

The Economic and Quality of Life Burden Associated With Parkinson's Disease: A Focus on Symptoms

Deborah F. Boland, DO, MSPT, and Mark Stacy, MD

Abstract

Parkinson's disease (PD) imposes a significant economic burden on the healthcare system. As the population continues to age and shifts to include a larger proportion of persons 65 years and older, the economic burden related to PD will continue to escalate. Clinicians should be mindful of striving for efficiency, making prudent choices, and allocating resources appropriately. The majority of treatment costs in PD are associated with advancing disease; specifically, the costs related to increasing need for care. Early identification of motor and non-motor signs and symptoms of disease allows for earlier treatment. Through early treatment strategies, symptom control is improved and patients will likely have less need for care. This leads to improvements in quality of life (QoL) and functional independence and reduced caregiver burden and thus results in decreased costs. In addition, although research thus far has not clearly demonstrated the ability of an agent to provide disease modification, as new, potentially neuroprotective therapeutic interventions are developed and become available as treatment options, the recognition of early disease will be more important. If earlier treatment with neuroprotective agents leads to slowing of disease progression, the result may be less need for care and decreased costs for patients with PD. This may have a measurable impact by improving QoL measures for both the patient and caregivers.

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For author information and disclosures, see end of text.

Introduction

The incidence and prevalence of Parkinson's disease (PD) increase with age; with disease duration, both direct and indirect annual costs associated with this disorder will likewise continue to escalate. Given that the population of those 65 years and older is expected to increase from 35 to 80 million by 2040,¹ intensive discussion will focus on healthcare economy, including efficiency, prudent choices by providers, and appropriate allocation of resources. It is anticipated that future treatment of patients with neurodegenerative diseases will require providers to optimize treatment with best available therapies, incorporate disease modification approaches (if available), and emphasize management of healthcare system resources by limiting both direct and indirect expenditures.

Among neurodegenerative diseases, PD especially is associated with a significant economic burden to both patients and society. Over an 8-year span from 1992 to 2000, Medicare beneficiaries with PD used more healthcare services in all categories and had more out-of-pocket expenses than those without this disorder.² While likely due to multifactorial causes, cost of care continues to place an increasing burden on patients with PD, caregivers, and society. This article will address the increasing local and societal burdens associated with the progressive disabilities of PD and will review potential strategies for patient care in an increasingly demanding, cost management–focused environment.

Clinical Features

All clinicians regardless of specialty should have some familiarity with motor and non-motor symptoms related to PD. The 4 cardinal features of PD are well known. Jankovic presented the acronym TRAP in a review paper of the clinical features of PD: Tremor at rest, Rigidity, Akinesia or bradykinesia, and Postural Instability.³ Early in the course of the disease, tremor and other parkinsonian signs are usually asymmetric but eventually become bilateral. Tremor in PD usually occurs at rest about 4 to 7 Hertz in frequency, and may be most noticeable in the arms or hands ("pill-rolling tremor"). Tremor may also involve the chin, jaw, tongue, and legs. Rigidity, or a passive resistance to movement, may be seen in the neck, shoulder, elbow, wrist, hip, knee, and ankle. Bradykinesia (slowness of movement)

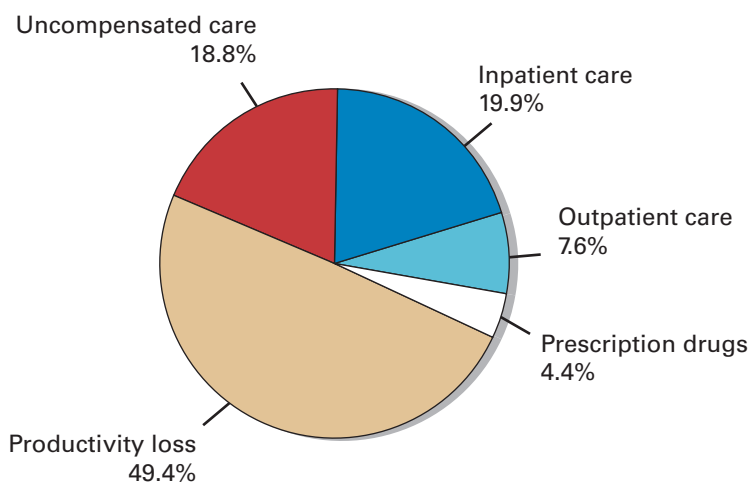
■ **Table 1.** Common Motor and Non-Motor Symptoms in Parkinson's Disease³

