CLINICAL PRACTICE

Diagnosis and Initial Management of Parkinson's Disease

John G. Nutt, M.D., and G. Frederick Wooten, M.D.

This Journal *feature begins with a case vignette highlighting a common clinical problem. Evidence supporting various strategies is then presented, followed by a review of formal guidelines, when they exist. The article ends with the authors' clinical recommendations.*

A 62-year-old man presents with an intermittent tremor in his left hand and some vague discomfort in the left arm. Physical examination shows a minimal rest tremor in the left hand that disappears with use of the limb, mild rigidity at the left wrist and elbow, slowness of finger tapping with the left hand, and decreased arm swing on the left while walking. How should he be evaluated and treated?

THE CLINICAL PROBLEM

Parkinsonism, the syndrome, is a common movement disorder, and Parkinson's disease, the most common cause of parkinsonism, is the second most prevalent neurodegenerative disease after Alzheimer's disease. Parkinson's disease is estimated to afflict about 1 million Americans, or about 1 percent of the population over 60 years of age.[1,2] As the U.S. population ages, this number is likely to double in the next 15 to 20 years.[3] The disease is uncommon before the age of 40; both the prevalence and the incidence increase steadily thereafter.[3,4] The incidence is higher among men than among women.[5] All races and ethnic groups are affected.[2] Although therapy can ameliorate the symptoms of Parkinson's disease and improve both the quality of life and life expectancy, Parkinson's disease continues to be associated with progressive disability and increased mortality.[6,7]

Parkinson's disease is caused by the disruption of dopaminergic neurotransmission in the basal ganglia. On pathological examination, the dopaminergic neurons in the substantia nigra are markedly reduced, and Lewy bodies (cytoplasmic inclusions) are present in the residual dopaminergic neurons.

More than 10 autosomal dominant and recessive genes or gene loci have been linked to Parkinson's disease, but mutation in a single gene is an uncommon cause.[8] Nevertheless, 10 to 15 percent of people with Parkinson's disease will have an affected first-degree or second-degree relative.[9] No clear environmental determinants of Parkinson's disease have been identified.[2]

STRATEGIES AND EVIDENCE

DIAGNOSIS

The diagnosis of Parkinson's disease is based on the presence of the core features of slowness and paucity of movement (bradykinesia and akinesia) and tremor when the limb is at rest or resistance to passive movement of the joints (rigidity), or both.[10,11] Postural abnormalities are often included in the definition but generally occur later in the course of the disorder and are nonspecific, making them of little clinical usefulness in early disease.[11] There are four common presentations of Parkinson's disease: tremor,

From the Department of Neurology, Oregon Health and Science University, Portland (J.G.N.); and the Department of Neurology, University of Virginia, Charlottesville (G.F.W.). Address reprint requests to Dr. Nutt at the Department of Neurology, Oregon Health and Science University, 3181 S.W. Sam Jackson Park Rd., Portland, OR 97239, or at nuttj@ohsu.edu.

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a weak and clumsy limb, a stiff and aching limb, and a gait disorder (Table 1).

The classic tremor of Parkinson's disease is a resting tremor in a limb, most commonly one hand, that disappears with voluntary movement. It frequently emerges in a hand while the person is walking. (A video clip can be viewed in the Supplementary Appendix, available with the full text of this article at www.nejm.org.) Rest tremor is virtually pathognomonic of Parkinson's disease. However, the diagnosis may be complicated by nonclassic findings, such as tremor when the person is holding the arms out or using the hands in voluntary movement or the absence of a tremor (about 20 percent of cases).[12]

Essential tremor is the entity that is most commonly confused with early Parkinson's disease.[13] Patients with essential tremor frequently report difficulty drinking from a cup because of their tremulous hands. Essential tremor generally causes a symmetric tremor in the hands, often accompanied by head and voice tremor. If the tremor of Parkinson's disease affects the cranial musculature, it is generally as tongue, jaw, and chin tremor, not as head tremor. Handwriting may differentiate the two conditions: in essential tremor, the handwriting is large and tremulous; in Parkinson's disease, it is small and irregular. Rigidity and bradykinesia are not associated with essential tremor.

