

An Evidence-Based Approach to Management of Early Parkinson's Disease

Case Study and Commentary:

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Parkinson's disease (PD) is a progressive central nervous system disorder caused by degeneration of dopaminergic neurons within the substantia nigra of the midbrain.¹ Because these neurons project into caudal and putamenal nuclei within the striatum and basal ganglia, diseases associated with their degeneration affect motor control. Consequently, PD is classified as a movement disorder.

PD is relatively common, affecting approximately 1% of all Americans older than 50 years.² However, early unrecognized symptoms of this movement disorder may affect up to 10% of Americans older than 60 years, thus significantly increasing the actual number of those affected by PD.³ Early-onset PD affects individuals in their 20s and results in significant costs, given the economic impact on and potentially diminished employability of those affected.² Men seem to develop PD more often than do women (approximate ratio, 3:2). Although PD was initially believed to affect white populations only, recent research has reported an equal prevalence of the disease in African Americans and whites living in the same US geographic area.⁴ Currently, there is limited knowledge of the epidemiology of PD within the Hispanic community, with conflicting information reported.⁵ An analysis of various geographic areas indicates that the disease is statistically associated with rural living environments, although the etiology of this finding is not clear.⁶

There have been major investigations into the possible genetic causes of PD. At present, several independent loci have been identified that are associated with familial PD: an autosomal dominant, adult-onset type of PD has been linked to a site on chromosome 4q,⁷ and an autosomal recessive, juvenile-onset type of PD has been mapped to chromosome 6q.⁸ Researchers also have successfully used gene therapy to prevent and reverse functional deficits and symptoms of early PD in experimental animals.⁹ Applying this knowledge to

humans may have important diagnostic and therapeutic implications in the future.

Experimental methods, such as single-photon emission computed tomography, show promise for diagnosis of the disease.¹⁰⁻¹² However, because there currently is no widely available test that is both sensitive and specific for diagnosing PD, a significant differential diagnosis must be considered when attempting to assess a patient with this suspected movement disorder. Multisystem atrophy, Shy-Drager syndrome, and olivopontocerebellar atrophy are all leading candidates for diagnosis when early dementia, orthostatic hypotension, wide-based gait, axial rigidity, other autonomic nervous system dysfunction, or lack of response to levodopa is observed in a patient.¹³ Some commonly prescribed drugs that can cause drug-induced motor disorder symptoms are haloperidol, antiemetic drugs (eg, prochlorperazine), gastrointestinal antitomotility drugs (eg, metoclopramide), and antihypertensive drugs (eg, reserpine); older female patients who take these drugs are more likely to develop extrapyramidal symptoms and other adverse effects.¹⁴ Thus, all medications that a patient is taking must be investigated.

Depression also can be a major part of the differential diagnosis for PD. Because patients who are depressed can have symptoms resembling the classic masked facies and bradykinesia of PD (eg, a sad facial expression and/or psychomotor retardation), the primary care

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physician must consider depression as a potential diagnosis. Of course, because depression and PD can coexist in the same patient, both diagnoses should be considered and, if necessary, appropriate treatment for both disorders initiated.¹⁵

As noted in the following case study, there are several medical interventions that can be used to treat patients with PD. In patients who do not respond to these medical treatments, neurosurgery may be an option.¹⁶ Surgical treatment of patients affected by PD is not new; in the 1960s, thalamotomy was often a treatment for the disease, even before levodopa was available. Although the surgery did reduce tremor and rigidity in many patients, its usefulness was limited because of potential negative effects on speech, swallowing, and vision.¹⁷ Presently, thalamic stimulation via insertion of an electrode wire into the ventral intermediate nucleus of the thalamus, using electrophysiologic guidance, provides similar benefits to thalamotomy without the risks associated with irreversible tissue loss. The inserted electrode is attached to an electrical pulse generator (similar to a cardiac pacemaker) and is implanted subcutaneously into the patient's pectoral area. The patient activates the unit using a small magnet when experiencing tremors; within seconds to minutes, patients who are responsive to this treatment are able to move without tremor, until the magnet is once again passed over the unit. Such treatment is most effective for PD patients whose primary disabling symptom is tremor¹⁸; bradykinesia and rigidity generally are not alleviated.

Pallidotomy is another surgical option for some patients. In this procedure, the patient's globus pallidus is lesioned permanently. This surgery usually benefits patients who have dyskinesias rather than tremors and has significant adverse effects, including potential hemiparesis, neuropsychiatric disorders, and visual field deficits.¹⁹ As such, it should be reserved for patients with significant disease that is refractive to other treatments.

Treatments that are less invasive than traditional neurosurgery are now being developed. For example, other methods of stimulation (eg, pallidal and subthalamic nucleus stimulation) and tissue transplantation procedures are being evaluated rigorously to test their short and long-term effectiveness, as well as any adverse effects.²⁰⁻²³

In summary, PD is a relatively common and debilitating movement disorder that has significant social and economic effects. As such, the disease places a large burden on both patients and their families. Consequently, primary care providers must be familiar with not only the differential diagnosis of the disease but also all potential treatment options. By identifying PD in its

early stages, providers can assist patients and their families in understanding this disease and living with it in the best manner possible.