Motor Symptoms
Tremor
Bradykinesia
Rigidity
Postural instability
Hypomimia (lack of facial expression)
Dysarthria (manifestations of muscular disorder of mouth, face, and respiratory system, eg, slurred speech)
Dysphagia (difficulty swallowing)
Sialorrhoea (excessive saliva production)
Decreased arm swing
Shuffling gait
Festination (involuntary increase in gait speed)
Micrographia (small, cramped handwriting)
Glabellar reflex (blinking induced by tapping on forehead)
Blepharospasm (eye spasm)
Dystonia (movement disorder resulting from diverse and sustained muscle contractions)
Striatal deformity (dystonia in the hands and feet resulting in deformed postures)
Scoliosis (abnormal spine curvature)
Camptocormia (abnormal forward curvature of spine)
Non-Motor Symptoms
Cognition
Cognitive impairment
Bradyphrenia (slowing of thought)
Word finding: tip-of-the-tongue phenomenon
Mood
Depression
Apathy
Anhedonia (inability to experience pleasure)
Fatigue
Sensory
Anosmia (loss of olfactory senses)
Ageusia (loss of ability to taste)
Shoulder and back pain
Paresthesias (unpleasant feelings on or under the skin, eg, pricking, tingling, burning)
Dysautonomia
Orthostatic hypotension
Constipation
Urinary and sexual dysfunction
Abnormal sweating
Seborrhoea
Weight loss
Sleep Disorders
REM behavior disorder
Vivid dreams
Daytime drowsiness
Sleep fragmentation
Restless legs syndrome
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affects activities of daily living, including standing, dressing, feeding, brushing teeth, and bathing. Bradykinesia is assessed in the clinic through finger tapping, hand clapping, wrist pronation-supination, and heel tapping maneuvers. Postural instability or loss of postural reflexes is characterized by propulsion or retropulsion and a tendency to fall. Most motor signs in PD are manifestations of these cardinal characteristics: lack of facial expression (hypomimia), sialorrhea, hypophonia, dysarthria, dysphagia, micrographia, shuffling gait, difficulty standing and turning when walking, difficulty turning in bed, start hesitation, freezing, and festination of gait (Table 1).³ The decline in mobility leads to increasing need for assistance and greater economic impact to care for this population.

Patients with PD also commonly develop autonomic dysfunction (orthostatic hypotension, sphincter disturbances, and/or constipation), cognitive changes, psychiatric effects (depression, psychosis, and/or impulse control disorder), sensory symptoms (pain and/or aching), restlessness, and sleep disturbances (Table 1).⁴ These non-motor symptoms are increasingly the focus of care in tertiary neurology clinics. While motor symptoms often benefit from dopaminergic therapies, such as levodopa or a dopamine agonist, non-motor symptoms may result from disturbances of other neurotransmitter pathways, such as cholinergic, serotonergic, or GABA-ergic.⁵ While the combination of motor and non-motor symptoms in PD increases the options for attaining clinical benefit, these interventions and their potential side effects will also drive up healthcare costs.

■ **Figure 1.** Distribution of Indirect Costs in Parkinson's Disease⁹



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Epidemiology

The aging of the world's population remains the most predictable factor in the increasing economic impact of PD. In 2004, a statewide registry in Nebraska estimated a prevalence of 329 persons with PD per 100,000 people within the total population.⁶ An analysis of prevalence studies estimated the number of people in the United States with PD in 2005 to be 340,000; the authors projected from this that by 2030, with the aging US population, the total number of people with PD would double.⁷ An epidemiologic study of 10 European countries found crude prevalence rates ranging from 66 to 12,500 per 100,000.⁸ The World Health Organization in 2004 estimated that there were approximately 4 million persons worldwide with PD. As the overall world population becomes older, PD prevalence will become greater, resulting in a shift of healthcare expenditures to a significantly larger proportion spent on the wide spectrum of parkinsonian disorders.

