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

Case Study and Commentary, Andrew Siderowf, MD, Heather J. Cianci, PT, GCS, and Tania R. Rorke, OTR/L

INSTRUCTIONS
The following case study, “An Evidence-Based Approach to Management of Early Parkinson’s Disease,” is accompanied by a continuing medical education (CME) evaluation that consists of 5 multiple-choice questions. After reading the case study, carefully consider each of the questions in the CME evaluation on page 75. Then, circle your selected answer to each question on the CME evaluation form on page 76. In order to receive CME credit, at least 3 of the 5 questions must be answered correctly. The estimated time for this CME activity is 1 hour.

OBJECTIVES
After participating in the CME activity, primary care physicians should be able to:
1. Understand the epidemiology and economic impact of Parkinson’s disease
2. Recognize the clinical features that differentiate idiopathic Parkinson’s disease from other parkinsonian syndromes
3. Know the treatment options for patients with early Parkinson’s disease
4. Recognize potential complications of antiparkinsonian therapy
5. Understand the role of physical and occupational therapy in the management of early Parkinson’s disease

INTRODUCTION
Parkinson’s disease (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 [1]. Estimates of the prevalence of PD in this population range from 0.01% to 0.02% [1]. Some door-to-door studies have found substantially higher prevalence rates, suggesting that PD may be underreported [2,3]. 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 [4,5]. 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 [6].

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 1987 [7] 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 Survey (NAMCS) [8] 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. 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 [9]. PD patients account for 2.2% to 6.8% of the U.S. nursing home population [10,11].

Notwithstanding the high rate of medical services use among PD patients, most of the economic burden of the
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CASE-BASED REVIEW

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.

• 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 Yahr [14] 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 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 [15]. 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 [16]. Other causes of parkinsonian 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 were only slightly lower than that of PD [17].

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 [18,19]. 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 [20]. 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 [21,22]. Because it is more widely available than PET, this imaging modality has the potential to become a useful diagnostic test in routine clinical practice.

**Table 1. Clinical Features of Parkinson’s Disease**

<table>
<thead>
<tr>
<th>Motor</th>
<th>Cognitive</th>
<th>Autonomic</th>
<th>Other</th>
</tr>
</thead>
<tbody>
<tr>
<td>3- to 5-Hz resting tremor</td>
<td>Depression</td>
<td>Orthostatic hypotension</td>
<td>Sialorrhea</td>
</tr>
<tr>
<td>Cogwheel rigidity</td>
<td>Anxiety</td>
<td>Constipation</td>
<td>Seborrhea</td>
</tr>
<tr>
<td>Bradykinesia</td>
<td>Dementia</td>
<td>Urinary bladder dysfunction (eg, urgency, frequency, incontinence)</td>
<td>Paresthesias</td>
</tr>
<tr>
<td>Facial masking</td>
<td>Hallucinations (drug-induced)</td>
<td></td>
<td></td>
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<tr>
<td>Impaired postural reflexes</td>
<td>Sleep disturbance</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Micrographia (small handwriting)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Cramping</td>
<td></td>
<td></td>
<td></td>
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<tr>
<td>Dystonia</td>
<td></td>
<td></td>
<td></td>
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<tr>
<td>Flexed posture</td>
<td></td>
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<tr>
<td>Hypophonia</td>
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</tbody>
</table>

**Table 2. Differential Diagnosis of Parkinson’s Disease**

<table>
<thead>
<tr>
<th>Neurodegenerative diseases with parkinsonian features</th>
<th>Hereditary diseases causing parkinsonism in younger patients</th>
</tr>
</thead>
<tbody>
<tr>
<td>Parkinson’s disease</td>
<td>Wilson’s disease</td>
</tr>
<tr>
<td>Progressive supranuclear palsy (PSP)</td>
<td>Huntington’s disease</td>
</tr>
<tr>
<td>Multiple systems atrophy (MSA)</td>
<td>Essential tremor</td>
</tr>
<tr>
<td>Shy–Drager syndrome</td>
<td>Drug-induced parkinsonism</td>
</tr>
<tr>
<td>Striatonigral degeneration</td>
<td>Toxin-induced parkinsonism</td>
</tr>
<tr>
<td>Olivopontocerebellar atrophy</td>
<td>Vascular parkinsonism</td>
</tr>
<tr>
<td>Parkinsonism</td>
<td>Hydrocephalus</td>
</tr>
<tr>
<td>Diffuse Lewy body disease</td>
<td>Post-traumatic parkinsonism</td>
</tr>
</tbody>
</table>

**Table 3. Differential Diagnosis of Parkinson’s Disease**

<table>
<thead>
<tr>
<th>Other causes of parkinsonism or parkinsonian features</th>
<th>Other causes of parkinsonism or parkinsonian features</th>
</tr>
</thead>
<tbody>
<tr>
<td>Drug-induced parkinsonism</td>
<td>Wilson’s disease</td>
</tr>
<tr>
<td>Toxin-induced parkinsonism</td>
<td>Huntington’s disease</td>
</tr>
<tr>
<td>Vascular parkinsonism</td>
<td>Essential tremor</td>
</tr>
<tr>
<td>Hydrocephalus</td>
<td>Drug-induced parkinsonism</td>
</tr>
<tr>
<td>Post-traumatic parkinsonism</td>
<td>Toxin-induced parkinsonism</td>
</tr>
</tbody>
</table>

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Risk Factors
A number of potential risk factors for PD have been suggested, including farming, rural residence, and herbicide and pesticide exposure [23]. 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 [24]. 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 [25].