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PD is the second most common neurodegenerative disease affecting older persons in the United States. The yearly incidence of idiopathic PD in the United States is approximately 10 to 20 cases per 100,000 persons older than 40 years.²⁴ Estimates of the prevalence of PD in this population range from 0.01% to 0.02%.²⁴ Some door-to-door studies have found substantially higher prevalence rates, suggesting that PD may be underreported.^{25,26} The prevalence of PD varies internationally, perhaps due to the racial composition of the populations surveyed. The highest rates are found among whites in Europe and North America, followed by Asians in China and Japan; prevalence is lowest among blacks in Africa. Some studies find a slightly higher prevalence in men. Typical age of onset is between 55 and 65 years; onset before age 40 (ie, young-onset PD) is decidedly unusual.

The medical literature contains few studies of the overall economic burden of PD. Estimates suggest that the annual cost of PD in the United States is between \$7.1 billion and \$24.5 billion (in 1998 dollars), including direct medical services, prescription drugs, and indirect costs such as lost productivity.^{1,27} To put this figure into context, in 1992 dementing illnesses were estimated to cost more than \$100 billion per year, the costs of stroke were estimated at \$17 billion, and the costs of epilepsy were estimated at \$600 million.²⁸

The high overall cost of disease associated with PD is due in part to the increased use of formal medical services by PD patients. A study based on data from the National Medical Expenditures Survey of 1987²⁹ found that total direct medical expenditures for PD patients were about twice as high as those for controls matched for age, rural-urban living, and comorbid medical conditions. Data from the 1991-1992 National Ambulatory Medical Care Survey³⁰ showed that PD was the third most common presenting diagnosis (after headache and seizures) at neurology outpatient visits. For patients older than 65 years, PD was the most common diagnosis, accounting for 16.9% of total neurology outpatient visits in this age group. In addition, PD is the second most common neurologic reason (after Alzheimer's disease) for home health care visits among patients older than 65 years, with an estimated 11,800 patients receiving such services annually in the United States.³¹ PD patients account for 2.2% to 6.8% of the US nursing home population.^{2,32}

Notwithstanding the high rate of medical services use among PD patients, most of the economic burden of the disease comes from indirect costs such as lost productivity and informal care provided by family members. In one study,²⁷ nearly two thirds of the annual cost of PD was attributed to lost productivity from the portion of the study sample younger than 65 years and a fraction of the patients between 65 and 74 years. Another study³³ found that costs from lost productivity and informal care provided by family caregivers were about 5 times greater than direct medical costs such as doctor visits, hospitalizations, and prescription drugs. These findings are consistent with the growing recognition that informal care provided by family caregivers contributes substantially to the economic burden in many chronic diseases.³⁴

It is important for physicians to be able to recognize the manifestations of PD and initiate appropriate treatment. Pharmacologic intervention has been shown to be effective in treating the symptoms of early PD. However, the recent approval of new dopamine agonists and the recognition that treatment choices may influence the likelihood of developing drug-induced side effects have increased the therapeutic complexity facing clinicians. This article discusses evaluation methods and an approach to treatment for patients presenting with PD in a primary care setting. Although patients with PD are frequently referred for specialty care following initial presentation, a number of symptoms in early PD can be managed by primary care physicians.

CASE STUDY

Initial Presentation

A 60-year-old man accompanied by his wife presents to his primary care physician with a chief complaint of tremor of his right hand.

History

The patient is not certain when the tremor began but believes that it has been present for at least the past 3 months and may have become slightly more prominent over this time. The tremor is most noticeable when the hand is resting or has been in a fixed posture for a period of time, such as when the patient holds a newspaper. The tremor goes away when the patient initiates an action with his right hand, such as when eating or writing. The patient states that the tremor does not limit his activity, but he feels it is noticeable and a minor nuisance. The patient's wife has noticed that her husband's right arm does not swing at his side when he walks.

The patient is right-handed. He takes no medications and has not been exposed to neuroleptic medica-

tions. He has no significant past medical history and denies any family history of tremor or other neurologic condition. He does not smoke and drinks 1 glass of wine per day. He is employed as a high school science teacher and is an avid gardener.

Physical Examination

Physical examination reveals a healthy-appearing man in no distress. Vital signs include a blood pressure of 120/80 mm Hg and a pulse of 80 bpm. There is mild seborrhea at the hairline and around the chin. The remainder of the general examination is unremarkable.

On neurologic examination, the patient is alert and oriented. Cognitive function is normal. Cranial nerve examination shows slight facial masking. Motor examination demonstrates slightly increased muscle tone in the right arm with "cogwheel" rigidity. A 3- to 5-Hz resting tremor is present intermittently in the right arm. In the hand, this tremor has the appearance of "pill-rolling," with the thumb moving in a circular motion across the first 3 fingers. The patient's movements are slightly slow when he is asked to tap his thumb and forefinger together or open and close his hand. Motor examination of the left arm and lower extremities is normal. Reflexes are normal, with flexor plantar responses. When the patient walks, there is decreased arm swing on his right side and occasional pill-rolling movements of the right hand.

