THE LONDON SCHOOL OF ECONOMICS AND POLITICAL SCIENCE

THE VALUE OF EARLY DIAGNOSIS AND TREATMENT IN PARKINSON'S DISEASE

A literature review of the potential clinical and socioeconomic impact of targeting unmet needs in Parkinson's disease

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CONTENTS

TABLE

PREFACE

Parkinson's disease (PD) is a chronic progressive neurodegenerative disease affecting approximately 7 million people globally, with devastating effects on quality of life and severe socioeconomic consequences on individuals, their families and society. Worryingly the global prevalence of PD continues to increase—without any available disease slowing therapy or cure to date, the approved treatment allows to ameliorate the symptoms patients endure. Therefore, the targeting of unmet needs in the management of PD grows more crucial, not only to help patients live with their disease, but also in addressing the increasing socioeconomic burden of the disease and to ensure sustainability in the treatment of this chronic condition.

This report sheds light on two sides of Parkinson's disease and its diagnosis: the evidence to support the need for early, if not prodromal, diagnosis and better symptomatic and preventive treatment, and the potential clinical and socioeconomic impact of targeting unmet needs. Since misdiagnosed, delayed or entirely missed identification of PD still occurs in parts of Europe, it is vital to search for and define a simple, easy to use, widely available and cost-effective diagnostic test. New developments of diagnostic tools for prodromal and early stage PD are encouraged, and, if established, should fast be utilised by medical professionals. A growing body of evidence from the medical literature describes numerous advantages of early symptomatic therapeutic intervention in PD. Nevertheless, so far clinical trials have failed to convincingly show that presently approved drugs are able to slow down disease progression. However, there is hope, as efforts in drug development over the last 20 years – focusing on the etiopathogenesis of PD – provide the first substances with a disease modifying potential for PD, and these compounds will enter early clinical testing in 2017.

This report takes the forefront position to be used as an important source of information for healthcare managers, as well as policy and practitioner stakeholders, to highlight the extreme urgency of early, if not preclinical, diagnosis and treatment of PD. Furthermore, it confirms that early diagnosis and treatment are paramount to reducing the risk of disease progression, limiting the effects of PD on quality of life, and potentially lowering long-term treatment costs. Adherence to now available treatment plans by patients and disease-management strategies by medical practitioners through the implementation of a chronic model of care is important to improve treatment adherence and rates of correct diagnosis. Clinicians should be properly informed regarding stringent diagnostic approaches in order to ensure diagnosis is performed appropriately and accurately.

This study is part of a broader investigation by the European Brain Council (EBC) on the cost of non-treatment and patient journey analysis, the Value of Treatment project 2015-2017. The project aims at developing and applying to brain disorders a new integrated care model framework and therefore promotes a more holistic management of chronic conditions in Europe, including PD. By providing an extensive review of the case for Parkinson's disease, the report sheds light on the crucial needs for the development of improved symptomatic therapy - and even more important – any disease modifying treatments for PD. This report provides a robust set of data and calls to action for meeting the ultimate challenge: to find a cure for PD.

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EXECUTIVE SUMMARY

Parkinson's disease (PD) is a chronic progressive neurodegenerative disease affecting approximately 7 million people globally with devastating socioeconomic effects on individuals, their families and society. Total European costs of PD in 2010 alone accounted for €13.9 billion. Worryingly the global prevalence of PD is increasing over time and it is expected to double within the next 20 years (up to 2% in people over the age of 60 and 6% in people over 80 years). **Targeting unmet needs in the management of PD is crucial for addressing the growing socioeconomic burden of the disease and to ensure sustainability in the treatment of this chronic condition.** The objective of this report is to summarise the key evidence available from the literature on the potential clinical and socioeconomic impact of targeting unmet needs in PD.

MISSED OR MISDIAGNOSIS AND DELAYS IN TREATMENT. There is no diagnostically conclusive test for PD yet, so the diagnosis is clinical in nature. In the clinical setting, PD is commonly missed or misdiagnosed since many symptoms of PD are also common to other diseases both neurodegenerative and non-neurodegenerative. The diagnosis and treatment of PD typically occurs when the disease has already progressed to a relatively advanced stage in which motor symptoms are clearly evident and substantial neurophysiological damage has already taken place. At this point, any possibility of delaying disease progression or, achieving neuroprotection may already be out of reach.

- **New developments in early diagnosis and treatment.** A revised definition of PD, together with the availability of novel diagnostic tools can allow for earlier diagnosis, and therefore treatment. **Non-motor symptoms**, which account for a large proportion of PD symptoms and usually emerge much earlier, are increasingly recognized as useful indicators to achieve earlier diagnosis. Furthermore, a number of **new and diverse diagnostic tools (i.e. biological and genetic biomarkers, imaging techniques)** are now available and have the potential to make earlier diagnosis, and consequently earlier treatment, possible.

- **The benefits of early diagnosis and treatment**. A growing body of evidence from the medical literature describes numerous advantages that may be associated with early therapeutic intervention in PD. The most evident benefit of early treatment with medicines other than L-dopa is the **reduction in symptoms** (for example difficulty or distortion in performing voluntary movements) and the delay of levodopa (L-dopa) initiation and therefore its immediate side-effects (for example hypotension, arrhythmia, insomnia and hallucinations) and the effects of its chronic administration (motor complications and drug resistance). Clinical trials also suggest that early treatment can **slow disease progression**.

  Both the decrease of symptoms and the potential for slowing disease progression, have a major impact on **improving patient quality of life (QoL) and reducing the costs associated**

with PD in the long run, as the great majority of costs attributable to PD occur when the disease is at its most advanced stage and when symptoms are most severe.

Despite this apparent benefit of utilizing dopamine agonists in early PD to delay the need for L-dopa and to achieve cost savings, **there is still controversy regarding when to initiate treatment**. If with early treatment we consider the disease being treated soon **after standard PD diagnosis has been achieved** there is economic evidence to demonstrate that treatments (other than L-dopa) can be cost-effective. If early PD is defined as that period **prior to the onset of significant motor symptoms**, then, as considered with clinical outcomes, few data are available on the real potential for cost savings.

NON-ADHERENCE. Non-adherence is common, critical, and costly in PD. It presents serious socio-economic consequences and well-being deterioration not only for the patients but also for family members. PD patients in general have poor adherence to prescribed therapies, especially therapies with complex dosing schedules.

- **The benefit of more convenient and adherence-friendly drug formulations, regimen simplification, mailed and telephoned reminders or reinforcement, counselling, and supportive care** may further help to improve outcomes and lower costs in PD.
- A series of **studies in the USA** reported that increased medication adherence can result in significant savings in direct costs related to hospitalisations, visits and medicines.

FUTURE RESEARCH DEVELOPMENTS

- **Rethinking what PD is and how/when it can be diagnosed.** The recent developments in PD diagnosis emphasise the necessity of rethinking what PD is and how, and when, it can be diagnosed. Clinicians are aware that the current diagnostic tools and guidance should be updated in light of current knowledge of PD to optimize its early detection.
- If **early PD** is defined as that ***period prior to the onset of significant motor symptoms, before substantial neurological damage may have occurred***, then more research would be needed to explore the real impact of early treatment both on clinical and economic outcomes.
- **The benefit of alternative approaches (such as integrated care models) should be further explored** as opportunities to improve outcomes and lower costs in PD. **The EBC Value of Treatment project for 2015-2017** aims at developing and applying to brain disorders a new integrated care model framework and therefore promote a more holistic management of chronic conditions in Europe. The project will provide policy recommendations on how to implement effective and cost-effective interventions for brain disorders across different European health systems and specific case studies, including Parkinson's disease.

1. PARKINSON'S DISEASE (PD), ITS MANAGEMENT AND SOCIOECONOMIC IMPACT

Parkinson's disease (PD) is a chronic progressive neurodegenerative disorder that causes significant disability and reduces quality of life (QoL), with significant impact on costs to the healthcare system and society as a whole.

