

SPECIAL DISEASE STATE UPDATE

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THE BURDEN OF PARKINSON'S DISEASE AND THE NEED FOR EARLY DIAGNOSIS AND EARLY TREATMENT

Parkinson's disease (PD) is a progressive and disabling neurologic disorder. The disease is the most prevalent type of parkinsonism, a clinical syndrome caused by lesions in the basal ganglia, predominantly in the substantia nigra, which produces deficits in motor behavior. PD occurs when certain neurons in the substantia nigra die or become impaired. See Figure 1. Normally, these cells produce the chemical dopamine, which allows for smooth, coordinated function of the body's muscles and movement.^{1,3} The symptoms of PD appear when approximately 80% of the dopamine-producing cells are damaged.³

After Alzheimer's disease, PD is the second most common neurodegenerative condition affecting an estimated 3% of Americans aged 65 and older.^{4,5} PD, which makes up approximately 80% of cases of parkinsonism, affects 4 million people worldwide.^{1,2} The brain disorder is more common in men, with a male-to-female ratio of 3:2.² As prevalence and incidence of PD increase with age, the number of individuals afflicted is expected to rise considerably.¹

Complications of PD

As PD progresses, patients may experience increased complications.

The tide is turning regarding early treatment of PD. Studies are showing that early diagnosis and early treatment may give patients an advantage.

See Figure 2. A cohort study of 20,016 patients with PD and a matched control group found that PD patients had significantly greater prevalence of conditions that may be sequelae of the disease.¹

Patients with PD, compared with controls, had 3-fold more frequent neuropsychiatric complications (predominantly dementia and depression), 57% greater incidence of falls and injuries (attributable to motor impairments), a 2-fold greater risk of sleep disorders (eg, insomnia and restless legs syndrome), and more than 2 times the prevalence of conditions resulting from autonomic dysfunction, such as dysphagia. Dysphagia, which is difficulty in swallowing, affects up to 75% of patients with moderate-to-advanced disease.^{1,3,6}

Burden of Illness

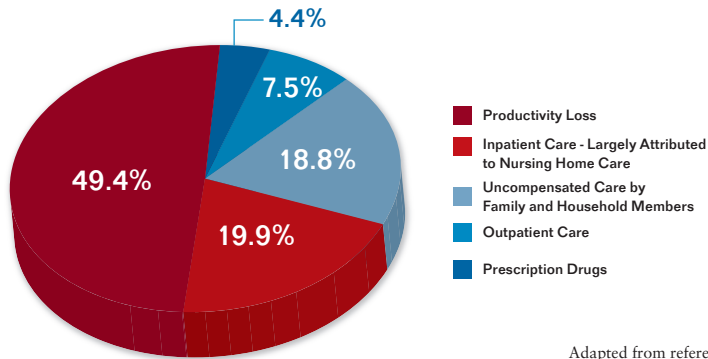
Early-onset and advanced PD poses economic implications for the healthcare system and long-term care providers. Furthermore, patients are faced with psychological challenges and lifestyle and employment adjustments. The disease also places a burden on caregivers.

Economic

The cost of PD can be calculated in direct (medications and healthcare use) and indirect (lost productivity, cost of providing care, and mortality) costs. In the United States, the increased direct medical care costs for PD equal more than \$10,000 per person annually. Because PD is characterized by prolonged disability, indirect costs of productivity loss (49.4%) and uncompensated care by family and household members (18.8%) represent the largest component of the total burden (68.2%). Inpatient care costs, largely attributed to nursing home care, are the biggest component of direct costs and account for 19.9% of total costs. The smallest portion of PD cost falls on outpatient care (7.5%) and prescription drugs (4.4%).^{1,5} See Chart.

Combining direct and indirect costs, the total burden of annual cost of PD in the United States is almost

Indirect and Direct Costs of Parkinson's Disease



Adapted from reference 1.