QUESTIONS

- **What are the clinical features of PD?**
- **How is PD distinguished from other forms of parkinsonism?**
- **What are the risk factors for PD?**

CLINICAL FEATURES

The case patient's history and examination are typical of idiopathic PD. He has the 3 cardinal features of PD—tremor, muscle rigidity, and bradykinesia—as well as facial masking. Tremor is the most characteristic and obvious sign of PD. Typically it is a resting tremor that is more prominent when the patient is sitting and relaxed. In their landmark study, Hoehn and Yahr³⁵ found that about 70% of patients with PD had resting tremor at the time of presentation. Rigidity is defined as resistance to passive movement that occurs in both flexors and extensors throughout the range of movement. Rigidity in PD often has a "cogwheel" quality, which may be perceived as an oscillation between free movement and resistance when moving the limb of a PD patient through a passive range of motion. Bradykinesia (hypokinesia or akinesia in severe cases) refers to the lack of normal spontaneous

Table 1. Clinical Features of Parkinson's Disease

Motor

3- to 5-Hz resting tremor
 Cogwheel rigidity
 Bradykinesia
 Facial masking
 Impaired postural reflexes
 Micrographia (small handwriting)
 Cramping
 Dystonia
 Flexed posture
 Hypophonia

Cognitive

Depression
 Anxiety
 Dementia
 Hallucinations (drug-induced)
 Sleep disturbance

Autonomic

Orthostatic hypotension
 Constipation
 Urinary bladder dysfunction (eg, urgency, frequency, incontinence)

Other

Sialorrhea
 Seborrhea
 Paresthesias

movement. This feature disrupts the patient's ability to initiate and execute movements and perform complex motor tasks. Other motor features frequently observed in PD are listed in **Table 1**.

Tremor is probably the least disabling of the cardinal manifestations. It often can be completely eliminated with little change in overall patient disability.³⁶ Bradykinesia and rigidity are the most disabling symptoms of PD during the initial phases of disease. They are responsible for difficulty with tasks such as fastening buttons and cutting food and for the decreased size of handwriting (micrographia). Balance disturbance is the most disabling feature of parkinsonism, but it does not occur until well into the course of disease.

DIFFERENTIAL DIAGNOSIS

Idiopathic PD is the most common cause of parkinsonism, accounting for approximately 75% of cases presenting to neurologists.³⁷ Other causes of parkin-

Table 2. Differential Diagnosis of Parkinson's Disease

Neurodegenerative diseases with parkinsonian features

Parkinson's disease
 Progressive supranuclear palsy (PSP)
 Multiple systems atrophy (MSA)
 Shy-Drager syndrome
 Striatonigral degeneration
 Olivopontocerebellar atrophy
 Alzheimer's disease
 Diffuse Lewy body disease
 Corticobasal degeneration

Essential tremor

Hereditary diseases causing parkinsonism in younger patients

Wilson's disease
 Huntington's disease

Other causes of parkinsonism or parkinsonian features

Drug-induced parkinsonism
 Toxin-induced parkinsonism
 Vascular parkinsonism
 Hydrocephalus
 Post-traumatic parkinsonism

sonian signs include other neurodegenerative disorders, intoxication with heavy metals, treatment with therapeutic drugs (especially neuroleptic medications), and chronic cerebrovascular disease (**Table 2**). Neurodegenerative disorders that cause parkinsonism include progressive supranuclear palsy (PSP) and multiple systems atrophy (MSA); they are thought to be less common than PD. However, a recent population-based study from Olmstead County, Minnesota, found that the incidence of PSP and MSA was only slightly lower than that of PD.³⁸

The definitive diagnosis of PD is based on characteristic neuropathologic findings of Lewy bodies and neuronal loss in the substantia nigra and other brainstem nuclei. The few autopsy-based series have suggested that neurologists using clinical criteria make an accurate diagnosis in only 65% to 75% of cases of early PD.^{39,40} The presence of certain clinical features increases the likelihood of PD. These features are asymmetric symptoms, presence of resting tremor, and unequivocal response to dopaminergic medications. When all 3 signs are present, the likelihood of PD is

greater than 90%. However, these signs may be absent in many cases of true PD, resulting in a high false-negative rate for this set of criteria. Sensitivity and specificity have been estimated for different sets of clinical criteria (Table 3).

Currently, no established diagnostic tests are available to support the diagnosis of PD, but these may become available in the near future. Positron emission tomography (PET) scanning using the tracer [¹⁸F]fluorodopa has been shown to detect abnormalities in patients with PD in the very early stages of disease.⁴¹ The drawbacks of PET are its high cost and limited availability, with only a few academic medical centers having access to this modality. Recently, single-photon emission computed tomography (SPECT) using dopaminergic tracers has been used to image the brain.^{42,43} Because it is more widely available than PET, this imaging modality has the potential to become a useful diagnostic test in routine clinical practice.