1.1. NEUROPATHOLOGY AND SYNTOMS

The two major findings when studying the nervous system tissue of individuals with Parkinson disease are loss of neuronal cell and the presence of Lewy bodies (abnormal aggregates of protein that develop inside nerve cells) in the mid brain (substantia nigra, that plays an important role in reward, addiction, and movement). [1,2] Both the cause and cure for PD are yet unknown. PD's symptoms are caused by a decrease in the levels of the chemical messenger dopamine, which allows messages to be sent to the parts of the brain that co-ordinate movement, due to the death of dopamine-producing nerve cells. With the loss of dopamine-producing nerve cells, these parts of the brain are unable to function normally, causing the symptoms of PD's to appear. These symptoms include tremor, slowed movement, rigid muscles, impaired posture and balance, loss of automatic movements, along with changes in speech and writing (see below).

1.2. EPIDEMIOLOGY

The European Brain Council (EBC) published a study on brain disorders and their epidemiology in 2005.[3] There are around 466 million people in Europe, 127 million (27%) of whom have brain disorders (both neurological and general mental health). If those with co-morbidities are excluded, that still leaves 104 million people (22%), roughly half of whom (51.2 million people; 11%) have a neurological condition. The number with PD is estimated to be around 1.1 million (0.2%).[4] In 2010 the overall European estimates increased this number to 1.25 million cases of PD[5].

PD is the second most common neurodegenerative disorder after Alzheimer's disease ([6]) affecting approximately 7 million people globally and is a major and increasing burden on patients, families, carers and healthcare systems.[7] A recent meta-analysis of the worldwide data showed a rising prevalence of PD with age (all per 100,000): 41 in 40 to 49 years; 107 in 50 to 59 years; 173 in 55 to 64 years; 428 in 60 to 69 years; 425 in 65 to 74 years; 1087 in 70 to 79 years; and 1903 in older than age 80.[8]

The prevalence of PD in industrialised countries, although the exact prevalence is difficult to accurately determine, is thought to be approximately 0.3%.[9] This rises to 1% in people over

the age of 60 and 3% in people over 80 years.[6] Country specific evidence is reported elsewhere (UK[10], Spain[11], USA[12] international comparison[13]).

Due to the ageing of the population, with a greater proportion of the population aged 65 and older, and due to the positive correlation between prevalence and age, PD is likely to become more prevalent in the next years and is expected to double within the next 20 years . The rise in prevalence brings substantial concerns with respect to the growing socioeconomic burden and sustainability of this chronic condition.

1.3. SOCIAL AND ECONOMIC COSTS, AND QUALITY OF LIFE

Cost of illness escalates as PD progresses, placing an economic burden on the healthcare system, society and patients themselves. According to the EBC data for 2004, annual spend in Europe on PD was €10.7 billion, consisting of €4.6 billion on healthcare costs and €6.1 billion on direct non-medical costs. This is more than 12% of the total spend on neurological diseases in Europe, which was €83.9 billion. In 2010 the total European cost of PD increased to €13.9 billion (30% more compared with previous estimates in 2004)[5]. DALY estimates (age15+) for the EU-27 population in 2010 is 174,0378.[14] In USA Kowal and colleagues[15] showed that the national economic burden of PD exceeds US$14.4 billion [€12.2 billion] in 2010 (approximately US$22,800 [€20,296] per patient). The population with PD incurred medical expenses of approximately US$14 billion [€12 billion] in 2010, US$8.1 billion [€7.21 billion] higher (US$12,800 [€11,393] per capita) than expected for a similar population without PD. Indirect costs (e.g., reduced employment) are conservatively estimated at US$6.3 billion [€5.6 billion] (or close to US$10,000 [€8,901] per person with PD).

Despite the progressive decline and comorbidity associated with PD, the lifespan of affected individuals, treated with innovative drug therapy, does not differ greatly from age matched individuals without PD.[16] As a result, people may live up to 20 or more years with PD. This finding has serious implications for the cost of treating PD over the individual's lifetime and suggests that the financial burden will escalate over time. In addition, the economic burden is likely to increase further as the proportion of individuals in Western societies aged over 65 increases.[17]

PD does not directly cause people to die and for the majority of people does not significantly affect their life expectancy even though some of the more advanced symptoms can lead to increased disability and poor health, which can make someone more vulnerable to infection. Despite little impact on life expectancy, PD patients experience progressive disability and reduced QoL at all stages of the disease and at all ages. Several studies indicate that QoL is affected not only by the motor symptoms of PD, but also by the pre-motor symptoms such as depression and cognitive state (for examples see [18,19,20]).

- **Impairments in motor function** such as tremor, slowed movements, loss of voluntary movements, muscular rigidity and postural instability cause problems with mobility and interfere with activities of daily living. Problems with balance and gait (rhythmic stepping movements for travel) can lead to falls and injuries, and the inability to perform everyday tasks. Other symptoms include poor hand co-ordination, problems with handwriting, and a sensation of tremor (shaking) in the arm.

- Early PD's symptoms often include **pre-motor symptoms** such as depression, dementia, feeling tired and weak, reduced ability to smell and to detect odours, acting out vivid dreams during sleep (REM sleep behaviour disorder), along with problems with blood pressure, heart rate, sweating, and digestion of food. Visual symptoms often precede the clinical diagnosis and increase over time.[12] Symptoms vary greatly from person to person and can sometimes take years to progress to a point where they cause problems.

2. UNMET NEEDS

1.4. MISSED OR MISDIAGNOSIS

PD is challenging to diagnose, since there are no well-established biomarkers to determine if the disease is present.[21] There is no diagnostically conclusive test for PD, so the diagnosis is clinical in nature and is made by identification of slowness of movements (bradykinesia) and at least one of the following symptoms: resting tremor, muscle rigidity, and postural instability.[22] Confirmation of a PD diagnosis also involves exclusion of other disease and presence of at least three positive criteria, which include: affecting one side of the body, shaking of the limb when the person is at rest (resting tremor), progressive disorder, persistent asymmetry affecting side of onset most prominently, excellent response to levodopa (L-dopa), severe involuntary movements affecting especially the shoulders, hips, and face induced by L-dopa, L-dopa response for 5 years or more, or clinical course of 10 years or more.[22,23] **Current diagnostic modalities in PD are limited by the fact that they identify PD by the presence of motor symptoms; by this point, around 70% of all dopamine neurons may have been lost[24]. Thus, the diagnosis of PD remains a challenge for clinicians, particularly in the pre-clinical, or early phase, before the motor symptoms appear.** Despite pre-motor symptoms preceding the clinical diagnosis, none of these are sufficiently specific to be used as stand-alone biomarkers, thereby preventing the achievement of an early diagnosis.

PD, in the clinical setting, is commonly missed or misdiagnosed. Many symptoms of PD are also common to a range of conditions, and this may cause missed or misdiagnosis of PD. These

conditions can be grouped as neurodegenerative, which primarily affect the neurons in the human brain, non-neurodegenerative, which do not affect the human brain. Among the neurodegenerative diseases, those most often confused with PD are **multiple system atrophy (MSA**; this cell degeneration causes problems with movement, balance, and autonomic functions of the body such as bladder control or blood-pressure regulation), **progressive supranuclear palsy** (PSP; uncommon brain disorder that affects movement, control of walking (gait) and balance, speech, swallowing, vision, mood and behaviour, and thinking), **corticobasal degeneration** (CBD; it is a rare condition that can cause gradually worsening problems with movement, speech, memory and swallowing), **dementia with Lewy bodies** (DLB; it is a type of progressive dementia that leads to a decline in thinking, reasoning and independent function because of abnormal microscopic deposits that damage brain cells over time), **normal pressure hydrocephalus (**NPH; is an accumulation of fluid in the brain that causes the ventricles in the brain to become enlarged), and **Alzheimer's disease** (AD; it implies a progressive mental deterioration associated with gradual death of brain cells).[25,26] **Essential tremor** (ET; that is a type of uncontrollable shake or tremble of part of the body) is also a common source of confusion in PD diagnosis, although many of these patients will go on to develop PD.[27] Furthermore people can develop DP symptoms following treatment with particular medications (**drug-induced Parkinsonism**); this form is very common and may constitute the second-most common cause of Parkinsonism.[28]