The bradykinesia of Parkinson's disease begins asymmetrically in about 75 percent of patients.[11] It is often described by the patient as a weakness of a hand or leg, but strength testing reveals no abnormalities. However, assessment of dexterity by finger tapping and toe tapping shows slowing, reduced amplitude of movement, and irregular cadence that become more apparent as the patient continues the movement (see video clip in the Supplementary Appendix). Fine movements are affected more than large movements, so that the patient first notices difficulty using small tools and fastening buttons. Repetitive movements also suffer; for example, brushing the teeth may be difficult.

The rigidity of Parkinson's disease may be experienced as stiffness associated with vague aching and discomfort of a limb suggesting musculoskeletal syndromes, particularly bursitis and tendinitis. In the arm, this rigidity may progress to a frozen shoulder.[14]

Early Parkinson's disease may cause slowing of gait, dragging of the foot, and decreased arm swing on the affected side that can suggest a mild hemiparesis (see video clip in the Supplementary Appendix). Patients may notice difficulty getting out of cars, rising from deep chairs, and rolling over in bed. However, a shuffling gait, freezing, and falls are rare in early disease. The separation of the feet in Parkinson's disease is normal or even narrow; a wide-based gait suggests other diagnoses. Shuffling gait disorders with other causes were the second most common misdiagnosis of Parkinson's disease in general practice.[13]

The diagnosis of Parkinson's disease is based on a careful history taking and physical examination. There are no laboratory tests or imaging studies that confirm the diagnosis. Magnetic resonance imaging of the brain or other tests may be appropriate in some patients, particularly those with prominent gait abnormalities, to exclude other conditions, but are seldom necessary in a typical case. Ligands that bind the dopamine transporter and are visible on single-photon-emission computed tomography provide a measure of the density of dopamine nerve terminals; such ligands are available in Europe and

Table 1. Common Presentations of Parkinson's Disease.

Presentation	Parkinsonism	Differential Diagnosis	Distinguishing Signs
Tremor	Asymmetric rest tremor	Essential and other tremors	Symmetric postural and action tremor
Clumsy or weak limb	Bradykinesia	Carpal tunnel syndrome, radiculopathies, and stroke	Altered reflexes, sensation, and strength
Stiff or uncomfortable limb	Rigidity	Musculoskeletal syndromes	Pain and limitation of movement
Gait disorder	Asymmetric slowness, shuffling, reduced arm swing, minimal or no imbalance	Multiple ischemic lesions in the brain, hydrocephalus, and musculoskeletal disorders	Symmetric shuffling, retained arm swing, wide-based gait, prominent imbalance, limited movement at knee and hip

are undergoing testing in the United States. Dopamine-transporter imaging may provide useful diagnostic information for treatment when clinical findings are subtle or equivocal.[15,16] The patient's response to a trial of levodopa has been suggested as a diagnostic test for Parkinson's disease but is of questionable value, particularly if the severity of symptoms does not justify long-term therapy with levodopa.[17]

DIFFERENTIAL DIAGNOSIS

There is a long list of causes of parkinsonism that includes toxins, infections of the central nervous system, structural lesions of the brain, metabolic disorders, and other neurologic disorders. Most of these causes are rare and are generally suggested by atypical features in the history or examination. In practice, the clinician routinely needs to consider two alternative diagnoses: drug-induced parkinsonism and "parkinsonism-plus" syndromes.

Drug-induced parkinsonism is important to recognize because it is reversible, although reversal may require weeks or months after the offending medication is stopped. Drug-induced parkinsonism accounted for 20 percent of cases of parkinsonism in a population-based study.[4] Dopamine antagonists, including neuroleptic agents, atypical neuroleptic agents, antiemetic drugs, and calcium-channel antagonists (flunarizine and cinnarizine), can induce parkinsonism. Other drugs, such as amiodarone, valproic acid, and lithium, may also cause parkinsonism, but uncommonly and by uncertain mechanisms. Dopamine antagonists also exacerbate Parkinson's disease and should be avoided, if possible, in the treatment of patients with the disease.