RISK FACTORS

A number of potential risk factors for PD have been suggested, including farming, rural residence, and herbicide and pesticide exposure.⁴⁴ Although acute high-level exposure to certain heavy metals and herbicides may produce parkinsonism, chronic low-level exposure to these toxins has not been clearly associated with parkinsonism in methodologically rigorous epidemiologic studies.⁴⁵ Thus, the association between the case patient's avocation as a gardener and his condition is questionable. Curiously, one of the strongest epidemiologic associations is with cigarette smoking. A number of studies have suggested that smoking may reduce the risk of PD, even after controlling for confounding factors.⁴⁶

Although the vast majority of PD cases occur sporadically, the role of genetics in the pathogenesis of PD is increasingly being recognized. An autosomal dominant pattern of inheritance has been identified in families with members who have PD.⁴⁷ More recently, a mutation in the α -synuclein gene on chromosome 4 was identified in one such family.⁴⁸ However, this mutation has not been found in a number of other families with autosomal dominant inheritance⁴⁵ or in cases of sporadic or young-onset PD.^{49,50} Twins studies using strictly clinical criteria have not demonstrated a higher concordance of clinical parkinsonism in monozygotic twins compared with dizygotic twins.⁴⁵ Studies using PET imaging, however, have demonstrated a high concordance of dopaminergic abnormalities in asymptomatic twins of patients with PD. These studies suggest that genetics has a role in the etiology of PD, probably as one factor interacting among other factors.

Table 3. Sensitivity and Specificity of Diagnostic Criteria for Parkinson's Disease

Criteria	Sensitivity (%)	Specificity (%)
Two of bradykinesia, rigidity, or rest tremor	99	8
Bradykinesia with either rigidity or tremor	82	33
Levodopa responsiveness	79	33
Rest tremor present	76	50
Parkinsonism and asymmetrical symptoms	75	75
Bradykinesia, rigidity, and rest tremor (all 3)	65	71

Adapted from Brooks DJ. The early diagnosis of Parkinson's disease. *Ann Neurol* 1998;44(3 Suppl 1):S11.

CASE STUDY: DIAGNOSIS AND FOLLOW-UP

The primary care physician makes a diagnosis of early PD based on the presence of the 3 cardinal features of PD and facial masking. Because the patient's symptoms are mild and are not causing functional impairment, the primary care physician decides against medical treatment at this point.

The patient returns in 6 months for a follow-up visit. His symptoms have progressed since the initial evaluation: he now has a slightly more noticeable tremor and more stiffness in his right arm. He reports that he is having difficulty with handwriting and gardening as a result of his symptoms. He still does not have symptoms on his left side or difficulty with balance or walking.

QUESTIONS

- What are therapeutic options for treatment of early PD?
- What treatment is indicated for this patient?

MEDICAL THERAPY FOR EARLY PD

An increasing number of therapeutic agents are available for the patient with early PD. Neuroprotection, or therapy that slows or arrests the underlying neurodegeneration, has long been the goal in PD, but all current treatments are symptomatic. Therefore, no single approach is correct for all patients; rather, clinicians must make treatment decisions based on the symptoms and degree of functional disability of the individual patient.

Two catechol *O*-methyltransferase inhibitors (tocapone and entacapone) were recently approved for use in PD; however, these are most often used in advanced disease and will not be discussed in this review.⁵¹

THERAPEUTIC AGENTS

Anticholinergics

Anticholinergic medications such as benztropine and trihexyphenidyl have been available for the treatment of PD for more than 100 years. Several studies have demonstrated that anticholinergic medications have an effect on parkinsonian tremor similar to that of levodopa.^{52,53} However, the same studies failed to show any effect of anticholinergic medications on the other more disabling features of early PD. In addition, anticholinergic medications may cause side effects such as drowsiness and confusion, particularly in patients with mild cognitive impairments.⁵⁴ Therefore, the most appropriate use of anticholinergic medications in early PD is for cognitively normal patients whose primary symptom is tremor and who otherwise have mild parkinsonism.

Amantadine

In the late 1960s, amantadine was observed to improve parkinsonian symptoms in patients who were taking the medication as prophylaxis against influenza.⁵⁵ Since then, a large number of clinical trials of varying methodologies⁵⁶ have been conducted to test the anti-parkinsonian effect of amantadine. Some authors have called attention to the transient benefit of amantadine, indicating that patients may develop tachyphylaxis to this medication after 6 to 12 months.⁵⁷ However, a recent review has challenged this contention.⁵⁸

Selegiline

Selegiline is an irreversible inhibitor of monoamine oxidase (MAO)-B.⁵⁹ In standard clinical doses (5 to 10 mg/day), selegiline is a selective MAO-B inhibitor and thus does not cause the hypertensive “cheese effect” associated with nonselective MAO inhibition. Selegiline retains its selectivity for MAO-B at doses commonly employed in clinical practice (less than 20 mg/day).⁶⁰ Originally introduced as adjunctive therapy for PD, selegiline is used in early PD because it has a mild effect on parkinsonian symptoms and because it may have a weak neuroprotective effect.

A great deal of controversy continues to surround the question of whether selegiline has neuroprotective properties. Two large prospective monotherapy studies^{61,62} attempting to assess selegiline’s neuroprotective effect found a large apparent reduction in progression of disability in the selegiline-treated patients. However, in retrospect, it is unclear whether this effect was due to the symptomatic benefits of selegiline or true neuroprotective effects. A third study with a design intended to reduce the impact of symptomatic effects⁶³ did find a small protective effect of selegiline. In con-

trast, a study in the United Kingdom⁶⁴ found that patients treated with selegiline as adjunctive therapy to levodopa had a 60% increase in mortality in comparison with those receiving levodopa alone. This study has been criticized on methodological grounds.⁶⁵ Nonetheless, the potential concern about increased mortality and the belief that the protective effects of selegiline are modest at best have reduced the role of selegiline in early PD.