The probability of misdiagnosis appears to be strongly related to whom is doing the diagnosing and whether or not the clinician is applying diagnostic criteria from clinical guidelines, although application of the clinical criteria is not a guarantee of diagnostic accuracy. There is evidence showing that nearly half (47%) of PD diagnoses are incorrect when performed in the primary care setting, and specialists whose expertise is not specific movement disorders have an error rate of approximately 25%, while movement disorder specialists are mistaken in only 6% to 8% of cases.[10]

1.5. NON-TREATMENT

Since there is currently no cure for PD, the main treatment goal is to manage the symptoms and there are several medicines available for the management of its symptoms. Although medicines can improve QoL[29], there is a significant decline in physical mobility, pain, social isolation and emotional reactions as the disease progresses.[25] Patients with PD who remain **untreated, or inappropriately treated**, will experience ongoing and substantial symptomatic deterioration and negative effects on their QoL.[30] In a recent survey 1,400 patients with essential tremor (including PD) identified a broad range of unmet needs that they felt were not addressed in their treatment[31]. The most reported issues related to what they felt was **inappropriate treatment** included:

- Lack of psychological services and support (33.9%);
- Lack of physical or occupational therapy (28.6%);

- Lack of support in handling embarrassment and social effects of tremor (15.8%);
- Feelings of not being in control (13.7%);
- Lack of detailed report and a more quantitative way of assessing tremor and tracking progression (12.7%);
- Lack of information about current treatment and medications (11.9%);
- Lack of empathy, compassion and a feeling of being heard (11.6%),
- Lack of alternative treatment approaches other than just medications and surgery (11.2%);
- Lack of discussion of all symptoms aside from tremor (e.g., cognition, balance; less than 10%).

1.6. NON-ADHERENCE

Medication non-adherence is prevalent in Parkinson's disease (PD) and results in substantial motor dysfunction. Leopold and colleagues (2004)[32] showed that only 10% of PD patients fully adhered to treatment. A further study identified that 20% of patients with PD were under users of anti-parkinsonian medication.[33] In addition, patients who satisfactorily adhered to medication (average total pill taking > 80%) all showed substantial problems with dose timing adherence (number of doses taken at the correct time interval). Kulkarni and colleagues (2008) conducted a retrospective longitudinal cohort study in people with PD and found the prevalence of sub-optimal adherence to be 67%.[34]

Medication non-adherence is therefore a significant problem in people with PD and it can be related to several factors, including[35]:

- **Polypharmacy** is very common with over half of patients taking at least two anti-parkinsonian medicines in addition to multiple prescriptions for non-motor manifestations and other comorbidities. Furthermore, dopaminergic medicines are often taken 3–4 times daily, with advanced PD patients taking as many as 6–10 doses per day. Greater regimen complexity is strongly correlated with non-adherence in PD.[36,37]

- **Depression** and mood disorders have been identified as an independent risk factor for non-adherence and a common non-motor manifestation of PD. Studies in depressed populations have found a threefold increase in non-adherence with all prescribed medications[38] and a single-centre study found non-adherence was associated with worse depression and poorer quality of life in PD.[39]

- **Deficits in the management (regulation, control) of cognitive processes**, including working memory, reasoning, flexibility, and problem solving as well as planning and execution is another common feature of PD and contributor to non-adherence. These

deficits are common in PD and have been independently associated with medication non-adherence.[40]

- **Additional factors** associated with non-adherence include poor quality of life and symptoms control, poor knowledge of PD, lack of social support/partner[39], non-modifiable demographic and educational factors[41] low health literacy[42], low income, maintaining employment, and the cost of medications.[43]

Consequences of non-adherence include worse disease control, with diminished mobility, greater movement problems, involuntary muscle movements, diminished voluntary movements and worsening quality of life. Non-adherent individuals are more likely to report being undertreated, rather than recognising that their sub optimally controlled symptoms may be caused by their non-adherence to treatment. Similarly the healthcare provider may react increasing the medication doses or frequencies, changing the medicine regimens, or questioning the diagnosis, leading to additional diagnostic testing, patient stress, and further non-adherence.[44]

1.7. WHY EARLY INTERVENTION AND ADHERENCE ARE IMPORTANT IN PD?

1.7.1 EARLY INTERVENTION

There is growing evidence that early intervention may help in preserving the functioning of the neurons, reducing symptoms, particularly difficulty or distortion in performing voluntary movements, slowing disease progression, improving patient QoL and, in turn, reducing the overall costs associated with PD[45]. However early treatment relies on early diagnosis and, as already pointed out, early diagnosis and treatment of PD can be difficult to achieve because the nature of diagnosis (mostly clinical). Therefore by the time motor symptoms emerge, significant neurological damage and the destructive structural changes have already taken place. PD diagnosis by conventional means identifies a disease which is already advanced, and any possibility of delaying disease progression, not to mention neuroprotection, may already be out of reach. Despite the fact that diagnosis remains mainly clinical, recently, the increasing recognition of pre-motor symptoms together with a number of new and diverse techniques for diagnosis have the potential to considerably alter the diagnostic landscape in the next future, making the early diagnosis, and therefore treatment, achievable.[46]

1.7.2 ADHERENCE

Poor treatment adherence is a significant challenge to optimizing outcomes in PD, and any therapeutic strategy must take into consideration those factors impacting treatment adherence.

In PD pharmacological management is essential for managing symptoms and maximising QoL; therefore medication adherence is paramount to securing effective treatment.[47] This is

especially relevant as motor function becomes progressively worse, requiring increasingly intricate medication regimes to manage symptoms.[48] Furthermore, as non-motor symptoms have been reported by patients and carers to be more negatively impactful than motor complaints in PD[49,50], adequately adhering to prescribed regimens is likely to be important for maximising health related QoL.

Fargel et al surveyed 500 patients with PD and 592 neurologists who treated patients with PD, in order to determine the causes of poor adherence.[51] The authors found that while physicians described themselves as being satisfied with the "pill load" of prescribed medications for their patients, the PD patients themselves were largely dissatisfied and wished for simpler medicine regimens as follow:

- **A reduction in daily tablet intake** was the most common request for treatment improvement;
- Moreover, patients expressed their preferences for **alternative delivery systems**, most of all transdermal patches, to facilitate the ease of delivery of their PD treatment (and this was reported also by the neurologists).

These results are consistent with a recently international study (2014) comparing patient preference for pramipexole in once daily versus 3-times-daily formulations in patients with either early or advanced PD; the majority of the patients (94.4%) reported their preference for the once-daily formulation.[52] In another from Spain (2012) it was reported as follow:

- Strong correlation between treatment adherence to L-dopa and the total number of daily medicines (as opposed to pills) prescribed;
- Poorer adherence associated with higher L-dopa doses;
- Higher rates of adherence in patients who were treated first with a dopamine agonist versus those first treated with L-dopa.[53]

A transdermal patch of the dopamine agonist rotigotine, which has shown safety and efficacy in early PD and non-inferiority to pramipexole, was recently approved for PD treatment by the FDA, and offers a therapy that is likely to be associated with higher rates of adherence compared with oral therapies.[54]

3. WHAT INFORMATION IS AVAILABLE IN THE LITERATURE ABOUT EARLY DIAGNOSIS AND TREATMENT?

3.1. DIAGNOSTIC TOOLS AVAILABLE TO ACHIEVE EARLIER DIAGNOSIS

Among the diagnostic tools which might help in achieving earlier diagnosis there are: non-motor (or pre-motor) symptoms, biomarkers (biological and genetic) and neuroimaging techniques.

3.1.1. NON-MOTOR (OR PRE-MOTOR) SYMPTOMS

Although motor symptoms are the most recognizable of symptoms in PD, and are those upon which a PD diagnosis is largely based on, **non-motor symptoms represent not only a large proportion of overall PD symptoms but, in many cases, emerge earlier than motor symptoms.** The non-motor symptoms could be present for up to 10 years before the diagnosis is made and have been shown to exert a greater negative influence on QoL than motor symptoms.[55,56] Thus, despite the fact that the standard diagnosis of PD still relies on motor symptoms, pre-motor symptoms hold promise for the early diagnosis of PD, and considerable progress has been made in recent years in establishing pre-motor symptoms as a means of identifying PD much earlier than in the past. One important observation is that PD is not simply a central nervous system (CNS) disease in which the peripheral nervous system (PNS) plays a minor part. Rather, PNS seems to play a much larger role than previously assumed, particularly in the early stages of the disease.[57] Many of the pre-motor symptoms that arise in early PD emerge in PNS structures, and there is compelling evidence suggesting that PD actually begins in the PNS.[58,59]

The manifestations of pre-motor symptoms in PD are diverse, affecting sensing smell, gastrointestinal and urinary function, mood and sleep, as well as a variety of cerebral activities (reasoning, memory, attention, and language and lead directly to the attainment of information and, thus, knowledge).