Approximately 25 percent of patients who received an initial clinical diagnosis of Parkinson's disease are found to have parkinsonism as part of another disorder, such as one of the so-called parkinsonism-plus syndromes.[12] Features suggesting other conditions include falls or dementia early in the course of the disease, symmetric parkinsonism, wide-based gait, abnormal eye movements, Babinski signs, marked orthostatic hypotension, urinary retention, and the development of marked disability within five years after the onset of the symptoms. The parkinsonism-plus syndromes respond poorly to antiparkinsonian medications and have a worse prognosis than does idiopathic Parkinson's disease. Neurologic consultation is warranted if the clinical features suggest these other diagnoses.

NONPHARMACOLOGIC MANAGEMENT

Support and education of patients are critical when giving a diagnosis of Parkinson's disease. Patients should understand that Parkinson's disease often has a course over decades, the rate of progression varies greatly from one person to another, and many approaches are available to reduce symptoms. Support groups that include patients with more advanced disease may be alarming rather than helpful to persons with newly diagnosed disease. Patients should be counseled about exercise, including stretching, strengthening, cardiovascular fitness, and balance training, although only small, short-term studies suggest that these may improve activities of daily living, gait speed, and balance.[18,19]

PHARMACOLOGIC THERAPY

The diagnosis of Parkinson's disease is not necessarily cause to begin drug therapy. Drug therapy is warranted when the patient is sufficiently bothered by symptoms to desire treatment or when the disease is producing disability; patients' preferences are critical to making this decision.

If the patient needs treatment for motor symptoms, efficacious agents for initial therapy include levodopa, dopamine agonists, anticholinergic agents, amantadine, and selective monoamine oxidase B (MAO-B) inhibitors (Table 2).[21,22] Except for comparisons of individual dopamine agonists with levodopa, there are no robust comparisons of efficacy among these agents, but clinical experience suggests that the dopaminergic agents are more potent than the anticholinergic agents, amantadine, and selective MAO-B inhibitors. For this reason, dopaminergic drugs are often the initial therapy recommended for patients with troublesome symptoms. Guidelines from the American Academy of Neurology[23] and the evidence-based review of the Movement Disorder Society[21] indicate that initiating therapy with levodopa or a dopamine agonist is reasonable.

Levodopa

Levodopa, a dopamine precursor, is considered the most effective antiparkinsonian agent. In randomized trials comparing levodopa and a dopamine agonist, activities of daily living and motor features of Parkinson's disease improved with levodopa by about 40 to 50 percent (as compared with approximately 30 percent with dopamine agonists).[6,24,25] Levodopa, combined with a peripheral decarboxylase inhibitor such as carbidopa to reduce the decar-

Table 2. Initial Therapy for Symptoms in Parkinson's Disease.*

Drug Class	Example	Initial Dosage	Usual Dosage	Side Effects
First-line dopaminergic agents				
Carbidopa plus levodopa				
Immediate release (Sinemet)	25 mg carbidopa, 100 mg levodopa	1/2 tablet three times daily	1 to 2 tablets three times daily	At initiation: anorexia, nausea, vomiting, dizziness, hypotension (a 1:4 ratio of carbidopa:levodopa reduces gastrointestinal symptoms), long-term therapy: motor fluctuations, dyskinesias, confusion, hallucinations
Controlled release (Sinemet-CR)	25 mg carbidopa, 100 mg levodopa	1 tablet three times daily	—	Same as for immediate-release preparations
	50 mg carbidopa, 200 mg levodopa	1/2 tablet three times daily	1 tablet three times daily	
Carbidopa plus levodopa plus entacapone (Stalevo)	12.5 mg carbidopa, 50 mg levodopa, 200 mg entacapone	1 tablet three times daily	—	Same as with preparations above, plus diarrhea
	25 mg carbidopa, 100 mg levodopa, 200 mg entacapone		—	
	37.5 mg carbidopa, 150 mg levodopa, 200 mg entacapone		—	
Dopamine agonists				
Nonergot	Pramipexole (Mirapex)	0.125 mg three times daily	0.5–1.5 mg three times daily	Nausea, vomiting, hypotension, ankle edema, excessive daytime sleepiness, compulsive behavior, confusion, and hallucinations
	Ropinirole (ReQuip)	0.25 mg three times daily	3–8 mg three times daily	Same as for pramipexole
Ergot	Pergolide (Permax)	0.05 mg three times daily	1 mg three times daily	Same as for nonergot drugs plus retroperitoneal, pulmonary, and cardiac fibrosis
Second-line alternatives				
Anticholinergic agents	Trihexyphenidyl (Artane)	1 mg three times daily	2 mg three times daily	Impaired memory, confusion, constipation, blurred vision, urinary retention, xerostomia, and angle-closure glaucoma
	Benztropine (Cogentin)	0.5 mg twice daily	1 mg twice daily	Same as for trihexyphenidyl
Selective MAO-B inhibitors	Selegiline (Eldepryl)	5 mg daily	5 mg twice daily	Insomnia, nausea, anorexia, hallucinations, potential for interactions with SSRIs and meperidine
NMDA antagonist	Amantadine (Symmetrel)	100 mg twice daily	100 mg twice daily	Dizziness, insomnia, nervousness, livedo reticularis, hallucinations, confusion