Antioxidant Vitamins

A number of antioxidants have been tested as neuroprotective therapy for PD. Among these, the most well-tested are vitamin E (α -tocopherol), vitamin C (ascorbic acid), and coenzyme Q₁₀. Vitamin E has been shown to have neuroprotective effects in several experimental systems⁶⁶ but not in epidemiologic studies.^{67,68} Moreover, the effect of vitamin E at a dose of 2000 IU per day was evaluated in the Deprenyl and Tocopherol Antioxidative Therapy of Parkinsonism (DATATOP) trial. After a mean treatment period of 14 months, no effect was observed in patients receiving vitamin E compared with placebo.⁶⁹ This adequately powered, negative trial suggests that vitamin E is not a potent neuroprotective agent.

As with vitamin E, several epidemiologic studies have failed to find a relationship between intake of vitamin C and the risk for PD.^{68,70} Conversely, in an unrandomized, open-label trial the need to introduce levodopa therapy was delayed by up to 2.5 years in patients treated with high-dose combination therapy with vitamins C and E compared with concurrent controls not treated with antioxidants.⁷¹ This result has not been confirmed in a randomized, placebo-controlled trial. Based on current evidence, the neuroprotective effects of vitamin C, like those of vitamin E, are probably quite modest at best.

Coenzyme Q₁₀ acts as an electron acceptor in complex I and complex II in mitochondria.⁷² Brain levels of coenzyme Q₁₀ decline with age and are about 50% greater in young adults compared with the elderly^{73,74}; they have been shown to be even lower in PD patients compared with age-matched controls.^{75,76} In a pilot study, patients treated with coenzyme Q₁₀ showed normalization of mitochondrial complex I activity.⁷⁷ These results provide a rationale for treating PD patients with this compound, but larger clinical trials are needed to definitively demonstrate its neuroprotective effects.

Dopaminergic Therapy

Dopamine agonists and particularly carbidopa/levodopa are the most effective treatment for PD.

However, therapy with dopamine agonists or carbidopa/levodopa is usually reserved until the patient begins to experience functional disability. Functional disability may be defined as interference with the patient's ability to perform adequately in his or her role at work, at home, or in hobbies or leisure activities. Clearly, this is a highly subjective determination that depends on the patient's level of activity and perception of his or her disability.

Levodopa. The role of carbidopa/levodopa in the management of early PD is controversial. Levodopa appears to provide the most effective relief of symptoms but may result in complications such as dyskinesia and motor fluctuations that limit the long-term benefits of therapy. Levodopa-induced dyskinesias are involuntary movements that usually are either choreo-athetoid or dystonic in nature but may include facial grimacing, head turning, and ballistic movements. Although the pathophysiologic mechanisms underlying drug-induced dyskinesia remain unknown, they generally are considered to result from chronic therapy with levodopa.⁷⁸⁻⁸⁰ Motor fluctuations are a more disabling complication than dyskinesias for most patients. Such fluctuations may begin with predictable "wearing off" at the end of each dose and progress to unpredictable changes in magnitude of motor response to a dose of levodopa (known as "on-off" phenomenon or "yo-yoing"). As a result of wearing off and on-off fluctuations, patients with advanced PD may spend as much as 50% of the waking day with an unsatisfactory motor response.⁸¹

The emergence of motor complications, including dyskinesia and on-off motor fluctuations, is one of the markers of the transition from early to moderate PD. Although a smooth and uncomplicated response is the rule when treatment with levodopa is initiated, this pattern does not last for most patients. After 5 years, dyskinesias develop in 68% of treated patients, and clinically significant motor fluctuations appear in 50%.⁸² As many as 75% of patients develop one of these complications, and most have both.⁸³

An additional concern regarding levodopa therapy is that exposure to this drug may be toxic to dopaminergic neurons.⁸¹ Simple experimental systems have provided evidence for levodopa toxicity, but the evidence in more complex in vitro systems and in experimental animals is limited.⁸⁴

Carbidopa/levodopa is available in immediate-release (IR) and controlled-release (CR) formulations. In the CR formulation, the active components are embedded in a slow-eroding matrix. There are several pharmacokinetic differences between the 2 prepara-

tions. The IR formulation achieves peak plasma concentration sooner, has a significantly higher peak, and has greater bioavailability. The CR preparation has a slightly longer plasma half-life⁸⁵ and thus may be dosed less frequently, particularly in patients with advanced disease.⁸⁶ In a large randomized controlled trial comparing CR with IR carbidopa/levodopa, the 2 formulations were comparable in most regards. However, there was a small but statistically significant difference favoring the CR preparation in improving a patient's ability to complete activities of daily living (ADLs).⁸⁷

Dopamine agonists. The dopamine agonists available in the United States are pramipexole, ropinirole, bromocriptine, and pergolide. Clinical evidence suggests that patients treated with dopamine agonists in early disease develop motor complications, particularly dyskinesias, less frequently than patients treated with levodopa. In an unblinded study, Montastruc⁸⁸ randomized 60 patients to either bromocriptine with levodopa added if needed or levodopa alone. The patients treated with levodopa alone developed both motor fluctuations and dyskinesias at a significantly higher rate than those treated with bromocriptine. These results have since been confirmed by a 5-year blinded, randomized controlled trial in which patients were treated with either the dopamine agonist ropinirole with levodopa added as needed or with levodopa alone. The latter group developed dyskinesias about twice as often as patients treated with the dopamine agonist.⁸⁹ No significant differences in the development of motor fluctuations were found between the 2 groups.

