Economic aspects of Parkinson's disease

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Abstract

Background

Next to Alzheimer's disease, Parkinson's disease (PD) is the second most neurodegenerative disease[1]. As the population structure in the industrialized and industrializing countries is changing, an increasing prevalence of diseases typical for the elderly is projected within the next decades. The burden of disease, cost driving factors and the effectiveness of disease management options are therefore important information, as health and social care systems must prepare for a rising demand for economic resources and trained personnel within the health care sector.

Objectives

The objective of this thesis was to describe different aspects of the economic burden of PD as drug costs, institutional care, hospitalization and the cost-effectiveness of the disease management.

Subjects

In the first study we evaluated a group of 286 consecutive patients with PD searching free advice in a German counseling program and a group of 152 consecutive Norwegian patients with PD being followed at the outpatient clinic of the Stavanger University Hospital.

In the second and third study we included the 108 patients with PD from a population-based prospective longitudinal study in Southern Rogaland, Norway, who were living in the municipality of Stavanger at baseline. Through the National registry we identified eight control subjects for every patient with PD that matched in sex and age and were living in Stavanger at baseline.

In the fourth study we included 199 patients participating in a population-based prospective longitudinal study of patients with incident PD from Western and Southern Norway. Among relatives and acquaintances of the patients 205 controls were recruited. We included a subset of 172 control individuals who provided the best possible group match regarding sex, age and education and complete information about their health status.

Methods

In the first study data about disease duration, disease severity as measured by Hoehn and Yahr (HY) stage[2], and drug use were collected for both patient groups in a cross-sectional study design.

In the second study, for patients with PD data about disease duration, disease severity as measured by HY stage, cognitive functioning as measured by the Mini Mental State Examination (MMSE)[3], date of permanent admission to a nursing home and date of death were collected from the patient files and the municipality's registration systems during a 12-year observation period. For controls, data about age, date of admission to a nursing home and date of death were collected from the municipality's registration systems and the National registry.

In the third study data about hospital admissions, length of stay and diagnoses at discharge were collected from the files of the Stavanger University Hospital for patients and controls over a 12-year observation period.

In the fourth study, for the patients with PD data about disease severity as measured by HY stage and the Unified Parkinson's Disease Rating Scale (UPDRS)[4], health status as measured by the Short form 36 (SF-36)[5] and drug use was registered during the first year of medical treatment. For controls independency in daily living as measured by the UPDRS part II and the SF-36 were registered during the same period. To evaluate health state values, the data of the SF-36 were converted to the Short Form-6D (SF-6D)[6].

Results

We found that drug expenses rose with disease duration and disease severity both in the German and the Norwegian study cohort. However, expenses were markedly higher in the German cohort with Euro 5.78 versus Euro 3.92 per patient and day, partly due to an earlier switch from mono- to multi-drug therapy during the course of the disease.

Patients with PD had a five-fold higher risk for living in a nursing home as compared to controls. Based on 2007 prices, the incremental costs for institutional care were Euro 14 897 per person year of survival.

There was no significant difference between patients with PD and controls regarding the number of individuals being admitted to hospital, numbers of admission, or length of stay. However, we found that patients with PD were more often admitted for trauma, while cardio-vascular diseases and cancer were markedly more common in control individuals.

Patients with PD had significantly lower health state values as compared to controls. Patients starting on antiparkinsonian drugs had an improvement in utility scores of 0.039 from 0.667 to 0.706. The incremental cost-effectiveness ratio (ICER) was Euro 45 259 per quality adjusted life year (QALY) during the first year of treatment, of which two thirds were caused by drugs and one third by costs for clinical consultations.

Conclusion

We could show that the use of control cohorts adds valuable information to the evaluation of the burden of disease and helps to discern costs related to a certain disease from costs caused by general age-related morbidity. We could further show that prescription habits may differ markedly from country to country and that the ICER during the first year of treatment is high. Therefore, disease management should be monitored carefully to provide an optimal quality of treatment as well as cost-effectiveness. However, more research is necessary to evaluate the full burden of

PD and to explore efficacy and effectiveness of the different disease management options.

List of publications

1. **Vossius C**, Gjerstad M, Baas H, Larsen JP. *Drug costs for patients with Parkinson's disease in two different European countries.* Acta Neurol Scand. 2006;113:228-32.

2. **Vossius C,** Nilsen OB, Larsen JP. *Parkinson's disease and nursing home placement: the economic impact of the need for care.* Euro J Neurol 2009; 16 (2): 194-200.

3. **Vossius C,** Nilsen OB, Larsen JP. *Parkinson's disease and hospital admissions: frequencies, diagnoses and costs.* (In press in Acta Neurologica Scandinavica.)

4. **Vossius C**, Nilsen OB, Larsen JP. *Health state values during the first year of drug treatment in early-stage Parkinson's disease.* (Re-submitted after major revisions to Drugs and Aging, May 2009.)

Contents

1. Introduction

The intermingling of medicine and economy has been an issue for several thousand years. Asclepius, the god of medicine and healing in ancient Greek mythology, was stricken to death by Zeus with a thunderbolt because he raised the dead and accepted gold for it. Hippocrates of Kos (around 460 to 370 BC.) said: "We are allowed only to accept payment from those cured, when given out of gratitude, not something the patients promise when under great duress."[7], and as well in the Bible, Exodus 21.19, this question is discussed. Up to today the availability and fair distribution of medical help remains an issue of great and unsolved ethical significance, as its administration depends not only on the appropriate knowledge but as well on sufficient economic resources.

Health economics is the branch of economics concerned with health and health care and the scarcity and allocation of resources within health care. Parkinson's disease (PD) is a common neurodegenerative disease of the elderly, and its prevalence is expected to increase due to increasing live expectancy. The general part of this thesis will give a brief overview over the disease and over the field of health economics. Furthermore, this thesis intends to describe some aspects of the economic burden of PD as drug costs, institutional care, hospitalization and the cost-effectiveness of the disease management.

1.1 Parkinson's disease

1.1.1 Epidemiology

Besides essential tremor Parkinson's disease (PD) is the most common movement disorder, and next to Alzheimer's disease the second most neurodegenerative disease[1]. In epidemiological research, the diagnosis of PD still relies on clinical criteria, as a definite diagnosis of PD requires post-mortem confirmation. The disease is found in all ethnic groups but with differences in prevalence[8]. Onset of sporadic PD in individuals under 50 years is only seen in 4% of the patients[9]. But both prevalence and incidence increases with age, and approximately 1-2% of the population over 65 years and 3-5% of those elder 85 years suffer from PD[10]. This indicates that about 0.5 to 1 million patients with PD are living in the European Union with approximately 500 million inhabitants[11].

Even if incidence studies are supposed to be more accurate as they are not influenced by mortality, reported incidence rates are showing substantial variance, probably due to methodological issues[8]. In the Western world, age-standardized incidence rates vary from 8.6 to 19.0 per 100 000 inhabitants[12]. Though results are contradicting and seem to differ with ethnicity, it is assumed that the incidence of PD is slightly higher in males[8].

1.1.2 Etiology and risk factors

Until now the origin of the vast majority of idiopathic PD cases is unknown, and the strongest confirmed risk factor is advancing age[13]. Increasing evidence suggests that PD represents a common clinical feature of heterogenic causes[14].

In several epidemiological studies, relatives to patients with PD were found to have a 3 to 4-fold increased risk for developing PD as compared to the general population[15, 16], and in approximately 10% of the cases a genetic cause is assumed. Until today

several gene mutations have been found, most of them causing juvenile or early onset PD, while others appear to cause parkinsonism resembling sporadic PD with respect to both clinical and demographical features[8].

A variety of non-genetic risk factors has been proposed. Most consistently, smoking is related to a reduced and exposure to pesticides to an increased risk for developing PD[17, 18].

1.1.3 Pathogenesis and pathophysiology

Since the 1960's it has been known that PD is caused by the degeneration of dopamine producing cells in the substantia nigra. Motor symptoms occur when 60 to 80% of the cells are destroyed[19, 20]. Today, however, there is evidence that PD is a multi-system brain disease, involving as well serotonergic, adrenergic and cholinergic systems[21]. Braak and colleagues suggested a sequential development of the disease, starting in the brainstem and spreading via the midbrain and mesocortex to the cortex[22, 23]. Neurodegeneration is characterized by typical inclusions of aggregated α-synuclein, called Lewy-bodies. Braak proposed six stages, of which the first two represent pre-symptomatic stages and the last two severe disability and dementia. These changes appear to be due to oxidative stress, mitochondrial dysfunction and impairment of the ubiquitin-proteasome system. However, it is not yet clear how these pathways leading to premature cell apoptosis and clustering of intracellular α-synuclein are triggered[24-26].

1.1.4 Clinical course and disease classification

1.1.4.1 Motor symptoms

PD is characterized by four so called “cardinal symptoms”: Tremor, bradykinesia, rigidity and postural instability. But not every patient has to present with every symptom. In idiopathic PD, symptoms normally start unilaterally and remain asymmetric during the whole course of the disease.

Tremor is the most common motor symptom in PD and is present in 60 to 70% of the patients at disease onset[27-29]. The amplitude is variable and increases with anxiety or tension, while tremor disappears during sleep. Initially only a resting tremor, it may progress to postural and activity tremor, interfering with activities of daily living (ADL) and become a challenge to disease management.

Bradykinesia describes a general slowness in movements, the difficulty to initiate movements and their decreased amplitude. This results in reduced facial expression and difficulties with alternating movements, progressing to gait inhibition with start hesitations and festinations and potentially severe impairment of ADL.

Rigidity describes an elevated muscle tone, resulting in increased resistance when passively flexing or extending a joint. The so called “cogwheel phenomenon” is a combination of increased muscle tone and tremor. Clinically, rigidity leads to discomfort and aggravates the impairment caused by bradykinesia. Both bradykinesia and rigidity are the symptoms best accessible by medical treatment.