* All antiparkinsonian drugs are started at low doses and increased slowly to reduce adverse effects. Likewise, slow withdrawal of these drugs after long-term treatment is prudent to avoid a marked worsening of parkinsonism or even the neuroleptic malignant syndrome (discussed by Keyser and Rodnitzky[20]). MAO-B denotes monoamine oxidase B, SSRI selective serotonin-reuptake inhibitor, and NMDA *N*-methyl-D-aspartate.

boxylation of levodopa before it reaches the brain, is available as immediate-release and controlled-release formulations. Carbidopa plus levodopa combined with a catechol *O*-methyltransferase inhibitor, entacapone, is another preparation designed to prolong the action of levodopa by preventing its *O*-methylation. Randomized trials have not found controlled-release preparations to be superior to immediate-release preparations as initial therapy.[23,26] Trials with entacapone preparations are under way.

There are many causes of failure to respond to levodopa, including the use of an inappropriate index of response such as tremor, inadequate doses, inadequate duration of treatment, and drug interactions (e.g., concomitant treatment with metoclopramide or risperidone). A trial of levodopa should be given for three months with gradual titration upward to at least 1000 mg per day (immediate-release form) or until the appearance of dose-limiting adverse effects before concluding that a patient does not have a response to levodopa. Because failure to have a response to an adequate trial of levodopa occurs in less than 10 percent of patients with pathologically proved Parkinson's disease,[27] failure suggests the possibility of another disorder and indicates that no pharmacologic or surgical therapy is likely to be beneficial.

Dopamine Agonists

Although dopamine agonists are slightly less effective than levodopa, they are alternative first-line agents for Parkinson's disease. The various dopamine agonists have similar efficacy. One potential advantage of these agents is that, as compared with levodopa, their use is associated with a lower risk by a factor of two or three of dyskinesia and motor fluctuations in the first four to five years of treatment, particularly among patients receiving dopamine-agonist monotherapy.[6,24,25] However, it is common for levodopa to be needed in addition to dopamine-agonist therapy within a few years after diagnosis to control advancing symptoms; it is unknown how long the risk of motor complications remains lower when levodopa is added to a dopamine agonist.[6] Dopamine agonists are avoided in the treatment of patients with dementia because of the drugs' propensity to produce hallucinations.

The older dopamine agonists, bromocriptine and pergolide, are ergot derivatives that can rarely induce retroperitoneal, pleural, and pericardial fibrosis.[28] In addition, an association has recently been reported between pergolide treatment and thickening and dysfunction of cardiac valves.[29] Echocardiography in patients receiving long-term treatment with pergolide suggests that restrictive valvular disease may be two to four times more common among these patients than among patients with Parkinson's disease who are not receiving pergolide.[30,31] Given this concern, agonists not derived from ergot, such as pramipexole and ropinirole, are currently preferred.

Other Pharmacologic Agents

In general, anticholinergic agents are not used for Parkinson's disease because of associated adverse effects. However, they are sometimes added if tremor is particularly bothersome and unresponsive to other drugs, although evidence is lacking to support a particular efficacy of these agents in treating tremor.[21] Anticholinergic agents are contraindicated for patients with dementia and are usually avoided in the treatment of patients older than 70 years. MAO-B inhibitors and amantadine have fewer adverse effects and require little titration to reach therapeutic doses, but because the effects tend to be moderate, these agents generally provide inadequate symptomatic therapy when used alone (Table 2).