The dopamine agonists may be divided into 2 classes: ergot-derived and non-ergot-derived. Bromocriptine and pergolide are derived from ergot precursors and have primary affinity for the D2 dopamine receptor. Pergolide also has affinity for the D1 receptor,⁵⁸ but the implications of this additional affinity are not well understood. Pramipexole and ropinirole are non-ergot agonists and have affinity for the limbic D3 receptor as well as D2. The hypothesis that the non-ergot agonists may act as antidepressants as well as antiparkinsonian drugs because of their D3 activity may soon be tested in a clinical trial. Several studies comparing the dopamine agonists with one another have shown that they are relatively similar in efficacy.⁵⁸ In a study comparing pramipexole and bromocriptine with placebo, both drugs were significantly better than placebo, but the 2 agonists were not significantly different in terms of their effect on patients' parkinsonian symptoms.⁹⁰ Another study of 335 patients comparing ropinirole with bromocriptine found advantages to

Table 4. Costs of Drug Regimens for Parkinson's Disease

Agent	Dose	Cost*
Levodopa preparations		
Carbidopa/levodopa	25 mg/100 mg	27.54
Sinemet	25 mg/100 mg	74.00
Sinemet CR	50 mg/200 mg	158.00
Dopamine agonists		
Bromocriptine	2.5 mg	168.00
Pergolide (Permax)	0.25 mg	120.00
	1 mg	370.00
Pramipexole (Mirapex)	1 mg	164.00
Ropinirole (Requip)	5 mg	177.00
Anticholinergics		
Trihexyphenadyl	2 mg	15.39
Benzotropine	0.5 mg	7.00
Amantadine	100 mg	16.88

*Average wholesale price of 100 tablets in 1998 dollars.

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ropinirole in some outcome measures, but the differences were generally small.⁹¹

TREATMENT SELECTION

Both levodopa and dopamine agonists produce adequate relief of symptoms for patients with early PD and limited disability. In a direct comparison of ropinirole and levodopa, the percentage of patients with mild symptoms who experienced definite clinical improvement was similar for both groups.⁹² Likewise, similar and generally tolerable side effects were reported for both groups. However, patients with more advanced symptoms had greater benefit from carbidopa/levodopa than from ropinirole in this study. Thus, most clinicians prescribe a dopamine agonist for patients who require dopaminergic therapy but who still have relatively mild symptoms, such as the case patient. Patients with more severe symptoms will probably require levodopa therapy. Some experts advocate continuing dopamine agonist therapy for patients who require levodopa,⁹³ with the rationale that dopamine agonists, even in combination with carbidopa/levodopa, may reduce the risk of motor complications.

CASE STUDY: INITIATION OF THERAPY

Because the patient's symptoms have begun to limit

him functionally, the physician prescribes a dopamine agonist. The physician describes the potential side effects of this therapy. A follow-up visit is scheduled for 3 months.

QUESTIONS

- What treatment side effects may be expected?
- What are the costs of dopaminergic therapy?

TOLERABILITY OF DOPAMINERGIC AGENTS

In general, levodopa and dopamine agonists are well tolerated in patients with early PD. The most common side effects for these medications are anorexia and nausea, sleep disturbance, dyskinesia, peripheral edema, and dizziness.⁹⁴⁻⁹⁶ Carbidopa/levodopa and particularly dopamine agonists are often prescribed at low doses initially and gradually titrated to effective doses to avoid these side effects. Rare cases of extreme somnolence have recently been reported for patients receiving the newer dopamine agonists pramipexole and ropinirole.⁹⁷ It is too early to know if this will emerge as a more pervasive problem for these medications.

COSTS OF THERAPY

Prescription drug treatment is a major component of the direct medical costs for PD patients. The new and established dopamine agonists have similar costs (Table 4). Although cost depends on the quantity of drug needed, a year of treatment with one of these drugs is likely to cost approximately \$2000, based on average wholesale prices.⁹⁸ Brand-name Sinemet preparations would probably be similar in cost as well. The yearly cost of carbidopa/levodopa therapy is \$600, based on 6 tablets per day. Anticholinergic medications are the least expensive antiparkinsonian drugs, but they are used less often due to their side-effect profile and limited effectiveness.

The only published study to evaluate the cost-effectiveness of antiparkinsonian interventions assessed the use of pramipexole in both early and late PD.⁹⁹ For both early- and late-stage patients, the pramipexole strategy was more costly and more effective than the baseline levodopa strategy. For early PD patients, the estimated cost-effectiveness ratio for the pramipexole strategy was \$8837 (in 1997 dollars) per quality-adjusted life-year (QALY) compared with the baseline treatment with levodopa alone. For advanced PD patients, the cost for each additional QALY is \$12,294. The ratios were sensitive to many of the input variables in the model. For example, the cost-effectiveness of pramipexole becomes more attractive (more effects for less cost) if one assumes the agent has a neuroprotective

effect, measured as a slower rate of change over time in Unified Parkinson's Disease Rating Scale (UPDRS) scores. When the annual rate of UPDRS change in the pramipexole group was reduced to 2 units or less, the pramipexole strategy actually becomes more cost-effective than levodopa therapy.

