivalent annual cost of the treatment as being 54.7 % higher than traditional therapy, other studies that included indirect costs (e.g. productivity losses) found evidence that DBS costs 34.7 % less.

More conclusively, a 2011 German review[22] comparing DBS versus BMT by estimating impact on patient HRQoL and cost from the societal perspective found that DBS was likely to be cost-effective compared with conventional treatment. From a lifetime perspective, the incremental cost-utility ratio (ICUR) for DBS was €10,227 per QALY gained. The high initial costs of surgery were traded off by long-term gains in HRQoL, giving a decreasing ICUR over time (year one = 408,600 €/QALY; year two = 68,500 €/QALY; year five = 25,200 €/QALY; year 10 = 17,500 €/QALY).

Finally, the 2011 review interpreting overall health economics data in PD suggested a similar conclusion.[2] When assessed via a small number of cost effectiveness analyses, DBS appeared cost-effective in the long term (i.e. over five years or more). ICERs for DBS ranged from approximately €10,000 per QALY to €50,000 per QALY, which would make DBS cost-effective according to World Health Organization (WHO) definitions.

Table 1: Incremental Costs per Quality-adjusted Life-year Gained per Patient with Advanced Parkinson's Disease Treated with Continuous Intraduodenal Infusion of Duodopa® versus Standard Care – Five Years' Simulation Analysis

	Duodopa	Standard Care	Difference
Total Costs (SEK)	1,674,295	1,410,643	263,652
QALYs	1.30	0.68	0.62
ICER	–	–	421,761

ICER = incremental cost-effectiveness ratio; QALYs = quality-adjusted life-years. SEK = Swedish crowns; Source: Willis and Gradl, 2010.[19]

Conclusions

New therapeutic developments as well as advanced treatments such as CDS via pumps and DBS have a true potential to improve the QoL of PD patients, both in early and advanced disease stages. Providing optimised treatment at the right time should therefore give significant cost benefits. The most obvious will be that patients stay longer in their normal housing, enjoy a good social life and remain longer at their place of work. This greater independence should lower the economic cost burden on society.

Although many of the advanced therapies may seem expensive, the investment they represent will reduce the indirect costs of PD in the long-term. One prerequisite for beginning optimised treatment earlier is the availability of simpler and more effective assessment methods that are available to more patients and that enable physicians to judge how and when to initiate these improved therapies. ■

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