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 [26]. More recently, a mutation in the α-synuclein gene on chromosome 4 was identified in one such family [27]. However, this mutation has not been found in a number of other families with autosomal dominant inheritance [24] or in cases of sporadic or young-onset PD [28,29]. Twins studies using strictly clinical criteria have not demonstrated a higher concordance of clinical parkinsonism in monozygotic twins compared with dizygotic twins [24]. 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.

Diagnosis and Follow-up
The PCP 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 PCP 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.

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 (tolcapone and entacapone) were recently approved for use in PD; however, these will not be discussed in this review [30].

Therapeutic Agents
Anticholinergics
Anticholinergic medications such as benztrapine 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 [31,32]. 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 [33]. 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 [34]. Since then, a large number of clinical trials of varying methodologies [35] have been conducted to test the antiparkinsonian 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 [36]. However, a recent review has challenged this contention [37].

Selegiline
Selegiline is an irreversible inhibitor of monoamine oxidase (MAO)-B [38]. 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 non-selective MAO inhibition. Selegiline retains its selectivity for MAO-B at doses commonly employed in clinical practice (less than 20 mg/day) [39]. 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 [40,41] 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 effects [42] did find a small protective effect of selegiline. In contrast, a study in the United Kingdom [43] 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 [44]. 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 systems [45] but not in epidemiologic studies [46,47]. Moreover, the effect of vitamin E at a dose of 2000 IU per day was evaluated in the DATATOP trial. After a mean treatment period of 14 months, no effect was observed in patients receiving vitamin E compared with placebo [48]. 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 [47,49]. 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 [50]. 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 [51]. Brain levels of coenzyme Q10 decline with age and are about 50% greater in young adults compared with the elderly [52,53]; they have been shown to be even lower in PD patients compared with age-matched controls [54,55]. In a pilot study, patients treated with coenzyme Q10 showed normalization of mitochondrial complex I activity [56]. 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 choreoathetoid 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 [57–59]. 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-yo-ing”). 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 [60].

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% [61]. As many as 75% of patients develop one of these complications, and most have both [62].

An additional concern regarding levodopa therapy is that exposure to this drug may be toxic to dopaminergic neurons [60]. Simple experimental systems have provided evidence for levodopa toxicity, but the evidence in more complex in vitro systems and in experimental animals is limited [63].

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 preparations. 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-life [64] and thus may be dosed less frequently, particularly in patients with advanced disease [65]. 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) [66].

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, Montastruc [67] 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 [68]. 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 [37], 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 [37]. 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 [69]. Another study of 335 patients comparing ropinirole with bromocriptine found advantages to ropinirole in some outcome measures, but the differences were generally small [70].

**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 [73–75]. 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 [76]. 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 [77]. 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.

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

<table>
<thead>
<tr>
<th>Agent</th>
<th>Dose</th>
<th>Cost*</th>
</tr>
</thead>
<tbody>
<tr>
<td>Levodopa preparations</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Carbidopa/levodopa</td>
<td>25 mg/100 mg</td>
<td>27.54</td>
</tr>
<tr>
<td>Sinemet</td>
<td>25 mg/100 mg</td>
<td>74.00</td>
</tr>
<tr>
<td>Sinemet CR</td>
<td>50 mg/200 mg</td>
<td>158.00</td>
</tr>
<tr>
<td>Dopamine agonists</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Bromocriptine</td>
<td>2.5 mg</td>
<td>168.00</td>
</tr>
<tr>
<td>Pergolide (Permax)</td>
<td>0.25 mg</td>
<td>120.00</td>
</tr>
<tr>
<td>Pramipexole (Mirapex)</td>
<td>1 mg</td>
<td>164.00</td>
</tr>
<tr>
<td>Ropinirole (Requip)</td>
<td>5 mg</td>
<td>177.00</td>
</tr>
<tr>
<td>Anticholinergics</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Trihexyphenidyl</td>
<td>2 mg</td>
<td>15.39</td>
</tr>
<tr>
<td>Benztropine</td>
<td>0.5 mg</td>
<td>7.00</td>
</tr>
<tr>
<td>Amantadine</td>
<td>100 mg</td>
<td>16.88</td>
</tr>
</tbody>
</table>


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.

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.

- 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 [79].

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% [80]. 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 [81]. 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 [82]. 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 [83].

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.

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 [69]. In a long-term study of PD patients treated with dopamine agonists [70], 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 [84]. Symptoms almost always become bilateral over time, generally within the first 3 years of disease [14], 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 [48,85]. 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 [86]. 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 [14]. More recent studies suggest that the development of severe gait disturbance may be delayed by therapy [87].