CASE STUDY: TREATMENT FOLLOW-UP

When the patient and his wife return for follow-up, the patient reports that he initially experienced some nausea after starting the medication, but this symptom has subsided. He feels that he has no limitations in his activities of daily living; however, the patient and his wife state that he has been somewhat depressed for the past several months. They had not mentioned this at their previous visits because they thought that the symptoms of depression were due to motor slowing. Examination shows improvements in all cardinal features of PD, particularly bradykinesia.

QUESTION

- **What are the nonmotor symptoms of PD?**

NONMOTOR SYMPTOMS OF PD

Patients with PD may have a wide range of nonmotor symptoms, including psychiatric symptoms (depression and apathy), sensory symptoms (paresthesias), and manifestations of autonomic dysfunction (Table 1). Skin changes such as seborrheic dermatitis may be present on the face and scalp. Olfactory dysfunction is frequently present at the onset of symptoms and may be unappreciated by the patient.¹⁰⁰

Depression is the most common neuropsychiatric disturbance in PD and may occur at any stage of disease. The mean reported frequency of depression in PD is 40%, and estimates range from 7% to 70%.¹⁰¹ Because depression in PD may be difficult to distinguish from akinesia and facial masking, it is important for physicians to screen carefully for this potentially treatable nonmotor symptom. In PD patients, depression may have a slightly different profile than typical idiopathic depression. Patients with PD have dysphoria and pessimism along with irritability, sadness, and suicidal ideation. Guilt, self-blame, and feelings of failure are less common.¹⁰² Dopaminergic therapy has little effect on depression symptoms, and there have been few large well-controlled trials of antidepressant medications in PD patients. Tricyclic antidepressants have been shown to be effective in randomized controlled trials of parkinsonian patients.¹⁰³ Selective serotonin reuptake inhibitors (SSRIs) have not been tested in a randomized controlled trial in parkinsonian patients

but are widely used. There has been some concern about possible serotonergic reactions when SSRIs and selegiline are used together; however, such reactions are probably very rare.¹⁰⁴

CASE STUDY: NINE MONTHS LATER

At a follow-up visit 9 months later, the patient reports that his depression has improved following treatment with an antidepressant. He has done well on dopamine agonist therapy but reports that 1 to 2 months ago he noticed that his symptoms were beginning to cause disability in spite of treatment. Although he has not fallen, the patient has noticed some impairment of balance. He has also become aware of tremor affecting his left arm as well as his right. The physician thinks that the patient may benefit from physical or occupational therapy and explains the benefits of therapy to the patient.

QUESTIONS

- **What is the nature of progression of PD over time?**
- **What is the role of physical and occupational therapy in the care of PD patients?**

PROGRESSION OF PD

As discussed earlier, many patients may be maintained on dopamine agonist monotherapy for extended periods of time. At the point where functional disability is present, levodopa may be added. In one study, only 11% of patients needed additional levodopa after 6 months.⁹⁰ In a long-term study of PD patients treated with dopamine agonists,⁹¹ the percentage of patients needing additional levodopa due to increasing parkinsonian disability over time was 15% at 1 year, 27% at 2 years, and 40% at 3 years. These figures may be lower than those encountered in practice because of patient selection and because they do not include study drop-outs.

The progression of PD from early stage with minimal disability to more advanced stages is quite heterogeneous. This heterogeneity has been documented clinically and with functional imaging.¹⁰⁵ Symptoms almost always become bilateral over time, generally within the first 3 years of disease,³⁵ but some degree of asymmetry is usually maintained throughout the course of disease. In early PD, symptom severity as rated by standard clinical scales increases by about 4% per year.^{69,106} This figure is quite consistent with data from [¹⁸F]fluorodopa PET imaging that suggests that the rate of dopaminergic cell loss is about 7% per year.¹⁰⁷ Studies from the era before the introduction of levodopa therapy suggested that disabling disturbances of gait and balance began about 10 to 15 years after initial symptoms.³⁵ More

recent studies suggest that the development of severe gait disturbance may be delayed by therapy.¹⁰⁸

PHYSICAL AND OCCUPATIONAL THERAPY IN PD

Although physical and occupational therapy are widely prescribed for PD patients, surprisingly little attention has been paid to their impact in the medical literature. The report by Comella and colleagues¹⁰⁹ is the only randomized controlled trial of physical therapy; other studies have been observational.

The role of physical and occupational therapy is to maintain the maximum level of functional mobility and capacity to perform ADLs. Early therapeutic intervention cannot reverse the course of PD, but it can delay potential deformity and functional decline. Therapy uses exercise, adaptive equipment, and safety education to enhance quality of life (QOL) for patients and their families. A comprehensive physical or occupational therapy evaluation probes many domains that may be overlooked by a busy physician and may identify areas where the patient's capacity to perform adequately is limited by disability. In addition, therapy sessions provide an opportunity to educate patients and caregivers on a range of topics, from energy conservation and work simplification methods that make completing daily tasks easier to home and work safety. This education may lead to modifications such as installing handrails on the stairs and in the bathroom, removing throw rugs and securely tacking down corners of area rugs, placing a night light in hallways and the bathroom, avoiding backless slippers and poor-fitting footwear, and removing clutter from frequently traveled paths.