\$23 billion. Factor in that the population of individuals aged 65 and older is expected to reach 80 million in 2040, even a conservative estimate of PD costs at that time is likely to exceed \$50 billion.^{1,5}

Psychological Challenges

Patients with PD go from being healthy individuals to being patients with a chronic progressive illness. In early diagnosis, patients often deal with more psychological issues, compared with physical problems. Adapting to the illness is difficult for patients because they know they will never return to their pre-illness state.³

As the disease progresses, patients may experience difficulty in adjusting psychologically to the challenges that PD may present. These difficulties include social withdrawal, hypersensitivity, frustration, and anger.³

Depression is the most common psychiatric complication of the disease, affecting 40% to 70% of PD patients. It is one of the most important factors impacting quality of life. The frequency of depression has 2 modes of distribution, peaking in early-onset mild disease and then again in advanced severe disease.^{2,6,7}

It has been estimated that the incidence of anxiety in PD patients is 25%, but greater in patients who also are de-

pressed. Usually, anxiety will manifest after the diagnosis of PD, but may appear prior to motor symptoms.²

Lifestyle and Work

Patients with PD are forced to make adjustments in their lifestyle and career. Patients may no longer be able to enjoy the same hobbies or athletics, for example. Therefore, lifestyle changes require assessment on what is important about their current lifestyle, what can be adjusted, and what has to be completely changed. Lifestyle modifications can be a result of changes in employment, finances, and disability.³

Often times, patients with early-onset PD do not have to make adjustments in their normal work habits or routines. This changes as the disease progresses, and patients may need to assess what they can realistically continue to do and what needs to be modified. Clinicians recommend that patients analyze their work environment, job duties, performance standards, job complexity, and type of work to get a better understanding of what adjustments can be considered.³

Caregivers

PD raises many concerns for caregivers, whether it is a spouse, partner, or another family member. The caregivers worry about the future, the risk of disability, job and eco-

nomie loss, and increased dependence. These concerns and the burden of responsibilities can cause anxiety and depression in caregivers.³ Often times family members are regularly involved in care, becoming the primary caregivers; they are supported by home healthcare nursing, physicians, and specialized therapists as the disease progresses.²

Diagnosing PD

The diagnosis of PD is based on clinical findings due to the lack of specific diagnostic tests or biomarkers for the disease. A clinical diagnosis of parkinsonism requires the presence of at least 2 of the 4 cardinal signs.⁵ See Table. There are specific clinical criteria that have been proposed for the diagnosis of PD; the most widely used are the UK Brain Bank criteria. The criteria include the presence of bradykinesia and an additional sign of rigidity, rest tremor, or postural instability.⁵

Prior to the presence of the 4 cardinal signs, one of the early symptoms of PD is an inability to identify certain odors, known as hyposmia (decreased sense of smell), and anosmia (complete lack of a sense of smell). Researchers recommend the use of a screening test to assess selective olfactory deficits when evaluating patients with possible PD.⁸ It is important to note that symptoms are highly individual and often not "textbook." For example, 30% of PD patients do not have resting tremor. Also, tremor-dominant and akinetic forms of PD are very different.⁹

Functional neuroimaging techniques of the dopaminergic system, including magnetic resonance imaging, positron emission tomography, and single photon emission computed tomography, identify abnormalities in

early PD, assess neuronal degeneration, and monitor progression as well as the effect of treatment.²

Because initial presentation is rarely the full-blown disease and the signs and symptoms evolve slowly, research suggests that there may be a prediagnostic phase of PD where neurodegeneration proceeds slowly without the appearance of symptoms.^{10,11} This prediagnostic period is followed by the premotor period of PD in which patients experience nonspecific premotor symptoms, which continue after specific motor symptoms commonly associated with PD manifest. This premotor, prediagnostic phase may last from 5 to 20 years.^{10,11} See Figure 1. Therefore, physicians who suspect patients of having PD should recommend that they see a neurologist to start managing declining dopamine levels, stabilizing symptoms, and reducing side effects.^{2,3}