Postural instability is seldom present in the early stages but develops over the course of the disease. Axial symptoms involve the typical stooped posture, but may as well lead to a posture leaning to one side. Postural alterations and decreased postural reflexes lead to propulsion and retropulsion with the impairment of gait and

an increased risk for falls. The successful management of rigidity and bradykinesia may as well improve postural instability.

1.1.4.2 Non-motor symptoms

As the motor symptoms in PD are quite dominant and – at least to a certain degree – treatable, non-motor symptoms often receive little attention. They are, however, present in close to 90% of all patients with PD and may severely affect the quality of life in both patients and caregivers[30]. They may develop during the course of the disease or even precede motor symptoms. Non-motor symptoms dominate the clinical picture of advanced PD and contribute to severe disability, reduced health-related quality of life (HR-QoL) and increased mortality[31].

Depression is common in PD. Prevalence figures differ widely, but an average of 25 to 40% is assumed. The diagnosis of depression in PD might be challenging, as there is an overlap with other features like fatigue, apathy, and reduced spontaneous motor functioning. There are no specific characteristics of depression in PD as compared to the general population, but anxiety, dysphoria and irritability are reported more often, while self-blame tendencies, feelings of guilt and suicidality are reported less frequently[32].

Cognitive decline and dementia are among the most common non-motor changes in PD with an 80 % life-time risk of becoming demented[33]. Mild cognitive impairment occurs even in early PD and is associated with a shorter time span to develop dementia[34]. It is characterized by executive impairment, attention shift and visuospatial dysfunction[35]. Other risk factors associated with dementia in PD are old age, disease duration, disease severity, and axial symptoms like postural instability or speech problems[36-39].

Hallucinations are most commonly visual hallucinations. They were previously considered as a side effect of the medical treatment of PD, but recent studies could not show any association between the development of hallucinations and the dosage

or duration of the treatment[40, 41]. However, hallucinations are normally treated with a reduction in antiparkinsonian therapy and the elimination of drugs that are supposed to especially evoke psychosis like anticholinergics and dopamine agonists. In addition, atypical neuroleptics can help to control them. Hallucinations are an independent risk factor for admission s to nursing homes and can be experienced as very distressing by both patients and relatives.

Fatigue is characterized by the subjective experience of a lack of energy, extreme tiredness and feeling of exhaustion after only small efforts. It can be both a physical and mental problem. Fatigue is not restrained to PD but can be seen in various neurological, psychiatric and systemic disorders. Even if there is overlap with other non-motor features like depression and apathy, it is assumed that as many as approximately 50% of the patients with PD experience fatigue[42].

Apathy describes a state of diminished motivation that leads to a reduction of initiative, flattening of affect or lack of emotional responses and lack of intellectual interest[8]. Until now there is little data published about apathy. A population–based cross-sectional study showed that apathy is common in the general PD population and may present as an independent behavioural disorder[43]. Apathy might be more often experienced as problematic by spouses than by the patients themselves.

Sleep disorders: As PD involves the brainstem and communicating pathways in the ascending arousing system through the hypothalamus and thalamus to the cortex, sleep disorders are not uncommon. In addition, other symptoms like depression or motor impairment might contribute, and dopaminergic drugs, especially dopamine agonists are linked to different sleep complaints[44, 45]. *Insomnia* is the most frequent sleep disorder with a prevalence of 90% in a population-based cross-sectional study[46]. *Excessive day time sleepiness* (EDS) is reported in 15% in the same study population and has been shown to increase with disease duration[47, 48] . *Sudden sleep attacks* have been linked to dopamine agonists[49] . *REM sleep behaviour disorder* (RBD) is a parasomnia characterized by motor activity during REM sleep due to the loss of skeletal muscle atonia normally present during that sleep phase, leading to

vocalization and movements during the sleep, normally associated with dreams. Patients with RBD have an increased risk to develop PD and other α-synocleinopathies like Multi system atrophy or Lewy-bodies disease, and up to one third of patients with PD are affected[50, 51]. *Restless legs* (RLS) and *periodic limb movements during sleep* (PLMS) are sleep disorders related to each other. There is evidence that these disorders are more common in patients with PD[52, 53]

Autonomic disturbances: Symptoms like orthostatic hypotension, hypersalvation, urinary problems, constipation, sweating and sexual dysfunction are signs of autonomic dysfunction in PD of which the most frequent are constipation and urinary problems[54].

1.1.5 Diagnosis and differential diagnosis of PD

Parkinsonism is a term describing a syndrome with the main motor features typical for PD (bradykinesia, rigor, tremor), despite its cause. Distinguishing idiopathic PD from other causes of Parkinsonism may be challenging, and even experienced neurologists fail[28]. Functional brain imaging using dopamine-ligands in single photon emission computed tomography (SPECT) or positron emission tomography (PET) may be used as supplementary diagnostic devices, but still in most patients the diagnosis is made according to the clinical symptoms and the effect of dopaminergic treatment. The use of strict diagnostic criteria therefore helps to improve diagnostic accuracy[55].

The **Stavanger PD diagnostic criteria** differentiate between clinical definite, probable and possible PD[56].

Clinical definite idiopathic PD: Asymmetrical presentation and tremor. In addition at least one of the following symptoms: rigidity, bradykinesia or postural abnormality. Good or excellent response to dopaminergic agents. No atypical signs at disease onset and CT or MRI of the brain without major pathology.

Clinical probable idiopathic PD: Two of the four cardinal symptoms present and not more than one of the following atypical features: dementia or clinically relevant autonomic failure at disease onset, symmetrical disease presentation, moderate response to dopaminergic treatment, or other atypical signs or symptoms that indicate another parkinsonian disorder.

Clinical possible idiopathic PD: At least two of the four cardinal symptoms and at least moderate response to dopaminergic treatment. Mild to moderate dementia and autonomic failure is allowed.

According to the **Gelb criteria**, the definite diagnosis of PD can only be made post mortem, when a clinical probable PD is confirmed by histopathologic confirmation. Table 1.1 shows a grouping of clinical features suggestive and non-suggestive for PD while table 1.2 shows clinical diagnostic criteria for PD as proposed by D.J.Gelb[57].

Table 1. Grouping of Clinical Features According to Diagnostic Utility

Group A features: characteristic of Parkinson disease
Resting tremor
Bradykinesia
Rigidity
Asymmetric onset
Group B features: suggestive of alternative diagnoses
Features unusual early in the clinical course
Prominent postural instability in the first 3 years after symptom onset
Freezing phenomena in the first 3 years
Hallucinations unrelated to medications in the first 3 years
Dementia preceding motor symptoms or in the first year
Supranuclear gaze palsy (other than restriction of upward gaze) or slowing of vertical saccades
Severe, symptomatic dysautonomia unrelated to medications
Documentation of a condition known to produce parkinsonism and plausibly connected to the patient's symptoms (such as suitably located focal brain lesions or neuroleptic use within the past 6 months)

Table 2. Proposed Diagnostic Criteria for Parkinson Disease

Criteria for POSSIBLE diagnosis of Parkinson disease:

At least 2 of the 4 features in Group A* are present; at least 1 of these is tremor or bradykinesia

and

Either None of the features in Group B* is present

Or Symptoms have been present for less than 3 years, and none of the features in Group B* is present to date

and

Either Substantial and sustained response to levodopa or a dopamine agonist has been documented

Or Patient has not had an adequate trial of levodopa or dopamine agonist

Criteria for PROBABLE diagnosis of Parkinson disease:

At least 3 of the 4 features in Group A* are present

and

None of the features in Group B* is present (note: symptom duration of at least 3 years is necessary to meet this requirement)

and

Substantial and sustained response to levodopa or a dopamine agonist has been documented

Criteria for DEFINITE diagnosis of Parkinson disease:

All criteria for POSSIBLE Parkinson disease are met

and

Histopathologic confirmation of the diagnosis is obtained at autopsy (see Table 3)

** Group A and Group B are detailed in Table 1.*

1.1.6 Disease management

PD is still an incurable disease, and disease management aims at the alleviation of the symptoms, improvement of the quality of life, support of patients and caregivers and

- to a certain degree - reduction of disease progression. Management strategies include antiparkinsonian drugs, surgery, physiotherapy, and information.

1.6.1 Drug treatment against motor symptoms

Pharmacological treatment of PD became available during the 1960's with the introduction of levodopa medication. Today, the gold standard of medical treatment in incident PD is levodopa in elderly patients, while younger patients start with a dopamine agonist. When the disease progresses and increasing the dosage either does not show satisfying effect or leads to side effects, a combination of levodopa, dopamine agonists or Catechol-O-methyltransferase (COMT**)** inhibitors are normally given. In addition, patients younger than 75 years often receive monoaminoxidase-B (MAO-B) inhibitors due to their assumed neuroprotective effect.

As antiparkinsonian drugs are a main part of PD management and therewith have a considerable impact on treatment costs, their indications, side effects and history are outlined here.

Anticholonergics

Anticholinergics were the first drugs used for PD, from the beginning of the last century, as they adjust the imbalance between acetylcholine and dopamine in the striatum. They have a certain effect on tremor and they improve some autonomic symptoms like excessive sweating and salivation. However, their effect on PD-symptoms is mild, while there are severe side effects, mainly hallucinations. Therefore, in today's treatment these drugs are hardly used any more.

Amantadine

Amantadine has been known as flu medications since the 1930's. For the use in PD it was approved by the FDA in 1969. Both its antiviral action and its antiparkinsonian effect are poorly understood, but amantadine is a weak NMDA receptor agonist and

an anticholinergic. Besides its use in improving motor symptoms in PD it has also been used to improve long term complications of PD treatment as fluctuations and dyskinesias.