Economic Burden of PD

Huse et al⁹ determined direct costs through medical and pharmacy data from the Medstat MarketScan Research Database from 1999 to 2002 for 20,016 PD patients. They determined indirect costs through estimations based on data reported by Whetten-Goldstein et al.¹⁰ The direct and indirect expenditures for patients with PD were compared with expenditures for the same number of matched controls without PD. Total annual direct costs were slightly more than double for PD patients compared with controls (\$23,101 vs \$11,247; *P* <.001). While additional costs were seen in

outpatient services, hospitalizations, and prescription drugs, nearly half of this excess cost was due to long-term care expenses. These authors conclude the total cost in the United States may be as high as \$23 billion annually when combining all indirect and direct costs. Due to the progressive neurodegenerative nature of PD, which leads to prolonged disability, the greatest costs were indirect costs, specifically costs due to productivity loss and uncompensated care (Figure 1).

Comparing populations beyond 65 years of age, Noyes et al² found the total unadjusted annual health expenditures of PD patients to be more than 2 times higher than annual health expenditures of the population without PD (\$21,899 vs \$10,732). Primary factors contributing to this differential include greater use of long-term care

and home healthcare services. Given the increasing burden of limited mobility in PD patients, services to assist with activities of daily living (ADLs) often become an early indirect expense. With disease progression, other causes of disability, such as cognitive decline, sialorrhea, dysphagia, and incontinence lead to further caregiver and financial burden. In the future, it will be of utmost importance to maintain a balance between quality of care and respect for the costs involved. The currently available treatment options present challenges for the clinician to achieve this goal.

O'Brien et al have attempted to describe direct costs by evaluating resource use. Using an expenditure model, PD patients were stratified to categories of healthcare utilization: 1) chronic, non-institutionalized management with a nonfatal acute event (which might require hospital admission), 2) chronic, non-institutionalized without an acute event, 3) permanent institutionalized care, and 4) death. Category assignment was based on data derived from the National Health Interview Survey on Disability (NHIS-D) and the National Ambulatory Medical Care Survey (NAMCS). Indirect costs included in the analysis comprised 3 elements: 1) lost wages due to missed work for people who were employed, 2) lost wages for caregivers who missed work, and 3) out-of-pocket expenses for in-home personal care. This model suggested that in a single year, 23% of PD patients would be chronic, non-institutionalized, and experience an acute event; 54% would be chronic patients managed on an outpatient basis; 11% would spend the year in an institution; and 12% would die. Direct costs per non-institutionalized chronic patient with an acute event were \$16,610; for chronic patients without an event, \$3573 (\$5363 if transportation and medical equipment costs are included); for institutionalized patients, \$47,807; and \$3769 for patients who died (Table 2). Indirect costs were \$9135 per patient: 23% due to lost wages, 51% due to lost caregiver wages, and 24% for death-related costs. US annual direct costs were estimated at \$6.2 billion, with a total expenditure estimate of \$11 billion when indirect costs are included.¹¹ Although these costs are approximately half of the estimated total costs reported by others, this study demonstrates that costs increase significantly when PD patients are transferred to institutional care.