Treatment of PD

While no treatment has been approved to slow or stop the progression of the disease, the long-term goal in treating PD is to keep the patient functioning independently for as long as possible.^{2,3} How to initially treat PD should be individualized after clinicians consult with the patient, family members, and other caregivers. This approach allows patients to report how they are doing and how motor and nonmotor symptoms impact their daily lives. Family members and caregivers can relate observations of symptoms of which patients may not be aware.^{2,5}

Treatment options include therapeutic agents and surgery. Levodopa, introduced in the 1960s, is considered the first effective symptomatic treat-

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ment for PD.^{2,12} The introduction of newer drugs, however, has provided alternatives for patients with PD, particularly younger patients. These newer drugs may help to avoid developing the complications associated with long-term use of levodopa.^{2,12} After being absorbed in the gastrointestinal tract, levodopa—the precursor of dopamine—is transported to the brain, where it is converted into dopamine. It is subsequently released by brain cells and activates dopamine receptors allowing for normal function of the movement control centers of the brain.^{3,6}

Studies on the side effects of long-term use of levodopa have raised concern among clinicians. One of the major limitations of prolonged use is the development of motor fluctuations and dyskinesia.⁵ Dyskinesia is the presentation of different types of involuntary movements.⁶ These motor complications occur in 50% of PD patients after 5 years of therapy.⁵ After several years of therapy, patients develop progressive shortening of the duration of benefit after a single dose, known as a “wearing-off” effect,

whereby previously controlled symptoms re-emerge toward the end of the dosing interval. Patients taking levodopa also can experience an “on-off” effect characterized by unpredictable, abrupt fluctuations in motor state from controlled to uncontrolled. Other treatment side effects include confusion, sleep disorders, hallucinations, and psychosis.^{3,6,13}

It is recommended that clinicians consider other antiparkinsonian agents first to delay the start of levodopa, especially in younger patients.² In as many as 90% of patients with PD who have received levodopa for 5 to 10 years, motor complications occur. This is specifically common in these younger patients who are aged 21 to 39 years.⁹

Early Treatment Is Vital

The decision regarding when to start treatment has been debated. The traditional approach was to delay treatment until the symptoms of PD significantly limited the patient’s ability to function in daily life. The rationale for this approach was based on the fact that treatments available were considered only symptomatic and could not modify the course of PD. Delaying treatment also spared patients the adverse effects and allowed them to wait until the drugs were really needed so they would have an extended response.¹⁴

One report found that 61% of newly diagnosed PD patients delay drug treatment in the first year of diagnosis.¹⁵ Although this rationale still dominates the practice and teaching of clinicians, consensus is growing to support early treatment, ideally beginning treatment as soon as a patient would benefit from it.^{5,14}

A multicenter longitudinal observational study of 198 drug-naive patients with PD looked at the benefits of starting treatment early based on the PD-specific quality-of-life questionnaire (PDQ-39), a validated disease-specific tool for self-reported health status in PD. The PDQ-39 has 39 questions and 8 domains/dimensions that cover mobility, daily living, stigma, emotional well-being, social support, cognition, communication, and bodily discomfort.¹⁶

The results showed significant deterioration in all 8 domains of the PDQ-39 scale in patients left untreated at the first presentation. This pattern worsened if patients did not begin treatment at first visit with further deterioration of quality-of-life scores at the second assessment. The researchers recommended that the PDQ-39 should be integral to the clinical assessment of patients at the initial diagnosis and visit and also while assessing response to treatment.¹⁶

The tide is turning regarding early treatment of PD. Studies are showing that early diagnosis and early treatment may give patients an advantage in staving off the deterioration of their health and well-being.^{5,10,12-14} Healthcare providers should, therefore, be encouraged to take an active role in diagnosing patients early and getting them on a treatment regimen sooner rather than later.