- **Dysfunctions of the stomach and the intestines** that manifest as pre-motor symptoms include gastroparesis (a disorder that slows or stops the movement of food from the stomach to the small intestine) and constipation (bowel movements are difficult or happen less often than normal). In this regard, the presence of Lewy bodies in the gastrointestinal tract may provide a means for early diagnosis of PD.[60]
- **Urinary dysfunctions**- Urinary frequency, urgency, and nocturia (condition in which you wake up during the night because you have to urinate) constitute urinary dysfunctions in early PD.
- **Sexual dysfunction** in both men (erectile and ejaculation dysfunction) and women (poor vaginal lubrication and difficulty achieving orgasm) have also been observed as PD pre-motor symptoms.
- **Mood disorders**, including depression and anxiety, are well documented in the pre-motor phase, while sleep disturbances, including REM behaviour disorder (acting out vivid dreams as they sleep) and excessive daytime sleepiness, are common premotor symptoms.
- Other non-motor PD symptoms that may play a role in the premotor phase include **pain, apathy (lack of feeling), attention/memory problems, restless legs syndrome** (RLS; it is a neurological disorder characterized by an irresistible urge to move one's

body to stop uncomfortable or odd sensations), **fatigue, and poor ability to discriminate colours**.[59]

- **Hyposmia (reduced ability to smell and to detect odours)**,[61] may be the most notable of non-motor symptoms observed in the pre-motor stage, in part because of the growing quantity of data demonstrating and explicating the role of smell loss in PD, but also because it may represent a highly useful means of achieving diagnosis of PD much earlier than has been possible up until the present.[57] The results of several studies investigating the smell function in PD have been encouraging in considering **smell testing as a means of early PD detection** either alone[62-64] or in combination with neuroimaging techniques.[64,65] However, hyposmia is also associated with other conditions, including Alzheimer's disease and dementia with Lewy bodies, and thus the presence of hyposmia may be useful for the identification of persons at risk for PD, rather than being conclusively diagnostic of PD.[66]

3.1.2. BIOLOGICAL AND GENETIC BIOMARKERS

Several different biological indicators (biomarkers) in body fluids such as the **brain and spine fluid** (cerebrospinal fluid; CSF) as well as the **blood** and **urine**, have been proposed for use in the diagnosis of PD. Challenges to the use of biomarkers revolve around the fact that changes over the course of the disease can affect their measurable levels, and even their presence. Moreover, the manifestations of biomarkers in other diseases characterised by reduction or impairment of cognitive function may be too similar to those seen in PD to allow them to be easily identified.[21] **It is common understanding that a combination of several biomarkers will be required to achieve reliable early PD diagnosis.**[67] In addition to biological biomarkers, recent research into genetic biomarkers for early PD have also shown promising results.[68,69]

3.1.3. NEUROIMAGING TECHNIQUES

Several neuroimaging approaches (various techniques to either directly or indirectly image the structure, function/pharmacology of the nervous system) have demonstrated viability in the detection of PD and are therefore used as an additional tool in the examination of the brain in order to make a diagnosis of brain diseases. A few **neuroimaging techniques** are currently available and they include single photon emission computed tomography (SPECT), transcranial sonography (TCS), positron emission tomography (PET), magnetic resonance imaging (MRI).[70] **Unfortunately, they have significant limitations:**

- **SPECT** is more accessible to clinicians than PET and less expensive; however it cannot differentiate PD from other disorders such as **multisystem atrophy (MSA**; it is associated with the degeneration of nerve cells in specific areas of the brain and can leads to premature death), **progressive supranuclear palsy (PSP**; a rare and progressive condition that can cause problems with balance, speech, swallowing,

vision, mood and behaviour, and thinking), and **corticobasal degeneration (CBD**; it is a rare condition that can cause gradually worsening problems with movement, speech, memory and swallowing).

- **TCS** is also more accessible and less expensive than PET and it has been proven to be a useful technique in the diagnosis and differential diagnosis of movement disorders.[21]
- **MRI** provides excellent resolution and diagnostic sensitivity and can facilitate the diagnosis of neurodegenerative conditions. Structural imaging with MRI is an alternative to SPECT, TCS and PET and particularly for patients with clinical features that are atypical for PD; however its utility as a diagnostic tool is not widely accepted.[71]

In vivo magnetic resonance spectroscopy (MRS) is an additional tool that can be used to complement the more common MRI in the characterization of tissue. MRS can provide a useful and objective tool for detection of metabolic changes of the brain in patients with PD and has been shown to meet many of the criteria of an ideal imaging biomarker. Indeed, MRS has good consistency (test-retest reliability) and, compared with PET and SPECT, is non-invasive and cheap, and it does not require contrast agents for the molecular imaging reducing exposure to radioactive substances. In addition, compared with some in vitro molecular biomarkers that require a complex analysis, MRS is not restricted to specialized centres to perform the analysis, making its extension to general public health centres possible. The recent technical advances of MRS allowed achieving in vivo detailed information on pathophysiology of PD. **Several studies demonstrated the usefulness of MRS to achieve a differential diagnosis of PD versus other forms of Parkinsonism, especially in early stages of disease in which signs and symptoms of different forms of Parkinsonism have greater overlap.**

All these neuroimaging techniques, in addition to offering a valuable tool to make earlier diagnosis of PD, could be also **used to monitor disease progression**. However, the utility of these modalities as biomarkers for evaluating the efficacy of therapeutic interventions to slow disease progression remains imperfect, and additional investigations are needed before being able to introduce them into clinical practice.[45]

3.2. THE CLINICAL BENEFITS OF EARLY INTERVENTION

Several studies have been undertaken to assess the clinical benefit of early treatment of PD with **levodopa (L-dopa)**[72,73], **dopamine agonists**[74-78] and **Monoamine Oxidase Type-B (MAO-B) inhibitors**[79-84] (Table). The majority of the studies evaluating the benefit of early treatment refer to studies investigating the clinical efficacy of a PD medicine (i.e. L-dopa or dopamine agonist or MAO-B inhibitor) in the early stages of the disease without directly comparing early vs. delayed treatment.[72-81] Only a few studies allow for such a comparison.[82-84] Details on the different studies are reported in the table below.

Table. Main studies of clinical benefit of early treatment of PD

Study	Type of study	Publication year	Intervention	Comparator	N	Follow-up	Main outcome
L-dopa							
ELLDOPA[72]	Clinical trial	2004	Carbidopa-L-dopa at various doses	Matched placebo	361	42 weeks	L-dopa improved UPDRS score* in a dose-related fashion
SPECT [123I] β-CIT uptake sub-study[72]	Clinical Trial	2004	Carbidopa-L-dopa at various doses	Matched placebo	116	42 weeks	SPECT demonstrated that L-dopa accelerates the loss of nigrostriatal dopamine nerve terminals
STRIDE-PD[73]	Clinical Trial	2010	Carbidopa-L-dopa plus entacapone	Carbidopa-L-dopa	747	134 weeks	Intervention group had shorter time to dyskinesia onset and increased frequency of dyskinesia
Dopamine agonists							
Rascol et al[74]	Clinical Trial	2000	Ropinirole	Benserazide-L-dopa	268	5 years	Intervention had longer time to dyskinesia; no significant difference in the mean change in UPDRS activities of daily living subscale scores between the two groups
CALM-PD-CIT [77]	Clinical Trial	2002	Pramipexole	Carbidopa-L-dopa	82	46 months	SPECT showed less dopamine neuron degeneration with pramipexole; UPDRS scores similar in both groups
REAL-PET[75]	Clinical Trial	2003	Ropinirole	Carbidopa-L-dopa	186	2 years	PET showed slower disease progression with ropinirole. However, better UPDRS motor score improvement with L-dopa.