Clearly, disease progression plays a major role in the costs of medical care in PD. A group of 70 PD subjects were classified as "good health" or "poor health" over a 3-year assessment period. Direct costs for the first year were similar

Table 2. Estimated Annual Costs for Chronic Management of PD Patients in a Single Year (2007 Dollars)¹¹

Chronic Management, Noninstitutionalized	
Service	Cost (2007 US Dollars)
Physician visits	310
Other professional visits	2
Laboratory tests	31
PD-related medications	3230
Transportation services	730
Durable medical equipment	1060
Total cost per patient	5363
Chronic Management, Institutionalized	
Service	Cost (2007 US Dollars)
Facility	43,950
Physician visits	1114
PD-related medications	2518
Hospital admissions	225
Total cost per patient	47,807

PD indicates Parkinson's disease.
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for both groups, although indirect costs (informal care and lost wages) were much higher in the "poor health" group. However, costs incurred during year 3 were substantially different. The direct costs for those in the "good health" group increased by 25% from year 1 to year 3 and the direct costs for the "poor health" group doubled. All costs increased for both groups, but for the "poor health" group the largest additional cost was nursing home care, which increased from \$564 to \$3941 from year 1 to year 3; interestingly, acute hospital cost increased by less than \$700 (all reported costs are in 1997 dollars).¹² While these cost estimates are daunting, when trying to manage a disease population, there are new avenues of expenditures that may be unique to the PD patients who develop impulse control disorders, such as pathological gambling, compulsive shopping, hoarding, binge eating, and hyper-sexuality.¹³ These disorders, which are especially associated with dopamine agonists, were only recognized and first reported in 2000, and are now seen in approximately 14% of this population.¹⁴

There is an unequal distribution of both direct and indirect costs associated with PD in the later versus earlier stages of the disease. Over time the cost is driven higher, as the motor and non-motor complications and complications associated with treatment play a greater role. Therefore it may be possible to decrease care cost by identifying disease-modifying therapies such as neuroprotective agents that arrest or slow

disease progression. This would also result in positive benefits on patient and caregiver quality of life (QoL). This concept is supported by studies demonstrating a strong correlation between disease severity and treatment costs.^{15,16} Given that motor symptoms of PD do not occur until the great majority of nigrostriatal cells are lost, early recognition of this disease is essential to maximize the potential benefit for protection of remaining dopaminergic neurons in the brains of patients with PD.¹⁷ Early treatment, based on early symptom recognition before significant neuronal loss has occurred, may prove to be the most clinically beneficial and cost-effective approach to PD management.¹⁸

Early Recognition and Diagnosis of PD

Although no specific agent has proven neuroprotective benefits in PD, it is increasingly important for clinicians to recognize early signs and symptoms of this condition. Recognizing motor symptoms is essential to clinical diagnosis; however, non-motor symptoms often occur at the very early, pre-motor stage in this disorder. It is therefore essential for clinicians to be alert to combinations of prodromal symptoms such as a change in sense of smell or taste, vivid dreaming or nightmares, constipation, and depression.^{19,20} In a recent summary, Adler²¹ reviews early signs and symptoms, noting that hyposmia or anosmia may occur in up to 96.7% of PD patients; evaluation of sense of smell is a useful screening test to identify an at-risk group for PD. He also notes that color and contrast discrimination are early visual changes in some patients. While sleep disorders are common in the aging population, it is increasingly accepted that REM-behavior disorder is seen in as many as 60% of PD patients. Constipation is an extremely frequent complaint of patients with PD and often predates the motor symptoms. In the Honolulu Aging Study, men with less than 1 bowel movement per day had a 2.7-fold increased risk of developing PD compared with those with 1 bowel movement per day.

The Parkinson At-Risk Syndrome Study (PARS) uses a smell test as the initial screening assessment to assess risk for the development of PD. In a study that screened 4999 subjects, 669 were at or below the 15th percentile based on age and gender, indicating hyposmia. The affected group more often experienced nonmotor features, including anxiety and depression, constipation, and REM sleep behavior disorder symptoms.²⁰ These subjects have agreed to participate in further testing, including dopamine transporter (DaT) imaging. A recent review suggests that DaTSCAN imaging may be useful in assisting with the clinical diagnosis of PD.²²

Effect on Quality of Life

The effect of PD (including both non-motor and motor symptoms) on QoL has been studied extensively. A Veterans Health Administration (VHA) study compared the effect of PD (adjusted for age, sex, race, education, and 15 comorbid conditions) on QoL in veterans compared with the effects of spinal cord injury, depression, congestive heart failure, stroke, chronic low back pain, arthritis, diabetes, and angina/coronary heart disease, by using a well-validated health-related QoL and functional status measure, Veterans SF-36. The study authors found the physical component summary score in the PD subgroup was worse than all other diseases, except for spinal cord injury. The summary score of the mental health component was worse among PD patients than all 8 other diseases with the exception of depression.²³ This study demonstrates that QoL is affected from both a physical mobility and mental health perspective in PD patients.