Levodopa

Levodopa was introduced during the 1960's; marking a turning point in the treatment of PD as it was the first effective drug for the disease. Levodopa is a precursor of dopamine and passes the blood-brain barrier. It is taken up by dopaminergic neurons and decarboxylated to dopamine, therewith compensating for the deficient dopamine production caused by degeneration of the substantia nigra. To prevent peripheral decarbocylation, levodopa is normally combined with either carbidopa or benserazide. Compared to other antiparkinsonian drugs levodopa has a favourable profile of side effect. However, long term use is associated with the development of fluctuations and dyskinesias, probably due to the pulsative stimulation of the dopamine receptors. In advanced stages of the disease the continuous application of levodopa via a trans-abdominal tube is possible. Despite of the development of several new drugs, levodopa has remained the most important antiparkinsonian drug until today.

MAO-B inhibotors

Selegiline was discovered by Jozsef Knoll in the 1950's and introduced to the drug management of PD in the late 1970's. It acts as a MAO-B inhibitor and therewith inhibits the degradation of dopamine in the striatum. Besides a mild antiparkinsonian effect several studies have shown that the use of selegiline reduces progression in PD and thus might have a neuroprotective effect, but until today the results have not been conclusive. Recently, selegiline has as well been used as antidepressant, and it has been promoted as an anti-aging drug. Today, **rasagiline** is the newest antiparkinsonian drug on the market. It is a MAO-B inhibitor and is promoted to have a decreasing effect on the progression of PD.

Dopamine agonists

Dopamine agonists directly stimulate the postsynaptic dopamine receptors. As a first short lasting agonist **bromocriptine** was introduced to the market in the 1970's, shortly after followed by **lisuride** and **alpha-dihydroergotamine**, all with a half-life period of three to five hours. In the 1980's **pergolide** was the first long acting agonist with a half-life period of approximately eight hours. During the 1990's **cabergoline** with a half-live period of 72 hours came to the market. At the same time the first non-ergot derivates were introduced, **pramipexole** and **ropinirole**, while **rotigotine** was the first transdermal application. **Apomorfin** is the only dopamine agonists for parenteral use. It can be applied subcutaneously either continuously in patients with severe motor complications or as a "rescue drug" to alleviate severe off-states.

Dopamine agonist can be used as monotherapy for PD, or in combination with other antiparkinsonian drugs, mainly levodopa, to enhance effect while avoiding side effects due to high dosages. Especially the longer acting agonists improved therapeutic options, as they offer a more constant stimulation of the dopamine receptors, thus being less inclined to cause fluctuations and dyskinesias. Most dopamine agonists are ergotamine derivates with a number of unfavourable side effects, of which fibrosis of the lungs and heart valves is the most severe. Therefore, non-ergot derivates as pramipexole, ropinirole and rotigotine are normally preferred nowadays.

COMT-inhibitors

COMT inhibitors prolong and enhance the effect of levodopa by inhibiting its conversion into 3-O-methyl-levodopa. As a first COMT inhibitor **tolcapone** was introduced during the 1990's, offering a new treatment option for patients with fluctuations. Due to some cases of fatal liver failure the drug was withdrawn from the market and its place was taken by **entacapone**. Entacapone has the inconvenience that it has to be taken together with every dosage of levodopa. A fast combination of levodopa, carbidopa and entacapone has therefore been developed. Due to the

enhanced effect of levodopa, dyskinesias are a frequent side effect and a challenge for drug management.

Drugs against tremor

Budipin is one of the few drugs that show a special effect on parkinsonian tremor. The substance has been known for some decades, but there has been doubt about the quality of the documentation of efficacy and safety. Arrhythmia of the heart is a severe side effect and limits the use of budipin. **Clozapine** is an atypical neuroleptic. It is as well effective in the treatment of parkinsonian tremor. One severe side effect is leukopenia. Especially during the first months of treatment thorough monitoring of the leukocyte level is therefore mandatory. For the treatment of psychosis in PD other atypical neuroleptics are therefore preferred.

1.6.2 Surgery

Surgical treatment of severe cases of PD had its first peak during the 1970's. In most cases a lesion in the ventral intermediate nucleus of the thalamus (VIM) was created in order to reduce tremor. Alternatively, a lesion in the globus pallidus interna (GPi) reduces dyskinesia. The definitive destruction of brain structures was problematic in less successful cases, and as medical treatment improved at the same time, surgical treatment was hardly used during the 1980's. First towards the end of the last century surgical treatment became more prevalent again with the introduction of reversible deep brain stimulation (DBS). Uni- or bilateral an electrode is placed in the nucleus subthalamicus (STN), VIM or GPi, and electric pulses induce a functional impairment in this brain region. Patients who potentially benefit from the treatment are those suffering from untreatable tremor or patients with severe fluctuations and dyskinesias that cannot be controlled medically. Eligible patients should have a good to excellent levodopa responsiveness, should not be older than 70 years and have no history of severe mental illness.

1.6.3 Physiotherapy

Until now it could not be proven that physiotherapy is effective in the management of PD. However, the clinical understanding is that physical activity is helpful in maintaining a good health state. Patients with PD have a reduced rotation of the spine while moving. They may as well have difficulties learning new movement sequences and have a disturbed balance. Young and active patients do not need guided training, whereas patients in more advanced stages will profit from physiotherapy that addresses these problems.

1.1.7 Prognosis

PD is a chronic and progressive disease and until today not curable. The rate of progression shows a great interindividual variation. Even if PD is not a fatal disease, both mortality and morbidity are increased[58]. Hoehn and Yahr reported a standardized mortality ratio (SMR) of 2.9[2], while a population based study of 245 patients in 2004 reported a SMR of 1,52 after 8 years of follow up[59].

In clinic-based studies, approximately 40% of patients developed motor problems within four to six years after disease onset[60], while over 78% of the patients in a community-based study did not experience motor fluctuations after over 6 years of levodopa treatment[61].

1.2 Health economics

(Sources: [62-65])

Economics are divided into micro- and macroeconomics, where macroeconomics look at the performance, structure and behaviour of a nation or region as a whole, while microeconomics study how individuals, households or firms make decisions in allocating scarce resources.

Health economics is a branch of economics concerned with health and health care and the scarcity and allocation of resources within health care. Its origin is dated to 1963, when Kenneth Arrow published an article that outlined the factors distinguishing health economics from "other" economics in a free market [66].

In a free market without any government intervention or regulation and without private fraud or force, property rights are exchanged at prices based on the mutual consent of buyers and sellers. Provided free competition, prices are a consequence of supply and demand. In theory, a free market will be the most effective of markets. Health care services do normally not meet the requirements of a free market. Governments tend to regulate the health care industry heavily, and they often bear the biggest burden of it. There is an information asymmetry between physicians and patients, and there is uncertainty related to health, treatment costs and treatment outcomes. In addition, effectiveness might not be the only concern when providing health care, but other factors like equity, accessibility and externalities may as well be important.

Alan Williams divided the discipline of health economics into eight distinct topics as shown in his "Plumbing diagram" in figure 1.1 [67].

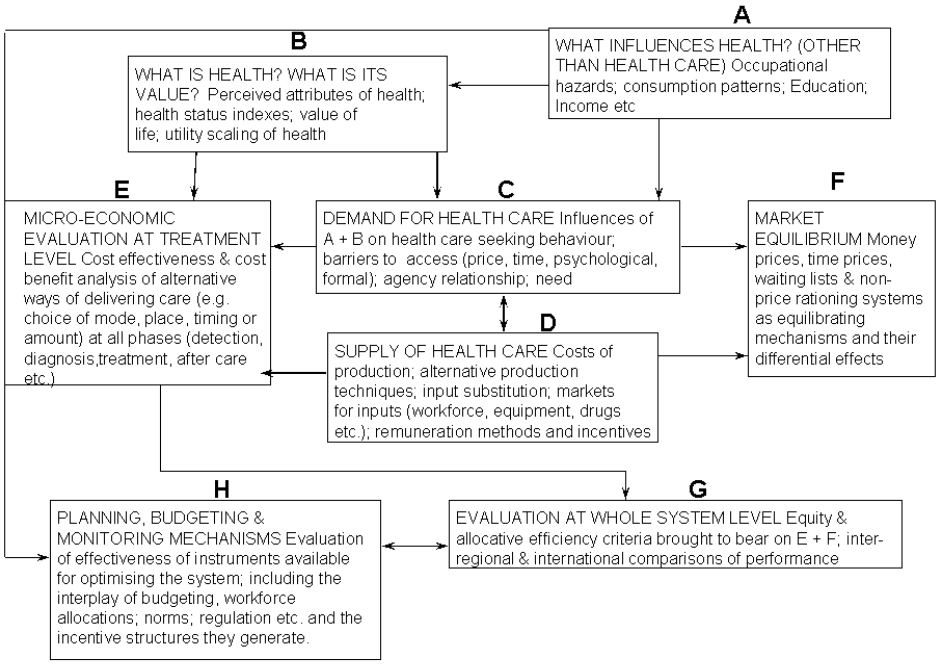

Figure 1.1: Alan William's "plumbing diagram" (1987)

1.2.1 What influences health (other than health care)? (A)

In 1974, the Lalonde report suggested that there were four determinants of health, including human biology, environment, lifestyle and health care organization [68]. This point of view is as well represented in the definition of health by the World Health Organization [69].

An example for health improvements that can not be attributed to health care services is the decline in population mortality rates in Europe after 1750 due to reduced exposure to infection by better water quality and sewage systems and the sanitary handling and treatment of foodstuffs (McKeown, p.121)[70].