Alternative Strategies

Integration of nonpharmacologic and wellness strategies should be a focus at disease onset.⁵ Physical therapy (PT), occupational therapy (OT), and speech therapy are examples of rehabilitative therapies that may be useful.

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PT in PD patients helps to optimize functional ability and reduce secondary complications.⁵ Formal PT will benefit patients as the PD advances. Therapy should be based on a needs assessment and specific goals. Exercises may improve the shuffling gait, stooped posture, and postural instability experienced by patients.²

OT should be offered to patients at all stages of PD. It is estimated that only 13% to 25% of PD patients are evaluated by an occupational therapist during their disease. In early PD, OT helps patients maintain their usual level of self-care, work, and leisure activities for as long as possible. As the disease progresses, OT becomes more focused on the development of modified activities and identification of new roles for the patient.⁵

Because speech disorders are common as the disease advances, speech therapy may be helpful for patients. However, data indicate only around 20% of PD patients are seen by a speech and language therapist.⁵ The purpose of speech therapy is to emphasize breathing control. Exercises are intended to increase the number of words spoken with each breath.

Complementary and alternative

medicine (CAM)—as an approach for treating PD—has also been documented in patients. It is estimated that up to 40% of PD patients use at least 1 form of CAM most commonly in conjunction with conventional therapies for the disease. CAM includes acupuncture, massage, exercise, and herbal medicines and nutritional supplements.⁵

Challenges of Adherence

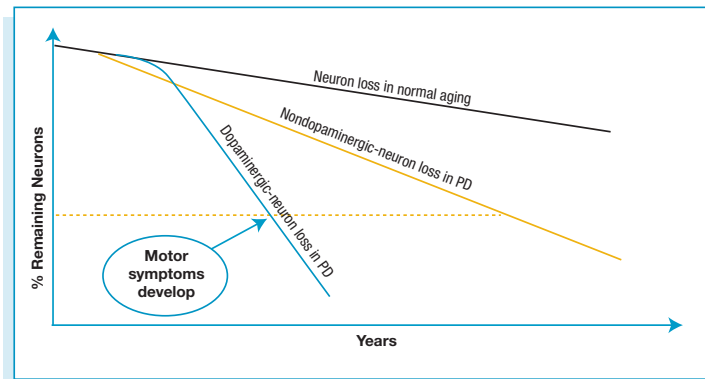
Patient adherence to drug therapy is paramount to treatment outcome, quality of life, and future healthcare costs. For elderly patients with PD, obstacles to adherence can be complex. General and specific factors influence adherence. This patient population often requires complicated dosing or titration schedules and has multiple comorbidities that necessitate administration of drug therapies from multiple drug classes. Furthermore, neuropsychiatric disturbances and cognitive impairment play a role in adherence.⁷

General Factors

Multiple studies have demonstrated that adherence declines when patients have to take a medication more than twice a day. Adherence also is affected by use of concomitant medications, which is likely in elderly patients with multiple chronic illnesses. Also, many patients take over-the-counter and herbal formulations, which may raise the odds for adverse events and drug interactions.⁷

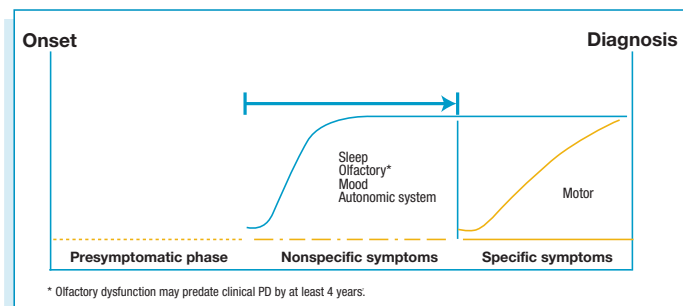
As patients age, they have more difficulty with medication-related tasks, which contribute to nonadherence. Memory disorders and cognitive impairment also affect an older person's ability to comprehend a medication's effect or follow a medication schedule.