Study	Type of study	Publication year	Intervention	Comparator	N	Follow-up	Main outcome
CALM-PD[76]	Clinical Trial	2005	Pramipexole	Placebo-L-dopa or carbidopa-L-dopa	301	48 months	Reduction in dyskinesia and wearing-off with pramipexole, but better total score and motor score and lower incidences of side effect (i.e. freezing, somnolence, and edema) in the L-dopa group
Stowe et al[78]	Meta-analysis	2008	Dopamine agonists	L-dopa	5247	n.a.	Less motor complications (i.e. dyskinesia, dystonia) with dopamine agonists compared to L-dopa, but more side-effects and poorer symptom control
PD MED trial[85]	Clinical Trial	2014	L-dopa	dopamine agonists (DA) and monoamine oxidase type B inhibitors (MAOBI)	1620	36 months	L-dopa provides better mobility and a higher quality of life than the two main alternatives, dopamine agonists (DA) and monoamine oxidase type B inhibitors (MAOBI)
MAO-B inhibitors							
DATATOP[80]	Clinical Trial	1993	Selegiline and/or tocopherol	Placebo	800	24 months	Selegiline delayed the onset of disability requiring L-dopa therapy and the decline in UPDRS total score compared with placebo or tocopherol
TEMPO[81]	Clinical Trial	2002	Rasagiline	Placebo	404	26 weeks	Rasagiline improved UPDRS scores; no difference in the frequency of adverse events

Study	Type of study	Publication year	Intervention	Comparator	N	Follow-up	Main outcome
Ives et al[79]	Meta-analysis	2008	MAO-B inhibitor	Placebo or L-dopa	3525	n.a.	Better total UPDRS scores, UPDRS motor scores and activities of daily living scores with MAO-B inhibitor
ADAGIO[82]	Clinical Trial	2009	Rasagiline 1 mg or 2 mg daily for 72 weeks	Placebo for the first 36 weeks, then rasagiline 1 mg or 2 mg daily for the remaining 36 weeks	1176	72 weeks	Improved UPDRS scores in the early-start group compared to delayed-start group, with rasagiline 1 mg but not with 2 mg dosage
Hauser et al[84]	6.5-year extension of the TEMPO study	2009	Rasagiline (early-start group)	Placebo for 6 months followed by rasagiline (delayed-start group)	306	6.5 years	Less worsening in total UPDRS scores in the early-start group compared to delayed-star group
Rascol et al[83]	prespecified and post-hoc analyses of the ADAGIO study	2011	See Adagio study[82]				UPDRS motor subscores and activities of daily living subscale improved with both doses of rasagiline relative to placebo in the early-start versus the delayed-start groups

The unified Parkinson's disease rating scale (UPDRS) is used to follow the longitudinal course of PD. It is made up of the 1) Mentation, Behaviour, and Mood, 2) ADL and 3) Motor sections. These are evaluated by interview. Some sections require multiple grades assigned to each extremity. A total of 199 points are possible. 199 represents the worst (total) disability), 0--no disability. **Single photon emission computed tomography (SPECT), positron emission tomography (PET).**

3.2.1. LEVODOPA (L-DOPA)-BASED REGIMENS

L-dopa is the standard therapy for motor control of PD and it **is still considered the most effective drug for relieving the widest range of symptoms**, including: tremor, stiffness, slowness, poor muscle control, balance, and difficulties in walking.

In one of the first studies Parkinson's Study Group examined carbidopa-L-dopa at various daily doses (compared with placebo; Earlier versus Later L-dopa Therapy in PD; ELLDOPA trial); the clinical data suggested that L-dopa either slows the progression of PD or has a prolonged effect on its symptoms. In contrast, the neuroimaging data suggested either that L-dopa accelerates the loss of nerve terminals or that its pharmacologic effects modify the dopamine transporter.

The potential long-term effects of L-dopa on PD remain uncertain.[72] Although L-dopa is the most widely used (and effective) therapy for PD, chronic treatment is associated with motor complications in the majority of patients. It has been hypothesized that providing more continuous delivery of L-dopa to the brain would reduce the risk of motor complications, and that this might be accomplished by combining L-dopa with entacapone to extend its metabolisim. The STRIDE-PD trial, comparing carbidopa-L-dopa with or without entacapone, showed that initiating L-dopa therapy with L-dopa/carbidopa/entacapone (LCE) failed to delay the time of onset or reduce the frequency of dyskinesia compared to L-dopa/carbidopa (LC). In fact, LCE was associated with a shorter time to onset and increased frequency of dyskinesia compared to LC. In addition they found no difference in longitudinal course of PD between the groups, but the incidence of myocardial infarction was 1.9% in the LCE group versus 0% in the LC group, concluding that the addition of entacapone to carbidopa-L-dopa may actually be deleterious with the increased risk of myocardial infarction.[73]

3.2.2. DOPAMINE AGONISTS

Because L-dopa controls the symptoms of PD so well (and with so few side effects at the beginning) there is some benefit for people who start treatment with L-dopa, rather than with a dopamine agonist. A person with PD who starts treatment with L-dopa may have more early years with better control of symptoms and fewer side effects. But it also is well documented that most people who take L-dopa develop motor problems (motor fluctuations or wearing-off) within 5 to 10 years after starting the medicine. These complications, including unpredictable swings in motor control between doses and uncontrollable jerking or twitching (dyskinesias), can be hard to manage and can become as disabling as some of the problems caused by the disease itself.

A number of studies have been undertaken to evaluate the effects of dopamine agonists (ropinirole[74,75] and pramipexole[76,77]) relative to L-dopa. All these studies suggest that compared with L-dopa, dopamine agonists may delay dyskinesia and showed less

dopamine neuron degeneration, although the value of this clinical effect remains uncertain and these agents do not improve total disability (using the unified Parkinson's disease rating scale (UPDRS) score[1]) compared with L-dopa.

In the attempt to delay the development of motor fluctuations, many providers are now treating individuals with PD on a dopamine agonist rather than L-dopa. A dopamine agonist may be used until it no longer adequately relieves symptoms, at which point the person starts taking L-dopa in addition to the dopamine agonist. Dopamine agonists can also cause severe sleep problems and hallucinations in some people. Having these side effects may be another reason to switch to L-dopa. As long as the individual's symptoms are adequately controlled and they can tolerate the medicine, dopamine agonists may be a good choice for treating early PD. The American Academy of Neurology now recommends this course of treatment for most people with early PD, regardless of their age [www.aan.com/Guidelines].

When considering symptomatic drug therapy for both early and complex PD, the NICE guideline can best be described as 'permissive'. The relative lack of comparative evidence between different classes of medicines precludes a firm recommendation for any one therapeutic strategy. Hence the guideline states that L-dopa, dopamine agonists and monamine oxidase type B (MAOB) inhibitors (see below) 'may' be used as a symptomatic treatment for early PD. ref

3.2.3. MONOAMINE OXIDASE TYPE-B (MAO-B) INHIBITORS

Recently, several studies have investigated the potential benefit of early treatment with MAO-B inhibitors such as seleginline[80], and rasagiline.[81,83,84] In 2004, a meta-analysis evaluating MAO-B inhibitors in patients with early PD found no difference in mortality among treatment versus control subjects.[79] Patients randomized to MAO-B inhibitor therapy had significantly improved total UPDRS scores, as well as subdomain UPDRS motor scores and activities of daily living scores at 3 months. The MAO-B inhibitors were also well tolerated, with adverse effects and patient withdrawals from the study similar in both groups. These results illustrated a potential benefit of MAO-B inhibitors, which reduce degeneration of neurons. MAO-B inhibitors can be considered for initial treatment of early disease. These drugs provide mild symptomatic benefit, have excellent adverse effect profiles, and, according to a Cochrane review, have improved long-term outcomes in quality-of-life indicators by 20-25%.[86] More details on the MAO-B inhibitors trials are reported in the table.

[a] **The unified Parkinson's disease rating scale (UPDRS)** is used to follow the longitudinal course of PD. It is made up of the 1) Mentation, Behavior, and Mood, 2) ADL and 3) Motor sections. These are evaluated by interview. Some sections require multiple grades assigned to each extremity. A total of 199 points are possible. 199 represents the worst (total) disability), 0--no disability.