1.2.2 What is health? (B)

In 1948, the WHO defined health as "a state of complete physical, mental, and social well-being and not merely the absence of disease or infirmity."[69] Though this definition is cited a lot, most people will settle for a less ambitious one. However, the definition emphasizes that health is not only an individual condition but is as well closely interrelated to the individual's living conditions.

1.2.3 Health care demand (C)

The demand for health care is really a demand for health. According to Michael Grossman, health can be seen as a stock of health capital, and health care is one mean to enlarge this stock or, in other words, produce health[71]. Another mean is investing time devoted to health-improving efforts like physical exercise. Health will last for a long period and does not depreciate instantly. It can therefore be considered as a capital. At the same time, health can be treated as both an investment good and consumption good. As consumption good it improves well-being. As an investment good it increases the number of healthy days and therewith the availability to work and earn money. In Grossman's model, the optimal level of investment in health occurs where the marginal costs of health capital are equal to the marginal benefit. As health depreciates over time, it becomes more and more costly to attain the same level of health as one ages while the marginal benefit decreases with age. As a result, the optimal health stock decreases as one ages.

Health care demand responds at least to some extend to microeconomic principles of supply and demand. When prices are high, the demand is low. But when prices decrease, the demand will increase. A typical example for that situation is health insurance. The higher consumption of health care services by insured individuals versus non insured individuals is called moral hazard.

1.2.4 The supply of health care (D)

Besides providing health, the health care system is as well operating as a large marked for work forces. In Norway, there are 31.6 nurses per 1000 inhabitants, far above the average of 9.7 practising nurses per 1000 inhabitants within the organization for economic co-operation and development[72]. In theory, the labour marked is controlled by the same mechanisms of demand and supply as other goods. The supply of work forces will thus increase with increasing wages and vice versa. There will as well be options for substituting various factors with each other, like for example technicians with radiologists or manpower with technical equipment. In general, it will seem more profitable to hire personnel with lower education for lower wages. On the other hand, higher educated personnel will be able to perform a larger number of different tasks, therewith enhancing the organization's elasticity in responding to different demands.

1.2.5 Micro-economic evaluation at treatment level (E)

"Economic evaluation is the comparison of two or more alternative courses of action in terms of both their costs and their consequences." (Drummond, p.9 [62]) There are several types of evaluation, differing in how consequences are measured. The exact terms are not fixed and may differ from country to country. The following types of evaluation are of interest: Cost-consequences analysis, cost-minimisation analysis, cost-effectiveness analysis, cost-utility analysis, and cost-benefit analysis.

1.2.5.1 Cost-consequences analysis

A cost consequences analysis is not necessarily a comparison between to options but rather a description of the costs of a certain action and the consequences this action results in. As, for example, the costs for hip replacement and different outcomes after surgery. Also “burden of illness analysis” belongs to this category.

As for other economic evaluations, the question of which costs and which consequences to include into the analysis has to be answered. As for the hip replacement, one could include only costs for surgery, or include as well costs for hospital stay, costs for rehabilitation, costs that are saved because of a gain in independency etc. This example illustrates as well the need to determine the perspective out of which the evaluation will be taken. The department of surgery might only be interested in surgery costs, whereas the hospital will include all costs arising during the stay, and the health care system will as well take rehabilitation into account. A societal perspective might as well be interested in the need for care in the future.

Costs of illness analyses describe the economic burden of a disease. According to DP. Rice, the costs for a disease are divided into direct and indirect costs[73]. Direct costs are subdivided into direct medical costs as drugs, hospital stays, rehabilitation, transport, and physician consultations, while direct non-medical costs derive from the need for care. Indirect costs are caused by the foregone opportunity to work due to reduced productivity or death.

1.2.5.2 Cost-minimisation analysis

As a requirement to a cost minimisation analysis the outcome of two different interventions must be proven to be equal. By evaluating the costs for each intervention, one will aim to determine the cheapest. As well in this kind of evaluation the result might depend on the choice of costs to be included. The time horizon, for example, may play a major role, as only present or also future costs could be integrated.

1.2.5.3 Cost-effectiveness analysis (CEA)

The requirements for a CEA are the complete evaluation of both the costs (input) and the consequences (output) of two or more intervention alternatives. In contrast to a cost minimisation analysis, the outcomes of the interventions might be different. The cost-effectiveness plane as shown in figure 1.2 illustrates the four possibilities of outcome in an evaluation with two treatment arms (whereof one treatment arm could as well represent "doing nothing").

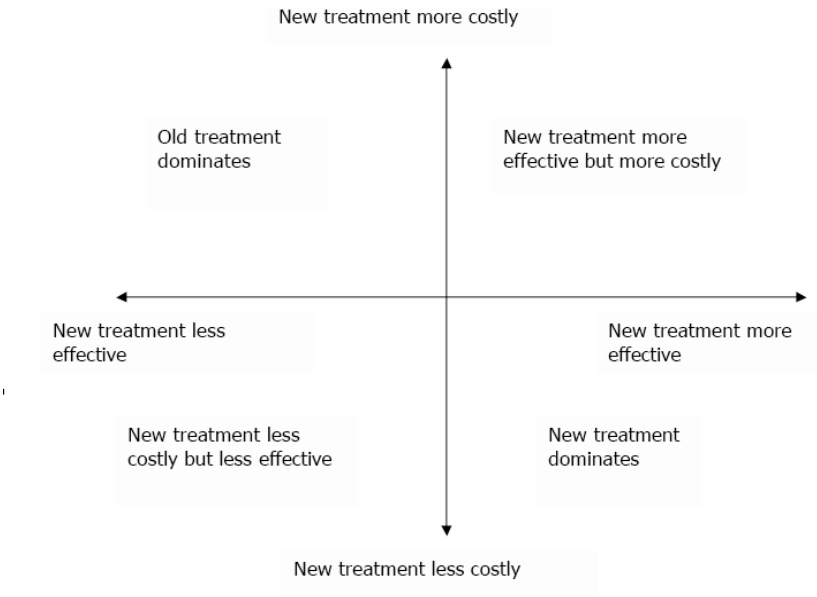

Figure 1.2: Cost-effectiveness plane (From: John Cairns: Tuition material, "Course in Health economics", Health economics Bergen, 2007)

The choice of which arm to prefer seems simple when one treatment arm is either both more costly and less effective (north-western quadrant) or more effective and less costly (south-eastern quadrant). Clearly preferable options are therefore called "dominant options".

However, in many cases the new treatment might prove as more costly and more effective at the same time. In these cases, an incremental cost-effectiveness ratio (ICER) will provide additional information. The ICER evaluates the price per unit of output, as for example lives saved, cancer cases detected, or points on any given scoring scale.

1.2.5.4 Cost-utility analysis (CUA)

In a CEA interventions can be compared to each other as long as the outcomes can be measured in the same unit. In a CUA the outcome measurement is converted to a universal unit which is called Quality adjusted life years (QALYs). Strictly speaking, the CUA is thus a special case of CEA. The concept of QALYs will be discussed later in more detail.

1.2.5.5 Cost benefit analysis (CBA)

In a CBA both the input and the output are measured in monetary terms, as for example the costs of an intervention and the savings due to avoided days of sick leave. The result can be expressed as a monetary net benefit or loss, or as the benefit-cost ratio. A CBA allows for the decision whether a programme pays for itself. On the other hand, not all health benefits can be captured in monetary terms, and a CBA may therefore be a supplementary evaluation to a CEA or CUA.

1.2.6 Market equilibrium (F)

Health care systems may function as free markets, but in many countries the state heavily regulates the health care industry. Within the healthcare system, private and public players may be active, both as health care providers and as health insurances. In the US, for example, the majority of the market is private while in Norway almost the entire health sector is run by the state or the municipalities.

In Norway, public health insurance is mandatory and a part of the tax payments, thus providing a nation wide risk pool. On the other hand, the unexceptionally public market of health care providers does not have to face any competition, and effectiveness has therefore been an issue in Norwegian health care services. Since 2002 all hospitals have become state run, and various incentives to improve effectiveness have been established. One example is the shift from a "Fee for service" reimbursement system to a production dependent system based on diagnosis-related groups (DRG), where the hospital is partly refunded based on the number of patients treated and the statistical use of resources according to the patients' diagnoses.

Licensures and authorisations are instruments to ensure quality of care. At the same time, they are as well an instrument of controlling competition by younger colleagues or immigrants. In Norway not only the number of specialized physicians working in hospitals is regulated, but as well the number of trainees for each specialty. This regulation is meant to ensure the quality of education, but may at the same time prevent an overproduction of specialists or even create an artificial shortage.

1.2.7 Evaluation at whole system level (G) - equity versus effectiveness

When evaluating health care systems by measuring the amount of QALYs that is "produced" by interventions, the best results would be achieved by treating individuals who are easily accessible and respond well, namely the rich and well educated. Seen from a societal perspective this might be less effective, because the overall health within a population might decline. It is as well in contrast to the general perception of fairness.

Nobel laureate Amartya Sen stated in the essay "Why health equity?" that equity in health was part of social equity and justice[74]. "Health equity cannot be concerned only with health, seen in isolation. Rather it must come to grips with the larger issue of fairness and justice in social arrangements, including economic allocations, paying appropriate attention to the role of health in human life and freedom." (p.659) In the

same way as Lalonde (1974) or the WHO, Sen emphasizes the social aspect in achieving and maintaining health, saying that health equity cannot merely be understood in terms of the distribution of health care, but must take into account how resource allocation and social arrangements link health with other features of state affairs. “Health and survival are central to the understanding not only of the quality of one’s life, but also for one’s ability to do what one has reason to want to do. The relevance of health equity for social justice in general is hard to overstress.” (p.663)

Allan Williams presented in 1997 the concept of “fair innings”, proposing that everyone is entitled to a normal span of life at a reasonable quality of life[75]. He suggests that individuals that have had their share of good years (approximately 60 QALYs) should step back when scarce resources are allocated. However, Williams’ concept has been criticized for being a too simple approach to health equity.