In a review paper Chaudhuri, Healy, and Schapira point out the extensive burden of non-motor symptoms which can be more accurately assessed by QoL measures, institutionalization rates, and health economics. They note that the economic burden of PD is comparable to congestive heart failure, diabetes, and stroke.²⁴

With regard to non-motor symptoms, specifically the mental health aspect of QoL in PD, depression is an important factor. Half of PD patients experience some form of depression; however, in 1 study, only 40% of patients received treatment.²⁵ Thus, it is necessary for the clinician to be cognizant of depression in PD in order to appropriately and aggressively treat its symptoms. However, depression is just 1 of the many contributing non-motor and motor symptoms that impact QoL in PD.

Chapuis et al reviewed the impact of motor symptoms in 143 PD patients using the PDQ-39, and demonstrated that motor disability had the greatest impact on functional mobility, activities of daily living, issues related to stigma, and communication with others. The study also demonstrated the negative effects of levodopa, a standard PD therapy, due to dyskinesias. "Peak dose" dyskinesias were associated with reduced mobility, cognition, and the emotional well-being domains of the PDQ-39. The authors also reported that nighttime akinesia was associated with deterioration in all QoL domains.²⁶

Winkler et al¹⁸ proposed a risk score to identify people at risk for developing PD. This type of screening, which emphasizes non-motor symptoms of PD, may assist in diagnosing patients early in the disease course, when there is greater potential to benefit from disease-modifying therapies.

A recent multi-center assessment of 411 subjects using the PD Non-Motor Symptoms Scale (NMSS) found that the

most common non-motor symptoms were nocturia (68.4%), fatigue (65.9%), and dribbling saliva (56.7%). The authors compared the correlations between QoL measured by the PDQ-39 and non-motor symptoms (per the NMSS) as well as motor symptoms, determined by use of the SCOPA-Motor instrument. There was a significantly greater correlation between non-motor symptoms and QoL than motor symptoms and QoL (0.70 vs 0.58; $P = .015$).²⁷

The vast majority of all PD patients experience at least 1 non-motor symptom early on in the course of the disease process. A large, multicenter Italian survey of 1072 PD patients identified at least 1 non-motor symptom in 98.6% of study subjects. Interestingly, of the 48 non-motor symptoms, 3 symptom domains—apathy, attention/memory, and psychiatric symptoms (eg, depression and anxiety)—did not correlate with the duration of disease or with dopaminergic therapies.²⁸ These findings support the notion that non-motor symptoms represent early disease and may be important in identifying more specific early diagnostic markers, as well as viable therapeutic targets for early treatment intervention.

Ravina et al evaluated depression in early-untreated PD patients who were enrolled in 2 phase II clinical trials and found that 27.6% of subjects had clinically significant depression, with 40% remaining untreated for these symptoms. Furthermore, there was a highly significant ($P < .0001$) association between depression and impairment of ADLs, along with an increased need for symptomatic treatment.²⁵ While gender studies in PD are infrequent, recently, a letter published in the *Journal of the American Geriatric Society* regarding QoL and frailty in PD patients noted that women in a community setting are more vulnerable to prefrailty than men. This suggests that an additional important dimension for clinicians to recognize is the potential differences among the sexes in QoL as it relates to frailty within community-dwelling PD patients.²⁹

It is important to consider that caregivers and family members may also experience a decline in QoL. A recent study from Malaysia indicated a significant relationship between the Caregiver Burden Scale (CBS) and the stage of PD, with a direct correlation between advancing PD and increasing CBS score. Also, caregivers who cared for older PD patients and/or cared for PD patients for a longer duration of time scored higher on the CBS.³⁰ As caregiver burden is increased, caregiver health both physical and mental can be affected, which can contribute to increasing the overall total costs in PD.