3.2.4. NONPHARMACOLOGICAL THERAPIES

Since 2013, a number of studies have enhanced the literature and have guided clinicians on successful treatment interventions outside of pharmacotherapy and surgery. Thirty-three randomized controlled trials and one large observational study on exercise and physiotherapy were published in this period. Four randomized controlled trials focused on dance interventions, eight on treatment of cognition and behaviour, two on occupational therapy, and two on speech and language therapy (the latter two specifically addressed dysphagia). Three randomized controlled trials focused on multidisciplinary care models, one study on telemedicine, and four studies on alternative interventions, including music therapy and mindfulness.[87] For example neuro-rehabilitation, including behavioural adaptations, can play an important role in the management of PD, by helping patients to deal with the decline in functioning while optimizing participation and quality of life. Its focus is on the patient as a person; the goals usually relate not only to disease symptoms, but also to social functioning and well-being.[88]

However, the scientific evidence on its effectiveness is increasing[87,89], and neuro-rehabilitation is increasingly being integrated in the multidisciplinary care pathways for patients with PD.[90] Many professional disciplines are involved in neuro-rehabilitation, including e.g. physiotherapists, occupational therapists and speech-language therapists; all these professionals need to integrate their own specific treatment contribution with each other, and align this with medical management.

3.2.5. MULTIDISCIPLINARY DISEASE MANAGEMENT STRATEGIES

A multidisciplinary approach combining pharmacological treatment with non-pharmacological interventions to manage a complex disorder such as Parkinson's disease might be beneficial.[91] Despite the shortage of evidence for effectiveness[92], guidelines recommend regular access to a broad range of medical and allied health-care professionals[93]. Indeed, many centres deliver integrated and multidisciplinary care for patients with Parkinson's disease.[94] However, a standard template for multidisciplinary care in Parkinson's disease does not exist, and guidelines do not clarify how a team approach should be organised and structured.

The IMPACT trial{van der Marck, 2013 #193} assessed the effectiveness of an integrated multidisciplinary approach compared with usual care. This integrated care approach offered only small benefits to patients with Parkinson's disease, and these disappeared after correction for baseline disease severity. These results and those of previous studies support further development of well-designed clinical trials to obtain more knowledge and scientific evidence on how to organise team-oriented care in Parkinson's disease.

3.3. THE ECONOMIC BENEFITS OF EARLY INTERVENTION

3.3.1. COST OF ILLNESS STUDIES

Early intervention is likely to have a significant impact on costs for the healthcare sectors but also society overall; a number of cost of illness studies have found that the great majority of costs associated with PD occur in the later stages of the disease, when symptoms are at their most severe and, consequently, there is more need for healthcare service or caregivers support. Motor complications (motor fluctuations, dyskinesias, dystonia as uncontrollable and sometimes painful muscle spasms) have been identified as factors increasing PD-related costs [95-106]. In all these studies severity of the disease was measured using the Hoehn and Yahr (HY) stage of PD (measured between 1, minimal disability, and 5, confinement to bed/wheelchair user)[2].

- **In UK (2007) -** Findley and colleagues[96] found that the total cost in the UK lies between £449 million and £3.3 billion [€621 million and €4.6 billion] annually, depending on the cost model and prevalence rate used. The rise in social services costs was particularly influenced by the severity of the disease and reached approximately £7,000 [€9,700] per patient per year at stage 5. Increasing HY stage was also associated with an increasing proportion of secondary care within NHS costs (27% in stages 0–1, 62% in stage 5). The study identified that disease severity was the single most important cost driver: patients at HY stage 5 had costs that were six times higher than patients at stage 0 or 1 (£2971 vs £18,358; €4,113 vs. € 25,418 per patient per year). A key factor in this difference was the cost of institutional care. Among participants in the study who received institutional care, costs were more than 4.5 times higher than for patients who remained at home. The financial burden of institutional care fell either on social services or on the patients themselves if they chose private care. Interestingly, medicine costs did not change with increasing disease severity and consequently they accounted for a lower proportion of the direct cost of PD in more severe cases. This study clearly shows how PD costs increase with the progression of the disease.

- **In UK (2003)** - In another study McCrone and colleagues[97] measured service use and costs for PD patients in the UK. The annual costs were £13,804 [€16,492] per patient. Formal care costs accounted for 20% of this amount, while informal care was related to 80% of the burden. Predictors of higher costs were identified, with male gender, level of disability and depression being the more significant ones.

[2] **The Hoehn and Yahr scale** is a commonly used system for describing how the symptoms of Parkinson's disease progress. It was originally published in 1967 in the journal Neurology by Melvin Yahr and Margaret Hoehn and included stages 1 (Unilateral involvement only usually with minimal or no functional disability) through 5 (Confinement to bed or wheelchair unless aided).

- **In UK (2007)** - A 2007 study developed in the UK[98] showed that Levodopa induced dyskinesia increased health care costs. Relationship between increasing cost of care and severity of the disease was proven to be statistically significant. A correlation was also found between the severity of the disease, patient's age and the use of Social Services.

- **In Italy (2003) -** A study published in 2003[99] assessed health care costs associated with PD in Italy. Annual direct health costs were €4,320 for mild stage (HY 1-2), €4,748 for moderate stage (YH 2.5-3) and €6,175 for severe stage (HY 4-5). The average was estimated at €4,808. These results were identified as lower than the real cost, as they didn't consider the societal perspective and neither informal care nor health care costs incurred in the private sector were included.

- **In Finland (2003)** – In Finland the total annual cost-of-illness for PD outpatients was USD 131 million [EUR 118 million], including direct costs of USD 54.7 million [EUR 49.2 million]. Keranen and colleagues[100] found a significant association between PD severity and annual costs. Total costs in HY stages 1 to 2.5 were comparable, whereas they doubled in stage 3 and again in stage 4. In early stages of PD, direct costs accounted for most of the economic burden of the disease. However, for patients with more advanced PD, with HY stages 3.0–4.0, indirect costs accounted for increasing amounts of the economic burden, accounting for as much as half of the total costs in HY stage 4.0.[100]

- **In Germany (2000 and 2004)** – Similarly in a German study[101] it was found that disease severity (i.e. HY stage) alongside with motor complications and age, affected the costs of PD. The resource utilization in two cohorts of PD patients recruited in 2000 (n=145) and 2004 (n=133) were compared. Direct and indirect costs were assessed based on a patient diary and structured personal interviews. In 2004, total annual costs for PD ranged from €18,660 for HY (1 to 2) to €31,660 for HY (2 to 5). As compared to costs in 2000, total costs increased in 2004 by 25-31%.

- **In Germany (2004–2006)** – In a subsequent German study[102], the total costs per patient were €20,860 per PD patient; they increased according to HY disease stage severity, from average cost of €3,400 for HY stage 1 to €15,000 for HY stage 5, with the majority of costs originating from outside the formal healthcare system. When analysing the costs by HY stage, in contrast to the findings of the Finnish study, indirect costs remained stable over the course of the disease, but the direct costs in the advanced disease stages increase disproportionately.

- **In Spain (2012) -** Matinez-Martin and colleagues[103] estimated the magnitude in which PD symptoms and health-related QoL determined PD costs over a 4-year period. Mean

(SD) PD total costs increased about 92%, from €2,082.17 (€ 2,889) in year 1 to € 4,008.6 (€7,757) in year 4. Total, direct and indirect cost increased 46%, 35%, and 70%, respectively, for mild disease (HY 1-3), whereas increases of 166% for total, 56% for direct and 348% for indirect costs in patients with moderate PD (HY 4) was observed. For severe patients (HY 5), cost remained almost the same throughout the study.

- **In Russia (2008).** Costs of PD illness were studied also in Russia within a cohort of 100 patients.[104] From the societal perspective, total annual costs per patient amounted to €5,240 per patient, with direct costs accounting for 67% and indirect costs for 33% of the total. The main drivers of the burden were informal care and drugs. Global costs for the nation were estimated at €1.1 billion per year.