1.2.8 Planning, budgeting and monitoring mechanisms (H)

As budgets within the health care sector are limited, there is the necessity to set priorities. To make informed choices, decision makers depend on tools that help to judge the social value of medical interventions.

Erik Nord[76] showed in a review of the guidelines for priority setting in health care in several Western countries that these guidelines converged in the following points:

A: Society demands that medical interventions satisfy a minimum requirement of effectiveness.

B: Society’s appreciation of medical interventions increases strongly with increasing severity of the patient’s condition.

C: Life saving or life extending procedures are particularly highly valued.

D: When a minimum requirement of effectiveness is satisfied, society worries less about differences in the size of the health benefits provided by treatment programs for different patient groups.

E: Society in most cases does not wish to discriminate between people with different potentials for health in decisions about life saving or life extension.

Weighing the social value of health programmes in terms of QALYs gained would not satisfy the requirement of social fairness and justice, as this method does not take disease severity into consideration (point B) nor does it distinguish between life saving interventions and those that improve the quality of life (point C).

Bleichrodt et al. therefore developed the Rank-dependent QALY model[77]. In this model patient groups are ranked according to the severity of their state. The worst-off group will get the highest equity weight assigned to, and therewith most resources, as this is the group the society or policy makers are most concerned of. Then the next-worse group and so on. The model is not sensitive to the magnitude of differences between groups but only to the ranking.

Cost-value analysis provides another numerical modelling of social valuation, where concerns of fairness and effectiveness are taken into consideration[78]. In a set of eight health states between healthy and dead, one step up the scale is valued more highly the lower the start point, and the marginal value decreases significantly with increasing treatment effect. This approach compresses several different aspects in health care: initial severity, potential for improvement and the actual health gain.

1.2.9 Quality adjusted life year (QALY)

The terms “utility”, “value” and “preference” are often used interchangeable, while “preferences” actually is an umbrella term for both “utility” and “value”. Strictly speaking, values are obtained by measuring outcome preferences under certainty,

while utilities are obtained by measuring outcome preferences under uncertainty. However, we will only use the term “utility” in the following.

In economics, “utility” describes the satisfaction from or desirability of the consumption of goods. In health economics, “utility” expresses preference-based measures of health.

QALY is a unit for measuring utility in health economics. Mathematically, the amount of QALYs can be expressed by the equation:

QALYs = utility score x time.

As shown in figure 1.3, the amount of QALYs is the area under the curve with time on the horizontal axis and utility scores on the vertical axis. The concept thus combines the health state with the duration of life. In the diagram, the individual will without intervention have a lower HR-QoL and a shorter time of survival, obtaining q1 QALYs, while the intervention leads to a higher HR-QoL and longer time of survival, obtaining q2 QALYs. The net gain in QALYs will thus be q2 – q1.

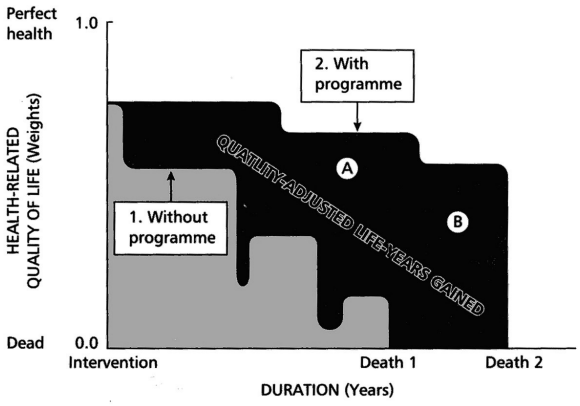

Figure 1.3: QALYs gained from interventions (From: Drummond: Methods for the Economic Evaluation of Health Care Programmes.[62])

Utility scores are a measurement for health state preferences. That means a ranking of different health states according to the abstract and subjective imagination of which state an individual would prefer to another. The question is asked to a large group of individuals, thus getting a statistical mean. Utility scores rank from 0 to 1, where 0 represents death and 1 perfect health. All other states are assigned weights between 0 and 1. However, some systems allow as well for weights below zero, indicating that there are states worse than death. There are several methods for measuring preferences for health outcomes and thus determining utility scores: The time trade-off [79], the visual analogue scale (VAS), and the standard gamble (SG), where the TTO and VAS represent measurements under certainty and the SG measurement under uncertainty.

- TTO: The respondents have to choose between a certain period of time in a state of ill health and a shorter period of time in perfect health.
- VAS: The respondents have to place various states of health on a scale from 0 = death to 100 = perfect health.
- SG: The respondents have to gamble between remaining in a state of reduced health for a certain period of time and a medical intervention with the chance of either being restored to full health or dying.

Preferences for health outcomes are specific for the cultural context of the respondent. Therefore, scoring systems may not be transferred from one country to another without adjustments in validation. In addition, respondents do normally not suffer from the affliction in question, as afflicted individuals on average assign a higher HR-QoL to the state.

As measuring preferences for health outcomes normally are a difficult and time consuming task, questionnaires have been developed to bypass these measurements.

There are several pre-scored multi-attribute health status classification systems. We will present two of the most widely used: The EQ5D and the SF-6D.

- EQ5D: This system was developed by the Western Europe EuroQoL group. It contains the five dimensions mobility, self-care, usual activity, pain/discomfort, and anxiety/depression. Each dimension has three levels: No problems, some problems, and major problems. The EQ5D allows for scores below zero ranking from -0.4 to 1 [80]. The EQ5D was validated by the preferences for health outcomes of about 3000 individuals in the UK.
- SF-6D: This systems was derived from the health status questionnaire, the Short form 36 (SF-36) [6]. The SF-36 is widely used, and the SF-6D provides an instrument for converting these data into utility scores. The instrument contains six dimensions: Physical functioning, role limitation, social functioning, pain, mental health, and vitality, each with four to six levels. The instrument was as well validated in the UK. Next to death, the lowest weight is 0.3.

As mentioned above does the concept of QALYs have the advantage of combining life expectancy with the health state. At the same time, the concept is easy to understand as well for non-economists. It has therefore become a popular tool for the allocation of health care resources. In the U.K, for example, there is an official cut-off for cost-effectiveness at a price of £ 30 000 per QALY. In Norway, there is an unofficial cut-off at NOK 600 000.

However, the QALY concept has been criticized as a too narrow measurement of benefits. It does not capture the quality of care, or the gain that lies in reassurance and information, nor does it capture any benefits to the patient's family or care givers. Other critics include the unreliability of the measurements, as the various methods can produce diverging outcomes. In addition, the fact that there are various questionnaires used to obtain utility scores diminishes the comparability of the results[81].

1.2.10 Disease adjusted life year (DALY)

The WHO developed the concept of DALY for measuring the burden of disease. It is designed for measuring the combined impact of premature death and disability, thus evaluating DALYs lost due to disease. The scoring spans from 0 = full health to 1 = death, and the scores are not evaluated by interviewing amateurs but determined by an expert panel. Japanese life expectancy is used as reference for premature death as Japan is the nation with the world's highest life expectancy. DALYs for individuals in the productive age get an extra weighting as they potentially provide for families. The concept of DALYs has been criticized for overrating the burden of disease, mainly because life expectancy is not adjusted to local conditions.

1.3 The economic burden of PD

The burden of a disease is described by its economic impact and its effect on the quality of life of the afflicted and his family. During the last two decades there has been an increasing interest in the burden of diseases. The world's population is not only growing in number but as well getting older. Population projections forecast an increasingly unfavourable ratio between the share of elderly and those who potentially can take care of them. The prevalence of diseases typically for old age will increase, as for example dementia, cancer, cardiovascular diseases, and of course PD. Besides the direct medical costs, the increasing need for formal and informal care will cause high non-medical costs and a rising demand for adequately trained caregivers. In addition to providing useful information for health care administrations, the evaluation of the burden of disease might as well help to identify cost driving factors and form the basis for further evaluations of treatment efficacy and efficiency. As one expects health to detoriate with advancing age, the burden of a disease should be related to the burden of morbidity in a population with a comparable age and sex structure or to the burden of other diseases typical for the same age group (like PD to cardiovascular diseases or dementia).

The WHO's study about the global burden of neurological disorders gives an estimate for 2005 and projections up to 2030, using a top-down approach[82]. According to this study, PD is responsible for 0.11% of all DALYs world wide today, and this number will rise slightly to 0.13 in 2030. However, in highly developed countries the amount of DALYs due to PD is almost 3-fold higher than for the average world population with 70.8 versus 25.1 per 100 000 population.

Most other studies on the burden of PD use a bottom-up approach, some of them analyzing the total economic burden, some of them analyzing only certain aspects of the disease. Due to differences in patient samples and methods, the results are often

difficult to compare to each other, and there are few studies using control cohorts, thus evaluating the incremental costs caused by the disease. The following studies evaluate either direct costs or total costs caused by PD:

Studies without control cohort:

- Whetten-Goldstein et al. (1997)[83] evaluated the costs to society of 109 patients with PD in a cross-sectional study in the US, finding total costs of $US 6115 per year. Earning loss of those less than age 65 was the greatest single element. Spouses providing informal care did so at mean 22 hours a week.

- Dodel et al. (1998)[84] evaluated the costs of 40 patients with PD over a three months' period in Germany, finding direct costs of $US 3390 ($US 13 560 per 12 months). Costs driving factors were disease severity and fluctuations.

- LePen et al. (1999)[85] followed 294 French patients with PD over a period of six months, evaluating both direct and indirect costs. He found mean costs of Euro 2358 over this period, with hospitalization being responsible for 39% of the costs. The main cost predictor was disease severity.