SURGICAL THERAPY

Thalamotomy and thalamic stimulation — deep-brain stimulation with the use of implanted electrodes — can be efficacious in treating the tremor of Parkinson's disease when it is severe and unresponsive to medication. Pallidotomy, pallidal deep-brain stimulation, and subthalamic deep-brain stimulation can improve all features of Parkinson's disease in patients in whom the response to antiparkinsonian medications is complicated by severe motor fluctuations and dyskinesia. Because this indication is absent in the early stage of the disease, and because of the risks and expense, surgical therapy has no role in early Parkinson's disease.

AREAS OF UNCERTAINTY

POSSIBLE NEUROPROTECTIVE THERAPIES

At present, there are no proven neuroprotective therapies. There are, however, clinical trials suggesting that selective MAO-B inhibitors,[32,33] do-

pamine agonists,[34,35] and coenzyme Q10[36] may slow the progression of Parkinson's disease. Data are needed to clarify the neuroprotective effects of these agents as well as of other putative neuroprotective therapies.[37]

TIMING OF THE INITIATION OF LEVODOPA

The optimal time for initiating levodopa therapy is uncertain. Limited in vitro data have aroused concern that levodopa may be toxic to dopamine neurons and may actually accelerate the disease process,[38] suggesting that its use should be delayed as long as possible. However, there is little evidence of in vivo toxicity in animals and none in humans.[39] In a randomized trial involving patients with early Parkinson's disease, those studied after 40 weeks of levodopa therapy (followed by 2 weeks of withdrawal), as compared with those treated with placebo, had better motor function, suggesting that levodopa was not toxic.[40] Neuroimaging, however, showed a reduction in dopamine transporters in the patients treated with levodopa; these results suggest the possibility of some toxic effect but alternatively, may reflect pharmacologic down-regulation of the transporters.[40]

CHOICE OF INITIAL THERAPY

It is uncertain whether levodopa therapy or dopamine-agonist therapy is the better choice for initial treatment for Parkinson's disease. The trade-off for reduced motor complications with the use of dopamine agonists is that the agonists are less efficacious antiparkinsonian agents and have a different spectrum of adverse events — namely, an increase in the rate of somnolence, hallucinations, freezing of gait, and ankle edema.[6,24,25] Measures of the quality of life do not differentiate between patients treated with dopamine agonists as initial therapy and those treated with levodopa as initial therapy.[25] Guidelines from the American Academy of Neurology suggest that initiating dopaminergic therapy with either levodopa or dopamine agonists is reasonable.[23]

It is also uncertain whether reducing pulsatile dopaminergic stimulation, as occurs with immediate-release oral preparations of levodopa, will decrease the risk of motor fluctuations and dyskinesia.[41] There is currently no evidence that controlled-release preparations of levodopa decrease this risk.[26,42] Ongoing studies are examining the effects of carbidopa, levodopa, and entacapone in combined preparations as initial therapy.

GUIDELINES

The American Academy of Neurology has issued clinical-practice guidelines for initial therapy in Parkinson's disease,[22,23] and the Movement Disorder Society has published evidence-based recommendations for Parkinson's disease therapy.[21,43] The recommendations in the present review are consistent with these guidelines.

SUMMARY AND RECOMMENDATIONS

The presence of an asymmetric rest tremor, rigidity, and bradykinesia, as in the patient in the vignette, are classic features of early Parkinson's disease. If there are no other neurologic signs inconsistent with the diagnosis, and if the patient is not taking drugs that may cause parkinsonism, the diagnosis of Parkinson's disease can be made with confidence without further testing. We would educate the patient about the disease, suggest useful Web sites (e.g., www.apdaparkinson.org, www.michaeljfox.org, and www.parkinson.org), and encourage regular exercise (although its efficacy in slowing disease progression is unclear). His mild symptoms do not necessarily require treatment. Patients who do not require pharmacologic therapy might be encouraged to enter trials of neuroprotective therapies. Were his symptoms interfering with function, we would discuss the pros and cons of various therapies. If the patient had no preference, and given that he is younger than 70 years and his cognitive ability is intact, we would start therapy with a nonergot dopamine agonist because of the low risk of motor complications during the first five years of treatment. Levodopa would be a reasonable, and more potent, alternative. If there were an inadequate response to the agonist at the maximal tolerated dose, levodopa could be added to the regimen.

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