Figure 1
Neuronal Cell Loss in Parkinson's Disease Occurs Before Symptoms Appear



Reprinted with permission. Adapted from Lang AE. The progression of Parkinson disease: a hypothesis. *Neurology*. 2007;68(12):948-952.

Figure 2
Premotor (Prediagnostic) Phase of Parkinson's Disease



* Olfactory dysfunction may predate clinical PD by at least 4 years.

Adapted figure. Reprinted from *Neurotherapeutics*, Vol 6, Halperin I, Morelli M, Korczyn AD, Youdim MB, Mandel SA. Biomarkers for evaluation of clinical efficacy of multipotential neuroprotective drugs for Alzheimer's and Parkinson's diseases, pages 126-140 Copyright 2009, with permission from Elsevier.

Table. The 4 Cardinal Motor Signs of PD

Rest tremor (shaking)—Widely known and most readily identifiable early sign of PD, and it is the first motor manifestation in about 75% of patients; affects the jaw, facial muscles or tongue, or the limbs; tremor improves or disappears with movement.

Rigidity—An increased tone detected on physical examination that is independent of speed and direction of movement.

Bradykinesia—Slowness of movement, reduced range, and difficulty with repetitive movement.

Postural instability—Difficulty with balance.

Nonmotor Features Associated with PD

- Stiff facial expression
- Muffled speech
- Depression
- Sleep disorders
- Pain
- Fatigue

Adapted from references 2,3,5, and 6.

These are common in PD patients. Forgetting is cited as the most commonly reported reason among older adults for nonadherence.⁷

Specific Factors

Patients with PD are at greater risk of nonadherence because of disease characteristics, multiple comorbidities, and the complexity and number of required treatments. Because PD is often accompanied by other comorbidities, patients require therapy with multiple drug classes and complex dosing and administration or titration schedules. This drug regimen may lead to concern about costs, drug interactions, and adverse events, which may lead to a patient's decision to stop taking a drug.⁷

In PD, cognitive impairment may happen as the disease advances. Cognitive impairment has been associated with both overadherence and underadherence. Dementia experienced by PD patients is very likely to affect medication-related behaviors. Patients having to take medications to address cognition may increase the complexity of multiple-drug ther-

apy and the potential for adverse events and drug interactions.⁷

Improving Adherence

Clinicians can work with caregivers and patients to devise effective adherence strategies. The participation of a caregiver in medication management in patients with cognitive impairment can improve adherence and subsequent response to prescribed therapies.⁷

The physician-patient relationship has a positive influence on adherence. Treatment success is more likely when the physician develops a partnership with the patient and caregiver, answers all the patient's questions, and communicates clearly and positively. Improved adherence also is more likely if there is cooperation and information sharing among all members of the healthcare team involved in a patient's care.⁷

A study of adults aged 65 years and older taking multiple drug regimens found that adherence was significantly better in patients who received medication education. Counseling also should happen consistently and at each visit. Simplified dosing regimens have led to better

success with adherence. Better adherence is associated with less frequent dosing. Adherence aids such as weekly pillboxes, calendars with color coding, reliance on cues, and automatic refill reminders can improve adherence.⁷

Future of PD

PD will continue to shorten life expectancy, cause significant decline in quality of life for both patients and caregivers, and place considerable economic burden on families and caregivers.¹⁴ The hope for better outcomes for patients with PD includes advances in therapeutic agents, neuroimaging techniques to help develop an objective diagnosis and improve on the sensitivity and specificity of the clinical diagnosis, and newer treatment approaches.⁶ Early diagnosis and treatment may serve as the best line of defense against the terrible physical and economic burdens inherent in a diagnosis of PD.

While a cure for the disease is still elusive, taking a proactive approach in treatment may help to reduce some of the burdens of this disease.^{5,10,12-14} ■

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