- Hagell et al. (2002)[86] followed 127 Swedish patients with PD over one year, evaluating both direct and indirect costs. He found annual costs of Euro 8000, of which 60% counted for indirect costs due to loss of production.

- Findley et al. (2003)[87] conducted a cross-sectional study of 444 patients with PD in the UK evaluating the direct costs caused by the disease. They found mean annual costs of £ 5993 per patient. Cost driving factors were independency in daily living, disease severity, quality of life and institutional care.

- Kerænen et al (2003)[88] conducted a study of 260 patients attending neurological outpatient clinics in Finland. He calculated costs from a societal point of view, finding that mean total costs were Euro 11 800 per patients of which the direct costs caused 41% and early retirement 43%. Of the direct costs hospitalization was the

biggest cost-driving factor accounting for 41%. Costs were related to disease severity and inversely to the quality of life. Patients in need for institutional care were not included.

- Spottke et al. (2005)[89] conducted a prospective study over six months with 145 patients, taking the perspective of the German public health care system. They found total costs of Euro 6560 with direct costs accounting for 51% and indirect costs for 49%. Cost driving factors were disease severity and reduced quality of life. As the study was conducted from the perspective of the public health insurance, costs for home care or nursing homes were not included.

- Mc Crone et al. (2007)[90] followed 175 patients with PD for one year in the UK. Direct medical and non-medical costs were included, though no patients were in need for institutional care. Mean costs per patient and year were £ 13 804, with 80% of the costs caused by informal care. Cost driving factors were male sex, depression and disability. The authors equalled costs for informal care with costs for formal care.

Studies using control cohorts:

- Rubenstein et al. (1997)[91] compared 43 patients with PD to a 3-fold larger matched cohort in the US, following them over one year. Patients with PD used more health care resources and caused $US 10 168 during that year, while controls caused a mean of $US 4743. Only direct medical costs were included.

- Guttman et al. (2003)[92]followed a cohort of 15 304 Canadian patients with PD and 30 608 matched controls over six years. He found that patients with PD had a higher use of health care resources, but the total incremental costs per year and patient are not specified in the paper.

- Huse et al. (2005)[93] evaluated data from health insurance claims of 20 016 patients with PD and an equally sized control group in the US during a follow up of a mean of 2 ½ years. Incremental direct costs for patients with PD were $US 10 349 per year.

- Noyes et al. (2006)[94] evaluated the health care utilization and expenditures of Medicare subscribers in the US between 1992 and 2000, finding incremental annual direct costs of $US 7710 for patients with PD and a higher need for home and institutional care.

- Leibson et al. (2006)[95] followed a cohort of 92 patients with PD and 92 controls over a period of 11 years in a population-based prospective study from the US. They found that there were no statistically significant incremental costs during the first five years after diagnosis, but that patients with PD caused incremental costs of $US 1146 per year during the last five years. The study included direct medical costs except out-of-pocket payments.

Summing up the results of the presented studies, there is a general agreement that the burden of PD is considerable. Patients with PD have a high use of health care resources and induce significant costs. Direct costs range from $US 1750 to $US 17 560 (2002 prices)[93]. Studies using insurance claims as data source report lower costs, possibly because they only reflect all costs. Of the four studies evaluating the incremental costs of PD, three report direct incremental costs between $US 7700 and $US 10 300 and one reports much lower costs of $US 1022 (2002 prices). Cost driving factors are disease severity, reduced quality of life, reduced independence in ADL, motor fluctuation, institutional care, and depression. In studies evaluating both direct and indirect costs, loss of production accounts for as much as 43% to 60% of the total costs, though only a minority of the patients is aged younger than 65. Unfortunately, none of the controlled studies evaluated indirect costs.

2. Aims of the study

The primary objective of this study was to achieve a better understanding of the economic burden of PD to society. To obtain that information we have:

I. compared the costs for antiparkinsonian drugs in a German and Norwegian cohort of patients with PD and evaluated the use of antiparkinsonian drugs in relation to disease severity, disease duration and national prescription habits (paper1).

II. examined the risk for living permanently in a nursing home for patients with PD as compared to age- and sex-matched individuals from the general population and calculated the costs related to long-term nursing home care in Norway (paper 2).

III. evaluated the possible incremental costs of hospitalization in PD as compared to the general population, and examined the distribution of diseases causing hospital admissions (paper 3).

IV. evaluated the health states of newly diagnosed patients with PD as compared to age- and sex-matched controls and calculated the incremental cost-effectiveness ratio (ICER) during the first year of drug treatment (paper 4).

3. Methods

3.1 Study design

3.1.1 Paper 1

Cross-sectional study.

3.1.2 Paper 2

Cross-sectional prevalence study at baseline and prospective longitudinal cohort study over a 12-year study period.

3.1.3 Paper 3

Prospective longitudinal cohort study over a 12-year study period.

3.1.4 Paper 4

Prospective longitudinal cohort study over a 1-year study period of patients with newly diagnosed PD.

3.2 Patient selection

3.2.1 Paper 1

The German cohort consisted of 286 consecutive patients with PD seeking advice at a PD counselling project and who were taking medication for the disease. In addition, they had to be able to give reliable information about their medical history and drug use. The counselling project was a free-of-charge offer for patients and their relatives

in the Rhein-Main area, Germany, that included advice in different aspects of the disease as disease management, diagnosis, coping and social problems. It did not include active disease management or drug prescriptions, and the patients were normally followed by outpatient clinics for movement disorders, neurologists in private practice, or general physicians. All patients included in the cohort were examined personally. The data were collected at the first contact with the patient during a 12-month period from March 1st 1998 to February 28th 1999.

The Norwegian cohort was drawn from the outpatient clinic of the Department of Neurology at the Stavanger University Hospital, Norway in the year 2001. Information on the patients was collected retrospectively from the hospital's medical files. 152 patients were included who had the clinical diagnosis of PD and used antiparkinsonian drugs, and where reliable data about disease duration, disease severity according to HY stage, and drug use could be obtained. To avoid bias between the two cohorts, patients visited in nursing homes were not included. As both COMT-inhibitors and the newer dopamine agonists came to the Norwegian market about two years later than to the German market, we chose to collect data in the year 2001 to have a comparable availability of drugs.

3.2.2 Paper 2 and 3

Between September 1992 and May 1993, a population-based prevalence study was conducted in Rogaland County, Western Norway [96]. To achieve complete case ascertainment, information from all relevant sources was obtained, as hospital files, general practitioners, nursing homes, district nurses, health workers and the Rogaland Parkinson's Disease Society. Of about 400 patients examined by neurologist with a special interest in movement disorders 245 were diagnosed with PD according to published diagnostic criteria [56], and 239 patients were able and willing to participate in the study. These patients have been followed in a longitudinal study later on, with clinical examinations in 1993, 1997, 2001 and annual clinical examinations from 2002 and up to today.

We used a subset of this patient population, including only the 108 patients who were living in the municipality of Stavanger in 1993. The municipality of Stavanger is the largest municipality in the area and provides complete and digitalized information about municipal services as long back as November 1993, while it was not possible to obtain reliable information in the other municipalities. The cohort of patients with PD was followed over a 12-year period from January 1st 1993 to December 31st 2004.

3.2.3 Paper 4

The Norwegian ParkWest study is a prospective longitudinal cohort study of patients with incident PD from Western and Southern Norway. The study area comprises a population of about 1 million inhabitants. During the period between November 1st 2004 and August 31st 2006 one sought to include all residents with incident PD in the study area. Patients who were diagnosed with possible or probable PD according to published diagnostic criteria[57] at the screening examination and who consented in participating in the study underwent baseline examination and have been followed since with clinical examinations at least twice a year and an additional consultation four weeks after the start of PD-medication. Patients that developed dementia during the first year of motor onset were excluded[97]. The Norwegian ParkWest study includes 212 patients. We excluded patients that were not drug-naïve at baseline or where information about the health status was incomplete. Four patients dropped out because of death. Our patient cohort consisted thus of 199 patients with newly-diagnosed PD.

3.3 Control subjects

3.3.1 Paper 2 and 3

Through the National registry we identified eight control subjects for each patient with PD who matched in sex and age and were living in Stavanger on January 1st 1994. The National registry is a government registration agency where each

Norwegian citizen is registered with name, address and an 11-digit social insurance number coding for date of birth and sex. In addition, the eventual date of death is registered. For the control cohort we had to delay the study period by one year, because it was too difficult to extract data from the National registry in 1993. In addition, there was no reliable data about long term nursing home admissions available before November 1993. Control individuals were therefore followed from January 1st 1994 to December 31st 2005. In paper 2 all 864 control individuals were included into the cross-sectional part of the study at baseline. Six individuals had to be excluded from the longitudinal part due to emigration from the study area during follow-up. In paper 3 four additional control individuals had to be excluded because according to the hospital files they had developed PD during the study period.

3.3.2 Paper 4

Among relatives and acquaintances of the patients of the ParkWest study 205 controls were recruited. We included a subset of 175 control individuals who provided the best possible group match regarding sex, age and education. We had to exclude three control individuals where information about the health status was incomplete. The control cohort consisted thus of 172 individuals.

3.4 Assessment of clinical data

3.4.1 Paper 1

For the German cohort, data was collected personally at the first consultation of the patient during the study period. Data about age, sex, disease duration and history was obtained in addition to present drug use. Disease severity as measured by Hoehn and Yahr (HY) stage[2] was determined by history and clinical examination.

For the Norwegian cohort, clinical and demographic data and information about drug use was collected retrospectively from the hospital files at the first consultation during the study period.

3.4.2 Paper 2

For patients with PD, clinical data about age, disease duration, disease severity as measured by HY stage and cognitive impairment as measured by Mini Mental State Examination (MMSE)[3] were collected at baseline examination. Information about permanent admission to a nursing home was collected at the clinical examinations and by the municipality's registration system for delivery of services "CosDoc" and "PLOMS". The date of death was provided by the hospital files for patients with PD and the National registry for control individuals.