Physical therapy for PD patients addresses the functional limitations caused by rigidity and bradykinesia; it may include an exercise program that focuses on maintaining flexibility, balance, and strength. Breathing exercises may help patients who are kyphotic. Exercises that may help to decrease facial rigidity include smiling, frowning and puffing the cheeks, twisting the mouth, pouting, enunciating consonants, and curling, pointing, and grooving the tongue.¹¹⁰ Stretching, passive range-of-motion exercises, and active exercises such as those from the Axial Mobility Exercise Program by Schenkman¹¹¹ for the anterior neck, shoulder, and upper trunk musculature may reduce PD patients' tendency toward forward head posturing and cervical/upper thoracic kyphosis and may decrease the potential for contractures and tendon shortening.

Patients with postural instability, short strides, or hesitancy with turning may benefit from gait training. Gait training may include such measures as an "obstacle

course" in which the patient is challenged to step over and around objects of different heights and to perform simultaneous tasks. If the patient does not improve or regresses due to the progression of the disease, it may be necessary to teach gait training with an assistive device such as a cane or rolling walker. Through these procedures (and if necessary through the use of an assistive device), the patient gains confidence in his or her ability to safely ambulate on different surfaces and in varying situations. Comella and colleagues¹⁰⁹ found that patients with PD improved their overall functional level following 4 weeks of physical therapy; however, when active therapy was terminated and physical activity at home was decreased or ceased, the improvements regressed to baseline within 6 months. Therefore, a maintenance program may be necessary to maintain the functional gains achieved through therapy.

Occupational therapy focuses on finding solutions to difficulties patients encounter performing ADLs. Patients should try to complete their ADLs independently when time is not an issue, and extra time should be set aside if needed. Assistance from a caregiver or through the use of adaptive equipment should be provided only when a patient is unable to complete ADLs independently or when the tasks become very fatiguing or frustrating. An occupational therapist can evaluate the situation and educate both the patient and caregiver on the level of assistance or type of equipment that needs to be provided. Often, elastic shoelaces, reachers, long-handled sponges, long-handled shoe horns, sock aids, grab bars, raised toilet seats with rails, tub benches, weighted build-ups for utensils and writing instruments, and velcro fasteners can improve a patient's independence with ADLs.

QUESTION

- **How is quality of life measured in PD?**

QUALITY OF LIFE IN PD

The measurement of QOL is emerging as an important part of the evaluation of PD patients and an endpoint for trials of antiparkinsonian interventions. Although no definition of QOL has gained universal acceptance, from a pragmatic point of view QOL refers to the patient's perception and self-evaluation of the effects of an illness on his or her life. QOL may be conceptualized as having several domains, including physical status and functional ability, psychosocial status, social interaction, economic and vocational status, and religious or spiritual status. Because of the combination of motor and nonmotor symptoms, PD may impact on many of these domains.

Instruments to measure QOL may be generic, measuring impairments that are common to all states of impaired health, or they may be disease specific. Although disease-specific instruments may be more sensitive to changes in disease status, they do not permit comparisons between the state of health of a patient with PD and patients with other medical conditions. Several disease-specific QOL instruments for PD have been developed, with the Parkinson's Disease Questionnaire-39 (PDQ-39)¹¹² probably being the most widely used. The dimensions of health measured in the PDQ-39 are mobility, emotional well-being, stigma, social support, cognition, communication, and bodily discomfort. This instrument produces scores for each domain ranging from 0 to 100 where 0 indicates no problem and 100 represents the maximum level of a problem. The PDQ-39 correlates well with scores from the Medical Outcomes Study Short Form-36 (SF-36) and global impressions of patients and physicians. The Parkinson's Disease Quality of Life Questionnaire (PDQL),¹¹³ another disease-specific instrument, is divided into 4 domains: parkinsonian symptoms, systemic symptoms, emotional functioning, and social functioning. The PDQL has been shown to correlate with established generic QOL scales.

In several studies of aggressive interventions such as stereotactic surgery and dopaminergic cell transplantation, changes in generic QOL scales have been documented.^{114,115} In one study of adrenal cell transplantation, improvement and subsequent decline in QOL mirrored changes in symptom severity.¹¹⁴ Generic QOL instruments have also been employed in randomized controlled trials of medical interventions. However, in several cases changes in generic QOL instruments did not reach conventional levels of statistical significance, even though there were significant changes in symptom severity as measured by standard clinical rating scales.⁹⁰ Disease-specific QOL instruments may be more sensitive to change in clinical trials of medical interventions, but results using these relatively new instruments have not yet been reported.

SUMMARY

The evaluation and management of patients with symptoms of early PD is a challenge for primary care providers and neurologists. Diagnosis continues to be based primarily on clinical findings, but emerging tests such as SPECT imaging may improve the accuracy of early diagnosis. The treatment of early PD has become more complicated in recent years with the introduction of new dopamine agonists. Likewise, new evidence that treatment choices may influence the likelihood of

developing drug-induced side effects including dyskinesias and motor fluctuations has also influenced treatment selection for early PD. Understanding the roles of medical and nonmedical therapies can help clinicians improve outcomes for patients with PD. **HP**

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