- **In Czech Republic (2010).** A more recent study[105] was performed in a cohort of 100 Czech patients with idiopathic PD to evaluate direct and indirect costs and to identify cost-driving factors. Results were assessed for a 6-month period and have been projected to annual costs. Total annual costs for PD were €11,020 per patient. Direct costs accounted for 60% of the total costs and indirect for 40%. Independent cost driving factors included disease severity, motor complications, psychosis and age.

- In a 6-month **international observational study of PD in France, Germany and the UK**[106], patients with different degrees of motor complications, measured using the Unified Parkinson Disease Rating Scale (UPDRS), and its effects on health care costs were examined. Dyskinesia was associated with significant increases in total health care costs. Each unit increase in dyskinesia score lead to €562 additional costs per patient over a 6-month period.

The economic evidence gathered in the literature shows that any strategy that would maintain PD symptoms in the earlier stages of the disease (when they are fewer and less severe) would likely prove substantially beneficial toward limiting expenditures. It is, therefore, possible that therapeutic interventions offered to patients before significant deterioration has occurred, when the potential for preserving neurophysiologic structures is maximized, may offer long-term cost savings. Indeed, little evidence points to the likelihood of short-term savings with early therapeutic intervention (although little evidence in this area exists in general), but long-term cost savings are entirely credible based on the delay of L-dopa therapy and of the motor symptoms that require more intensive therapeutic interventions.[45]

3.3.2. COST-EFFECTIVENESS STUDIES

A number of cost-effectiveness studies have also been undertaken to determine the economic value of early intervention for PD, and the results have been largely, if not unanimously, positive.

- **Dopamine agonist or MAO-B inhibitor (compared with L-dopa; UK 2009)** [107]- A study in the UK found that early treatment was cost-effective when patients with PD were treated with a dopamine agonist or MAO-B inhibitor (from a United Kingdom payer perspective). Early treatment delayed onset of dyskinesia and L-dopa initiation, and were associated with cost savings over a 5-year study period. More specifically, in this Markov model economic evaluation, data from 2 trials of dopamine agonists (rasagiline, pramipexole) in early PD were examined for effectiveness (time to L-dopa and time to L-dopa-induced dyskinesia), cost, and quality-adjusted life-years (QALYs). Rasagiline was found to reduce costs by 18% per patient over 5 years and demonstrated a 25% prolongation of time to L-dopa and a 10% delay in onset of dyskinesia. Rasagiline also demonstrated a 5% gain in QALYs relative to pramipexole.

- **Dopamine agonist (compared with L-dopa; USA 2005)** [108]- Another cost effectiveness study conducted from a US societal perspective found that treatment with pramipexole in patients with early PD was more cost effective and was associated with cost savings versus L-dopa in patients with depression and low baseline QoL. Under the base-case assumptions, the ICER for pramipexole was 42,989 US$ per QALY [€33,178 per QALY]. The probability that pramipexole was cost effective relative to L-dopa over the first 4 years was 0.57, 0.77 and 0.82 when a QALY was valued at 50,000 US$ [€38,589], 100,000 US$ [€77,178], and 150,000 US$ [€115,767], respectively. Over time, the ICER for pramipexole improved and uncertainty around the ICER decreased. If, after treatment withdrawal, QoL improved in pramipexole subjects and declined in L-dopa subjects (best-case scenario for pramipexole), the probability of pramipexole being cost effective increased to 0.88, 0.96 and 0.98, respectively. Factors that improved the ICER of pramipexole were a decrease in the relative price of pramipexole and having low QoL or depression at baseline.

- **Dopamine agonist (compared with baseline treatment patterns; USA 1998)** [109]- In an older study, Hoerger et al also found that pramipexole was cost-effective compared with baseline treatment despite initially higher medicine costs, especially in patients with early PD. For patients with advanced PD, the ICER was US$12,294/QALY, whereas for patients with early onset of PD, the ICER for pramipexole was US$8,837/QALY.

All these economic analyses demonstrate that treatments other than L-dopa, especially when initiated early, may be cost-effective. However, despite this apparent benefit of utilizing

dopamine agonists in early PD to delay the need for L-dopa and to achieve cost savings, there is still controversy regarding when to initiate treatment. These studies referred to early treatment in the sense of the disease being treated soon after standard PD diagnosis has been achieved.[45] If early PD is defined as that period prior to the onset of significant motor symptoms, then, as already considered with clinical outcomes, few data are available on the real potential for cost savings.

3.4. THE BENEFITS OF TREATMENT ADHERENCE

3.4.1. THE CLINICAL BENEFITS

Patients with PD should take their medication as prescribed for numerous reasons.

Firstly, sudden withdrawal of dopaminergic drugs can result in suppression of central dopamine transmission and thus trigger the neuroleptic malignant syndrome, which may lead to fatality.[110]

Secondly, sporadic dopamine levels in blood plasma, partly from inadequate timing of medication taking, correlate with alternating high and low levels in the brain. Such erratic stimulation (the so called peak and trough effect) is proposed to result in motor fluctuations. Researchers evaluating the effect of reduced pill intake in PD showed that non adherence was associated with the 'wearing off' of the treatment effect.[111] This was shown to result in motor fluctuations and increased risk of worsening symptoms compared to medication adherent individuals. Furthermore, poor adherence to treatment was associated with more unplanned hospital admissions for PD related problems and an overall poorer prognosis.

Interestingly, and perhaps unique to PD, non-adherence to medication is not specific to sub-optimal pill intake. **Patients may also non-adhere by over medicating.** Excessive intake of dopaminergic agents was prevalent in 10% of patients diagnosed with PD at a younger age.[39] The consequences of over medicating can be substantial and include severe medication induced dyskinesia, behavioural disturbances and potentially even psychosis.[112,113]

Medication non-adherence in PD also has serious consequences for other parties involved. **From the perspective of family members**, their relative's health is likely to deteriorate leading to poor QoL and increasing care requirements. This can place significant burden on the spouse/carer which can greatly affect their health and QoL. **For treating clinicians**, future management decisions are based on the premise that the patient is correctly taking the intended treatments. Dose escalation, adjunctive therapy use and, in some cases, diagnostic reconsideration may all be consequences of poor adherence.[114] [115]

3.4.2. THE ECONOMIC BENEFITS

Several **USA-based studies** reported that treatment adherence may have an impact on direct costs.

- Davis et al (2010) employing insurance claims data from 30 managed care plans (using the Integrated Health Care Information Services Database), estimated that 61% of PD patients were non adherent to therapy over a 12-month period.[48] Mean medical costs were significantly higher among non-adherent versus adherent subjects (US$15,826 vs US$9,228 [€11,885 vs. €6,930]; *P* <0.01) despite the former having significantly lower prescription medicine costs (US$2,684 vs US$3,854 [€2,015 vs. €2,894]; *P* <0.05).

- These data are consistent with results from another study in the USA (2011) showing that patients who were satisfactorily adherent to L-dopa/carbidopa/entacapone therapy had 39% fewer PD-related hospitalizations, 9% greater PD-related prescriptions, 47% lower inpatient costs, and 18% lower total costs than patients with unsatisfactory adherence. Overall all-cause total costs were US$3,508 [€2,360] less for those with satisfactory versus unsatisfactory adherence.[116]

- Data from a national database of managed care plans (2010) found that non-adherer patients had significantly higher rates of yearly hospitalizations, healthcare visits, and higher total medical costs (US$15,826 vs. US$9,228; €11,885 vs. €6930) despite lower prescription medicine costs. Overall non-adherence was associated with a US$3,451 [€2,591] yearly increase in medical costs.[117]

- More data from the USA (2013)[118] showed that, although total drug mean costs were higher for compliant patients than non-compliant patients (driven mainly by the cost of PD-related medications), the mean costs associated with emergency room and inpatient visits were higher for patients non-compliant with their prescribed medication. Overall, the total all-cause annual healthcare mean cost was lower for compliant than for non-compliant patients (US$77,499 vs. US$84,949; €59,286 vs. €64,985).