3.4.3 Paper 3

For patients with PD, clinical data about age, disease duration, and disease severity as measured by HY stage were collected at baseline examination. Data about hospital admissions, department of admission, length of stay and discharge diagnosis were obtained from the files of Stavanger University Hospital. As this is the only hospital within two hours of driving, we did not collect data from other hospitals. The discharge diagnoses were categorized as PD, vascular disorder, cancer, trauma, pulmonary disease excluding cancer, muscle/connective tissue disorders, diseases of the genitourinary tract, rehabilitation and other.

3.4.4 Paper 4

For the patients, information about their medical history including age and disease duration was collected at baseline. Information about disease severity and drug use was collected at every clinical consultation. Data about health status was collected at

baseline and after one year. For controls, data about health status and independence in ADL was collected at baseline and after one year.

Disease severity was assessed by the Unified Parkinson's Disease Rating Scale (UPDRS)[4] including the modified HY staging. The health status was assessed by the Short form 36 questionnaire (SF-36)[5] which was completed by both patients and controls at baseline and after one year. To calculate utility scores, the data of the SF-36 were converted to the Short Form-6D (SF-6D)[6, 98]. For controls, independence in ADL was measured by using the UPDRS part II.

3.5 Assessments of costs

3.5.1 Paper 1

Drug costs were determined according to the price list from the German drug compendium "Die Rote Liste 1999", the Norwegian drug compendium "Felleskatalog 2001" or the pharmacists' price quotes. We included only drugs that were prescribed for the treatment of motor symptoms of PD. Costs were expressed in "Costs per patient per day".

3.5.2 Paper 2

As each nursing home in Norway has its own economy and its own pricing, there are no official calculations of the costs for institutional care in Norway. We used prices as quoted by the accountant centre of the municipality of Stavanger as an estimation of costs for the year 2007. We verified these costs by comparing them to the costs quoted by the municipality of Bergen and Oslo. We calculated costs from the societal perspective and therefore included both costs refunded by social services and users' fees. As it was not possible to obtain reliable information on costs for institutional

care as long back as 1993, we could not calculate the actual costs that emerged during the observation period. We therefore projected the costs to the year 2007 by evaluating the percentage of the time an individual spent in nursing home during the study period and multiplying it with the annual costs for institutional care. Costs were thus expressed in "Costs per person year of survival".

3.5.3 Paper 3

In Norway all costs related to hospital admissions are borne by the National Health Service. We therefore assumed that these costs were the total costs emerging to society. Up to 2001 hospitals were refunded based on patient-days of in-hospital stay. Since 2001 refunding has been based on a combination of a fixed budget and a flexible refund based on the patients' discharge diagnoses following the "diagnose related grouping" (DRG) system. Both systems do not reflect the patients' real costs but operate under the assumption that some patients will cost more and some patients less than refunded, and that this will be levelled out when large numbers of patients are treated. We chose to calculate costs for in-hospital stay by an average price per day for the Stavanger University hospital as quoted by SAMDATA[99] and the hospital's accounting centre for the year 2005. We expressed costs as "Costs per patient per year of observation period" and "Costs per person year of survival".

3.5.4 Paper 4

Costs related to medication for the treatment of PD motor symptoms and consultations at the outpatient clinics of Neurology were used as treatment costs, as data about physiotherapy and transport were missing. Drug costs were determined by using the price list in the drug compendium "Felleskatalogen 2007" or the pharmacists' price quotes. We included the costs for four outpatient clinic consultations (baseline, four weeks after the start of PD-drugs, after six months, and after one year), as this would correspond to normal clinical practice in the catchment area of the Norwegian ParkWest study. The costs were calculated according to the

refunding rates to the clinics by the Norwegian Labour and Welfare Administration. The ICER was calculated by the ratio of these costs and the gain in QALY during the observation period.

3.6 Statistical analysis

Student's t test was used to compare means for continuous variables and Chi-square test for testing differences in proportions for categorical variables. Two-sided *p*-values less that 0.05 were considered statistically significant.

In paper 2 the observed curves for survival and nursing home admission were calculated by the Kaplan-Meier method. In the cross-sectional study the relative risk (RR) for living in a nursing home was obtained by dividing the share of patients living in nursing homes at baseline by the corresponding share of control individuals. In the longitudinal study the RR for *being admitted to a nursing home* was obtained by dividing the share of patients admitted to nursing homes during follow-up by the corresponding share of control individuals. The RR for *living in a nursing home* was obtained by dividing the share of time alive that was spent in nursing homes for patients with PD by the corresponding share for control individuals.

In paper 3, the RR for in-hospital stay was calculated by dividing the mean number of in-hospital days per year of survival for patients with PD through the corresponding number of days for controls.

In paper 4 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 confidence interval (CI) for the mean of the PD-drug costs was calculated by bootstrap analysis.

In paper 1, the software programs SPSS 11.0 (SPSS inc., Chicago, IL, USA) and STATA (StataCorp LP, College Station, TX, USA) were used for statistical analyses. In paper 2 and 3, the software program SPSS 14.0 and in paper 4 SPSS 15.0 was used.

4. Results

4.1.1 Paper 1

We found that drug expenses rose with disease duration and disease severity in both countries, but that expenses were markedly higher in the German cohort as compared to the Norwegian cohort with Euro 5.78 versus Euro 3.92 per patient and day. A higher proportion of the German patients were treated with two or more drugs, and the switch from mono- to multi-drug therapy was done earlier in the course of the disease.

4.1.2 Paper 2

Patients with PD had a 5-fold higher risk for living in a nursing home as compared to controls, both in the cross-sectional study at baseline and during the 12-year follow up. Based on 2007 prices, the incremental costs for institutional care were Euro 14 897 per person year of survival. With a prevalence of 1.5 per 1000 population, costs for institutional care of patients with PD in Norway would come to Euro 132 million per year.

4.1.3 Paper 3

Over the 12-year observation period there was no significant difference between patients with PD and controls regarding the number of individuals being admitted to hospital, numbers of admission, or length of stay. Incremental costs for the use of in-hospital services were Euro 822 per year of survival for patients with PD, but the difference in costs between the two cohorts was statistically not significant. However, we found that patients with PD were more often admitted for trauma, while cardio-vascular diseases and cancer were markedly more common in control individuals.

4.1.4 Paper 4

Patients with PD had significantly lower health state values as compared to controls. Patients starting on antiparkinsonian drugs had an improvement in utility scores of 0.039 from 0.667 to 0.706 during the one year follow-up. The ICER was Euro 45 259 per QALY for patients with incident PD during their first year of treatment, of which two thirds were caused by drugs and one third by costs for clinical consultations.

5. Discussion

To evaluate the economic burden of a disease can be a problematic task, as the costs are compounded by many different factors. Some may be easy to assess, but in many cases accuracy is limited by either the selection of patients available for examination, or the lack of information about costs, or both. In an ideal world, a population-based patient cohort would have a confirmed diagnosis, would suffer only of the disease in question, would be treated according to standardized procedures, and all direct and indirect costs ever emerged to the individual would have been recorded in a stable health and social care system. Further, there would be a completely healthy control cohort where – of course – as well all costs have been recorded.

The range of studies presented in chapter 1.3 illustrates some of the problems of economic evaluations: Health care systems and their refunding policies vary widely from country to country. Economic evaluations may therefore be difficult to transfer to other health care systems. Patient samples that are not population-based will be biased for disease severity, management, long-term complications, and need for care. Insurance claims as data source may give an incomplete picture of the real costs as they only reflect costs refunded by the health care system or private insurances. Formal care may be refunded by the health care system, private insurers or social care system, and refunding may cover all expenses or only parts of them. Availability and refunding will thus have an impact on the demand for formal care, both institutional and home care. Information about informal care relies on the correct report of the patients and their care givers. The refunding of informal care is debated in health economics and can range from prizing informal care the same as formal care to not prizing it at all but just indicating the hours spent. Indirect costs depend not only on the age composition of the patient sample but as well on a country's sick leave regulations and pension system.

The findings of our studies illustrate that the use of control cohorts adds valuable information to the evaluation of the burden of disease. In the developed countries, up

to 15% of the GNP is spent for health care services[72]. Thus, health is expensive and the findings that diseases cost a lot of money are not necessarily news. First when the consequences of a disease are seen in comparison to other patient groups or to the general population, a statement about the relative impact can be made. We could show that prescription habits may act as a cost driving factor when comparing two different countries to each other. We could further show that institutional care causes high incremental costs, but that in-hospital care by contrast did not cause incremental costs. Finally, we found that the treatment of incident PD has an ICER that is high but still within cost-effectiveness limits in Norway.

5.1 Methodology

Norway provides some conditions that are beneficial in performing health care research. First, there are only few private actors on the health care market. The use of health care services is therefore nearly completely registered by the state-run or municipality-run providers. Second, population density is low, and hospitals are often the sole health care institution within a radius of several hours' driving and with large catchment areas. The Stavanger University Hospital serves as an exclusive provider for emergency care, in-hospital care, and specialized outpatient care for about 320 000 people. Hospital files are thus reliable sources of information on a patient's medical history. In addition, the department of Neurology at the Stavanger University Hospital is the initiator for a population-based longitudinal prevalence study about patients with PD that have been followed since 1993. Further, in 2004, a multi centre population-based longitudinal study on incident PD has been started in Western Norway.