Impact of Early Therapeutic Intervention

Neuroprotection and disease modification remain fun-

damental therapeutic goals in PD, and if established could potentially decrease cost and improve QoL of both patients and caregivers. At present, there are no clinically proven therapies that modify disease progression in PD. Although the US Food and Drug Administration did not approve disease modification as an indication for rasagiline, work continues to address this elusive, unmet need.^{31,32} It is also possible that early treatment may have beneficial effects in delaying overall disease progression. If this is proved, then identification of non-motor or premotor symptoms in largely asymptomatic PD may offer a means of identifying candidates for early intervention.³³

A number of studies have demonstrated the importance of early therapeutic intervention. The ELLDOPA study, by the Parkinson Study Group, concluded that those with early PD who are on levodopa, even after a washout period, have lower UPDRS scores than those who took placebo, thus suggesting that levodopa possibly slows disease progression.³⁴ The TEMPO study showed early intervention with rasagiline compared with delayed intervention resulted in less worsening of UPDRS scores through 5.5 years of follow-up.³⁵ The ADAGIO trial again demonstrated that early versus delayed rasagiline treatment decreased the need for symptomatic PD treatment.³⁶ The REAL-PET study demonstrated that ropinirole, a dopamine agonist, may also influence disease progression compared with subjects randomized to levodopa.³⁷ The CALM study reported that intervention with either pramipexole or levodopa in early PD resulted in similar QoL outcomes over a 4-year period, but did have different efficacy and side effect profiles.³⁸ A study with an acute mouse model of MPTP intoxication has suggested neuroprotective effects with rotigotine.³⁹ Many research teams throughout the world continue to work on the identification of specific neuroprotective mechanisms and novel treatment approaches.

Advanced PD is associated with increased cost and decreased QoL; thus delaying disease progression through specific neuroprotective mechanisms has implications for treatment costs and improvement of QoL in PD patients. Treatments that can sustain relatively better health in PD patients will help to lower treatment costs. Unfortunately, limited clinical trial data have been produced that directly address the cost-effectiveness of early intervention in PD.

Impact of Specialist Care

The results of a recent study by Willis et al suggest that the training and expertise of the clinician treating PD patients may influence treatment outcomes. The study found that PD patients who were referred to and treated by a neurologist

Reports

were less likely to be placed in a skilled nursing facility and had a lower risk for hip fractures.⁴⁰

Summary

PD is a disease with growing prevalence and negative effects on QoL. Direct and indirect costs associated with PD are estimated to reach 23 billion annually in the United States. The bulk of treatment costs is associated with more intensive manifestation of symptoms and advancing disease. Motor symptoms tend to garner greater attention in PD with regard to diagnosis and treatment, but non-motor symptoms are more common and widespread. Non-motor symptoms also antedate motor symptoms in PD and may offer signals for early diagnosis and therapeutic intervention. Early intervention in PD is often associated with a slowing of disease progression and symptoms, and thus may have some neuroprotective benefit. Early treatment of PD will likely, in a large proportion of cases, have a beneficial effect on QoL while potentially lowering long-term treatment costs. Therefore it is prudent for the clinician treating patients with PD to be mindful of not just the easily recognizable motor signs, but also the less obvious non-motor symptoms. Furthermore, the training and expertise of the clinician treating patients with PD may influence treatment outcomes.

Author affiliations: Movement Disorders Center, Division of Neurology, Department of Medicine, Duke University, Durham, NC (DFB); Department of Neurology, Department of Medicine, Duke University, Durham, NC (MS).

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Address correspondence to: Mark Stacy, MD, Duke University, 932 Morreene Rd, Durham, NC 27705. E-mail: mark.stacy@duke.edu.

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