3.4.3. NEW INTERVENTIONS TO SUPPORT ADHERENCE

A Cochrane review of interventions for enhancing medication adherence across numerous medical conditions found only a small number to have a statistically significant impact on short- and long-term adherence, with improvement in treatment outcomes even less common. Of the successful interventions, most were **complex combinations of increased**

follow-up, regimen simplification, mailed and telephoned reminders or reinforcement, counselling, and supportive care.[119]

For example, a study in the UK (2007) compared **targeted verbal and written patient education on the continuous dopaminergic theory** to usual care. Electronic medication monitoring devices assessed adherence to medication timing before and after the educational intervention.[120] At baseline, only 17–21% of all medications were taken at the appropriate time interval, with a statistically significant increase to 39% of all doses in the active group post-intervention. There were no statistically significant differences between QoL, UPDRS scores, or adverse events between groups. The study was limited by short follow-up and substantial attrition in both groups. A second study is evaluating a brief form of cognitive-behavioural therapy focused on medication adherence in patients and caregivers with PD.[121] This study, too, is limited by a short duration of planned follow-up, and the assessment of medication adherence by a surrogate marker rather than a gold standard.

Further research is necessary to explore the patient characteristics, beliefs, and decision-making processes associated with medication non-adherence. These investigations should include for example **electronic medication monitoring caps** (medication monitoring systems that track medication usage without active input from the patient)[114] and account for the frequent involvement of family and caregivers in PD management.

It is also important to consider the complexity of PD, and the fact that it is a chronic disease with a spectrum of manifestations that appear and change as the disease progresses. Consequently, treatment efficacy and patient well-being are improved when a **multidisciplinary disease management approach** to PD is implemented and specialists (i.e. neurologists) are part of the management team alongside other healthcare professionals as appropriate.[122] By employing a multidisciplinary disease-management strategy, healthcare professionals with expertise in PD can provide informed guidance with regard to the selection of treatments that are likely to be most effective and to which patients are most likely to be adherent.

4. KEY MESSAGES FROM THE LITERATURE

The literature confirms that early diagnosis and treatment of PD are paramount to: reducing the risk of disease progression; limiting the effects of PD on QoL; and potentially lowering long-term treatment costs.

Standard current approaches to PD diagnosis rely on the presence of motor symptoms; therefore the diagnosis is mainly clinical, and may occur at later stage of the disease, when significant irreversible neurological damage may have already occurred and there is no opportunity to delay disease progression.

However, the combination of a new definition of PD (to include early pre-motor symptoms) and new diagnostic tools may allow for early diagnosis, and therefore treatment of the disease. Biologic biomarkers offer some of the most useful tools for reliable early PD diagnosis. In addition, neuroimaging techniques, particularly SPECT and MRS, also show enormous potential because of their high degrees of sensitivity and specificity in diagnosing early PD. However a widespread use of such screening strategies may be limited by practical constraints due to the limited availability of the medical technologies and their high costs. Any cost savings resulting from an early diagnosis achieved through the implementation of better neuroimaging techniques should take into account the implementation cost.

Patient's treatment adherence has also been identified as a key area which is able to impact clinical outcomes and costs. Finally, a disease-management strategy through the implementation of a chronic model of care, is important to improve treatment adherence and rates of correct diagnosis. Clinicians should be informed regarding proper diagnostic approaches, ensuring diagnosis is performed by those clinicians with appropriate skill sets, and availing them of emerging techniques for early and accurate diagnosis.

It is important that healthcare managers and policy makers recognise the changes taking place in the detection and treatment of PD, and take advantage of opportunities for the earliest possible intervention in PD before major neurological damage occurs and treatment may become less effective and more expensive.[45]

5. WHAT HAS NOT BEEN ADDRESSED SO FAR AND SHOULD BE CONSIDERED IN FUTURE RESEARCH?

5.1. RETHINKING WHAT PD IS AND HOW/WHEN IT CAN BE DIAGNOSED

The recent developments in PD diagnosis emphasise the necessity of rethinking what PD is and how, and when, it can be diagnosed. Clinicians are aware that the current diagnostic tools and guidance should be updated in light of current knowledge of PD to optimize its early detection. Critical issues to be solved with regard to the current PD definition includes:

- ***Who decides what PD is and what is the gold standard for a "final" diagnosis? What clinical features fit under the definition of PD and should be incorporated into the diagnosis? With regard to defining disease onset, can PD be defined before classic motor features develop? Are new diagnostic tools needed to fit the new definition of PD?***

  In recognition of the profound changes in the understanding of PD, the International Parkinson and Movement Disorders Society (MDS) has recently commissioned a task force to discuss these critical issues and to consider a redefinition of PD.[123] More research is needed to further explore these key areas which should be informed by solid real-world evidence rather than by limited clinical practice.

- ***How do we define early PD?*** Despite the evidence of the beneficial effects of early diagnosis and treatment, all the studies found in the literature define **early PD** only in the sense of ***the disease being treated soon after standard PD diagnosis has been achieved, i.e. after the presence of motor symptoms (when around 70% of all dopamine neurons may have been lost)***.[45]

If, however, **early PD** is defined as that ***period prior to the onset of significant motor symptoms, before substantial neurological damage may have occurred***, then limited data is available that describes the real potential of early treatment in terms of clinical and economic outcomes. Thus, more research would be needed to explore the real impact of early treatment both on clinical and economic outcomes.
Furthermore, with the advent of new diagnostic tools, such as genetic biomarkers, forthcoming studies should assess the impact of these medical innovations in terms of clinical and economic outcomes.

5.2. DO WE HAVE PREFERRED TREATMENT OPTIONS?

Although the literature seems to confirm that early treatment is beneficial, there is still debate regarding whether treatment (with L-dopa which is limited by eventual wearing-off

effects) should be initiated immediately or delayed until greater motor functional disability presents.[124] In addition to the wearing-off effect, there is also some risk of additional side effects involved with starting treatment early. Certain medicines commonly used in PD including L-dopa, anticholinergic agents, and dopamine agonists are associated with different side effects (e.g hypotension, arrhythmia, insomnia, hallucinations) that can have a negative impact on patient' QoL and therapeutic adherence. Nonetheless, early treatment of PD might bring important benefits, such as potentially enhancing the effects of mechanisms that compensate for the deficits caused by PD. What is still unclear is whether early treatment can bring neuroprotection or whether outcome modification can be achieved. Also being questioned is the effect of early initiation of a therapy other than L-dopa on disease progression.[72] **The benefits of alternative medicine formulations, regimen simplification, or non-pharmacological interventions** (for examples see neuro-rehabilitation[89], the introduction of ICT [information and communications technology] wearable sensors[125] and integrated care models[126]) **should be further explored** as these may present opportunities to improve outcomes and lower costs in PD.

Considering health systems reforms taking place all over Europe and the challenges related to the management of chronic conditions, including co-morbidities and ageing, **new models of care that include a societal benefits approach need to be examined to ensure more coordinated and integrated care**. **The EBC Value of Treatment project for 2015-2017**[127] aims at developing and applying to brain disorders a new integrated care model framework and therefore promote a more holistic management of chronic conditions in Europe. The project will provide evidence on how to implement effective and cost-effective interventions across a series of brain disorders, including Parkinson's disease.

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7. LIST OF ABBREVIATIONS

Alzheimer's disease (AD)
Central nervous system (CNS)
Cerebrospinal fluid (CSF)
Corticobasal degeneration (CBD)
Dementia with Lewy bodies (DLB)
Essential tremor (ET)
European Brain Council (EBC)
Hoehn and Yahr (HY)
Idiopatic parkinson's disease (IPD)
Incremental cost effectiveness ratio (ICER)
Information and communications technology (ICT)
Levodopa (L-dopa)
L-dopa/carbidopa/entacapone (LCE)
L-dopa/carbidopa (LC)
Magnetic resonance imaging (MRI)
Magnetic resonance spectroscopy (MRS)
Managed care organizations (MCOs)
Monoamine Oxidase Type-B (MAO-B)
Multiple system atrophy (MSA)
Multisystem atrophy (MSA)
Non-motor symptoms scale (NMSS)
Normal pressure hydrocephalus **(**NPH)
Parkinson's disease (PD)
Peripheral nervous system (PNS)
Physical therapy (PT)
Positron emission tomography (PET)
Progressive supranuclear palsy (PSP)
Quality-adjusted life-years (QALYs)
Quality of life (QoL)
Single photon emission computed tomography (SPECT)
Transcranial sonography (TCS)
Unified Parkinson's disease rating scale (UPDRS)