Patients and controls

A frequent problem in health economic evaluations is that information is drawn from selected patient populations as for example patients visiting specialized outpatient clinics, or patients participating in medical trials. Patients may thus have more advanced disease severity or at the contrary be rather healthy individuals with no co-morbidity. To get a representative profile of patients we drew patients from population based studies or, in paper 1, from unselected patient groups. The control cohorts are drawn from the same catchment areas, thus ensuring that the availability and costs of nursing home placement, medical care and other socio-demographic factors were comparable. However, the control cohort in paper 4 was recruited among the patients' relatives and friends, and these individuals volunteering to participate in a longitudinal study may constitute a control 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[100]. In paper 2 and 3 we had to delay the observation period for the control cohort with one year for practical reasons. This may have caused bias between the patient and control cohort due to changes within the local health care services. Still, we considered the time lag of one year as compared to a 12-year observation period of minor impact.

The assessment of costs

In paper 2 we projected the total costs emerging from nursing home placement of patients with PD in Norway to society. Unfortunately, we were not able to assess the opportunity costs. Opportunity costs describe the costs occurring as compared to the second best alternative. In the case of institutional care, this would be a maximum of formal home care with four to six visits a day in addition to a certain amount of informal care.

In paper 3 we presented costs as "Costs per patient and year" and "Costs per patient year of survival". We chose both ways of presenting costs as they describe different aspects. i) "Costs per patients and year" describes the actual costs within a certain observation period. Individuals dying early may cause considerable costs while being

alive, but after death they do cause no additional costs. This method thus describes the costs emerging per incident individual. ii) "Costs per person year of survival" is a way of incorporating mortality into the calculation of costs. It thus describes the costs of a population with a certain disease and known prevalence.

Both in paper 1 and in paper 4 we evaluate drug costs caused by the treatment of motor symptoms in PD. When assessing the incremental costs, these are the drugs most unequivocally related to the treatment of PD, while drugs used for non-motor symptoms like depression or cognitive impairment may as well be used for symptoms not related to PD. Thus, we did not assess all incremental costs caused by drug use in PD. As we compared two cohorts of patients with PD in paper 1, this issue is of minor importance. In paper 4 it might lead to an underestimation of the ICER.

5.2 The evaluation of direct and indirect costs in PD

We evaluated several aspects of direct costs in PD as drug costs, costs for neurological follow-up, costs caused by in-hospital care and costs caused by institutional care. We did not evaluate costs caused by transportation, costs for physiotherapy, therapeutic appliances, or adjustments at home. More importantly, we did not assess costs for formal home care or the amount of informal care; neither did we assess indirect costs due to loss of productivity.

In regard to the total costs, our findings are in general agreement with previous observations. We found drug costs of Euro 5.78 per day for German patients and Euro 3.92 for Norwegian patients, while previous studies found daily drug costs between Euro 2.83 and Euro 5.50[84-87]. The risk of living in a nursing home for patients with PD has been reported to be 4.6 and 6.7[101, 102]. In one study in the US incremental costs for institutional care were Euro 6747[93], while we found incremental costs of Euro 14 897. This difference may be partly due to different prices for nursing home placement. Unfortunately, annual prices for institutional care in the US are not

given in the paper cited. But as an example, prices for nursing home placement are twice as high in Norway as in the UK (personal communication). Costs for hospitalization have previously been found to be between Euro 1100 and 7400 per year (transferred to 2005 prices in EUR)[83, 85, 86, 88, 90]. With Euro 3300 our findings are in the middle range. Our findings do as well confirm the findings of Parashos et al[102], who found no increased risk for hospital admissions between patients with PD and controls during a 7.5-year follow-up, though other studies with shorter observation periods report increased risks of 1.44-fold and 3-fold, respectively[92, 93].

However, when looking at the incremental costs, our results cannot confirm the findings of previous studies. Several studies mention hospitalization as an important cost factor [85, 88], while we found no statistically significant incremental costs. Further, only few studies report the need for care as an important cost driving factor[87, 94], while most of the presented studies either do not include direct non-medical costs or only have few patients in need for institutional care. We found that 14% of the patients with PD were living at a nursing home in a cross-sectional study and about half of the patients were admitted during a 12-year observation period. The need for care is thus a considerable cost driving factor, with incremental costs of Euro 14 897 for nursing home placement, while incremental drug costs amounted to Euro 1430 and incremental costs for hospitalization were Euro 822 and not statistical significant.

5.3 Cost-effectiveness in the treatment of PD

Cost-effectiveness can be evaluated in monetary terms, with one treatment option being cheaper than the alternative while not being less effective. However, a treatment option can as well be regarded as cost-effective when the results obtained seem to be worth the expenses. In cost-utility analysis, results are expressed in QALYs as a measurement for gains or losses in health states. The incremental cost-effectiveness ratio (ICER) evaluates the costs per QALY gained. It is then up to the

decision maker to decide whether these costs can be considered cost-effective. Different countries may have differing cut offs for what is being considered cost-effective. An acceptable price per QALY lies around Euro 30 000 in the UK, Euro 50 000 in the US and Euro 60 000 in Norway.

The evaluation of the impact of 29 chronic conditions on the health states in a Finnish population using the EQ-5D showed that PD had the largest negative effect on the health state at the individual level, while due to prevalence, musculoskeletal disorders have the greatest impact on a population level[103] A review from 2006 on HR-QoL and the economic impact of PD showed that there are few studies evaluating cost-effectiveness by using QALYs as an outcome measurement[104]. Only one study evaluating the cost-effectiveness of surgery in PD was conducted as a cost-utility study finding that surgery was cost-effective if the improvement in the quality of life was more than 18%[105]. A later study on the same subject found as well that surgery was cost-effective as compared to best medical treatment with an ICER of Euro 34 389 per QALY[106]. Of the studies evaluating cost-effectiveness in drug treatment of PD, seven of ten used a Markov model. In three studies patient cohorts were examined, evaluating the cost effectiveness of pramipexole, ropinirole and sustained-release carbidopa-levodopa, respectively, as compared to levodopa[107-109], but only one study was conducted as a cost-utility study using the EQ-5D as measurement of health states[107]. To our knowledge, no study evaluating the ICER of PD treatment in an unselected patient population has been conducted until now. Schrag et al. evaluated the health state values of 93 patients drawn from a population-based cross-sectional study finding a median EQ-5D score of 0.62[110]. We found an improvement of the SF-6D score of 0.039 from 0.667 to 0.706 during the first year of drug treatment in newly diagnosed PD and an ICER of Euro 45 259 per QALY.

5.4 Future research

In this thesis we put emphasis on the use of control cohorts. The comparison between diseased and healthy individuals, hence the incremental costs, are a more valid

measurement of the economic burden of a disease than the statement of the absolute costs, as the costs caused by age-related morbidity are subtracted. According to our numbers, care is by far the largest factor of the direct costs in PD. Costs for institutional care are 10-fold higher than the costs for drug treatment. Formal care is not only costly but requires as well trained staff that needs to be recruited and educated and that in consequence will lead to a lack of work force in other sectors. Our findings implicate that interventions that enhance independency in ADL and prevent nursing home admissions probably will be cost-effective. They suggest as well that informal caregivers should receive optimal support to avoid institutionalization. Caregivers often experience a reduced quality of life[100, 104, 111] and caregivers' stress increases the risk for nursing home admission[112]. Measures like specialized PD nurses, information seminars, patient and caregiver networks, and thorough medical follow-up may contribute to provide optimal treatment conditions and to increase the quality of life of both patients and their caregivers.

Future research should evaluate the amount of formal and informal home care patients with PD receive as compared to the general population. Further, intervention studies should examine the potential for preventing nursing home admissions and decreasing the amount of home care. At the same time, the quality of life of caregivers is an important issue, and a reduction in formal care must not transfer the burden to the informal caregivers. Possible interventions may include the decrease of disease progression, improved drug management in late-stage PD, support of informal caregivers by enhanced networks, home visits of PD nurses and the relief of strain on the caregivers by day care centers.

Furthermore, we could show that the ICER of drug treatment in incident PD is high. However, the full evaluation of the effectiveness of drug treatment should include the long-term effects on disease progression and thus the need for care. Longitudinal studies following patients during the whole course of the disease will be necessary to provide conclusive data.

6. Conclusion

The aim of this thesis was to obtain more knowledge about the direct costs causes by PD. For this purpose we examined various populations of patients with PD and controls in both cross-sectional and longitudinal study designs.

In the first study we compared a German and a Norwegian cohort of patients with PD with regard to drug use, drug costs and prescription habits. We found that drug expenses rose with disease duration and disease severity in both groups, but that expenses were markedly higher in the German group and the switch from mono- to multi-drug therapy was done earlier in the course of the disease.

In the second study we followed a population-based cohort of patients with PD and a control cohort over a period of 12 years finding that the risk for living in a nursing home was 5-fold increased for patients with PD as compared to controls, both in a cross-sectional study at baseline and during follow-up. The incremental costs for institutional care were Euro 14 897 per patient year of survival for patients with PD.

In the third study we followed the same patients and controls as in study 2 finding that there was no significantly increased risk for hospitalization for patients with PD as compared to controls and thus no incremental costs related to in-hospital care. However, we found that patients with PD were more often admitted for trauma, while cardiovascular disease and cancer were more common in control individuals.

In the fourth study we examined the health state values and treatment costs in a population-based cohort of patients with incident PD during the first year of drug management. We showed that the patients with PD had lower health state values than the age- and sex-matched control cohort, but that health state values were improved by medical treatment. The ICER was Euro 45 259 per QALY, of which two thirds were caused by drug costs and one third by costs for clinical consultations.

In conclusion, we could show that disease management requires constant evaluation, in regard of the quality of treatment as well as of cost-effectiveness. We could further show that the use of control cohorts adds valuable information to the evaluation of the burden of disease and helps to discern costs related to a certain disease from costs caused by general age-related morbidity. Our findings confirm that the need for formal and informal care of patients suffering from chronic progressive diseases will be a 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.

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