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 colleagues [88] 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 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. (See patient information sheet on page 71 for additional suggestions.)

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 [89]. Stretching, passive range-of-motion exercises, and active exercises such as those from the Axial Mobility Exercise Program by Schenkman [90] 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 colleagues [88] 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 activities of daily living 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.

• How is quality of life measured in PD?

Quality of Life in PD

The measurement of quality of life (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) [91] 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) [92], 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 [93,94]. In one study of adrenal cell transplantation, improvement and subsequent decline in QOL mirrored changes in symptom severity [93]. 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 [69]. 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.
Coping with Parkinson’s Disease at Home

Parkinson’s disease (PD) is a progressive neurologic disorder that disrupts a person’s control over body movement. The major symptoms of PD are tremor, slowness of movement (bradykinesia), and stiffness in the muscles (rigidity). These symptoms can cause secondary problems, including difficulty with balance, walking, or writing. Some symptoms will become worse over time. As they do, simple daily tasks will become more challenging. However, a number of strategies can help you accomplish your tasks and make your home life more safe and comfortable.

Throughout your home
• Remove all loose rugs; make sure all carpets are securely fastened down
• Keep rooms, hallways, and frequently traveled paths free of clutter
• Place a night light in hallways and the bathroom
• Make sure stairways are well lit and have handrails
• Maintain the temperature in the home a little above average to avoid the trouble of putting on extra clothing
• Wrap tape around pens, toothbrushes, and other devices to make them easier to grip
• Wear comfortable shoes with a low heel and leather soles to avoid tripping or slipping

In the kitchen
• Use long-handled mops, sponges, and dustpans to avoid stooping
• Keep frequently used items in easily accessible locations
• Use a long-handled reacher to retrieve items from high shelves
• Use an electric can opener and jar opener

In the bathroom
• Place nonskid strips on the tub or shower floor
• Use a hand-held shower head and shower stool
• Install grab bars in the tub/shower and next to the toilet
• Use a raised toilet seat and arm rails
• Adjust storage shelves to a convenient height

In the bedroom
• Elevate the head of your bed to make it easier for you to sit up and swing your legs out of bed
• Use a knotted rope tied to the foot of the bed to pull yourself into a sitting position
• Install a grab bar on the wall near your bed

Other coping strategies
• Practice tasks that you find especially difficult
• Give yourself extra time to complete your tasks
• Stay active. Daily activity and exercise will help you keep your joints flexible and muscles strong. Be sure to talk with your physician before beginning any exercise regimen.
• Contact a PD support group or association. These organizations offer support for persons with PD and their caregivers. They are also good sources for advice and educational materials on a range of topics, including diet, exercise, and coping skills.

Resources
• The American Parkinson’s Disease Association: www.apdaparkinson.com; (800) 223-2732
• National Parkinson Foundation, Inc.: www.parkinson.org; (800) 327-4545
• The Parkinson’s Disease Foundation: (800) 223-2732
• Parkinson’s Support Group of America: (301) 937-1545
• United Parkinson’s Foundation: (312) 733-1893


References


67. Montastruc JL, Rascol O, Senard JM, Rascol A. A randomized controlled study comparing bromocriptine to which levodopa was later added, with levodopa alone in previously untreated patients with Parkinson’s disease: a five year follow up. J Neurol Neurosurg Psychiatry 1994;57:1034–8.

68. Rascol O. Ropinirole reduces the risk of dyskinesia when
used in early PD. The 056 Study Group. Parkinsonism Related Disord 1999;5:83.
1. The 3 clinical features that most reliably differentiate idiopathic Parkinson’s disease from other parkinsonian syndromes are
   (A) Resting tremor, asymmetric symptoms, and good response to levodopa
   (B) Bradykinesia, resting tremor, and rigidity
   (C) Masked faces, bradykinesia, and rigidity
   (D) Postural instability, rigidity, and good response to levodopa

2. Which of the following is NOT a sign or symptom of Parkinson’s disease?
   (A) Seborrhea
   (B) Depression
   (C) Dry mouth
   (D) Micrographia

3. The largest contributor to the overall economic burden of Parkinson’s disease is
   (A) Prescription medications
   (B) Home health aids
   (C) Physician visits
   (D) Lost income of caregivers

4. Which of the following medications is NOT appropriate therapy for early Parkinson’s disease?
   (A) Carbidopa/levodopa
   (B) Catechol-O-methyltransferase (COMT) inhibitors
   (C) Dopamine agonists
   (D) Selegiline

5. A therapeutic strategy that avoids early use of carbidopa/levodopa may delay the emergence of which of the following symptoms?
   (A) Dyskinesias
   (B) Orthostatic hypotension
   (C) Hallucinations
   (D) Postural instability
To receive CME credit for this case study, read the case study and then answer the multiple-choice questions on page 75. Circle your answers below. Also, please respond to the four questions that follow. Then, detach the evaluation form and mail or FAX to:

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2. A B C D
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   ❑ excellent ❑ good ❑ fair ❑ poor
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4. Name three clinical topics you would like explored in future JCOM® case studies:
   Topic 1: ____________________________________________
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