Parkinson disease (PD) is a progressive degenerative neurological disorder characterized by resting tremor, bradykinesia, cogwheel rigidity, and postural instability. In the later stages, approximately 25% or more of patients develop cognitive compromise. The cardinal pathological features of PD are degeneration of dopaminergic neurons in the substantia nigra pars compacta and their axons, which project principally to the caudate and putamen, and the presence of cosinophilic intracytoplasmic inclusions, Lewy bodies. Although the loss of neurons is most conspicuous in the substantia nigra pars compacta, neuronal loss and/or Lewy bodies are found in other brain regions (eg, the locus coeruleus, entorhinal region, and amygdala), which suggests that treatments that target only the nigrostriatal dopaminergic system, though they may substantially benefit patients, are unlikely to completely resolve the deficits of PD.

The neurologist or movement disorders specialist caring for patients with Parkinson disease (PD) often is confronted with the following questions: Is there a treatment that slows the progression of PD? Which medication(s) should be used first in the treatment of PD? What should be done for patients who have begun to have motor fluctuations and/or dyskinesia? What is the role of surgery in the treatment of PD, and which surgical treatment is best? What can be done for patients with cognitive compromise and/or hallucinations? Are new treatments on the horizon for PD? In this article, I provide a synthesis of the available information regarding each of these questions.

IS THERE A TREATMENT THAT SLOWS THE PROGRESSION OF PD?

The first goal of PD treatment should be to slow the degeneration of the nigrostriatal dopaminergic system and functional decline in patients with PD, but no therapy has been proved unequivocally to do so. Selegiline hydrochloride, also referred to as deprenyl, which irreversibly inhibits monoamine oxidase B but may have neuroprotective effects independent of monoamine oxidase B, was the first agent to be evaluated for its ability to slow the clinical decline in PD. The Parkinson Study Group found in the Deprenyl and Tocopherol Antioxidative Therapy of Parkinsonism study in patients with early PD that 5 mg of selegiline twice a day delayed the time until levodopa was required by approximately 9 months. However, improvement in the scores on the motor portion of the Unified Parkinson Disease Rating Scale (UPDRS) after beginning selegiline treatment (wash-in) and worsening after withdrawal of selegiline treatment (washout) suggested that the effect was more likely because of a symptomatic effect caused by reduction in the metabolism of dopamine than because of a neuroprotective effect. Authors of other studies have also reported a significant wash-in effect, and because of this confounding symptomatic effect of selegiline, a neuroprotective effect has not been unequivocally demonstrated.

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Two studies compared ropinirole hydrochloride or pramipexole dihydrochloride with levodopa in patients with early PD (see details presented later) and ancillary components of the 2 studies used \[^{18}F\] fluorodopa positron emission tomography or \[^{123}I\]-2β-carbomethoxy-3β-(4-iodophenyl)-tropane (β-CIT) single-photon emission computed tomography, respectively, as biological markers of the preservation of remaining nigrostriatal dopaminergic axons. Patients treated initially with ropinirole had greater \[^{18}F\] fluorodopa accumulation in the striatum than did those treated with levodopa 2 years after initiation of therapy, and patients treated initially with pramipexole had greater \[^{123}I\]-β-CIT binding in the striatum than did those treated with levodopa 2 years after study entry. However, the effects of levodopa and dopaminergic agonists on accumulation of \[^{18}F\] fluorodopa and \[^{123}I\]-β-CIT are not known, and these agents may cause adaptive changes in \[^{18}F\] fluorodopa metabolism and/or \[^{123}I\]-β-CIT binding, so the results cannot be unequivocally interpreted as indicative of preservation of nigrostriatal dopaminergic axons.

Shults et al\(^8\) reported in a phase 2 trial of 3 dosages (300, 600, and 1200 mg/d) of coenzyme Q\(10\) vs placebo in patients with early untreated PD a positive trend toward slowing functional decline as measured with the UPDRS. The authors stress that the results need to be confirmed and extended in a definitive phase 3 trial before the recommendation can be made for widespread use of coenzyme Q\(10\) for PD.

Recently, Fahn and colleagues in the Parkinson Study Group\(^8\) compared carbidopa-levodopa (12.5 mg of carbidopa and 50 mg of levodopa, 25 mg of carbidopa and 100 mg of levodopa, or 50 mg of carbidopa and 200 mg of levodopa) 3 times a day with placebo and found a dose-dependent reduction in the total score on the UPDRS. The benefit persisted for 2 weeks after discontinuation of treatment with levodopa. This suggests the possibility that levodopa slowed the degeneration of the nigrostriatal dopaminergic system. However, imaging the dopamine transporter with \[^{123}I\]-β-CIT single-photon emission computed tomography indicated greater reduction in transporter level with levodopa treatment; this discrepancy and the possibility that treatment with levodopa may cause adaptive changes in the nigrostriatal dopaminergic system make interpretation of a neuroprotective effect of levodopa uncertain. Fahn's study should allay concerns that use of levodopa accelerates clinical decline in patients with PD. No drug has been shown unequivocally to slow the progression of PD.

**WHICH MEDICATION(S) SHOULD BE USED FIRST IN THE TREATMENT OF PD?**

Introduction of levodopa revolutionized treatment of PD.\(^3\)

Unfortunately, one third to one half of patients treated with levodopa develop motor fluctuations (“wearing off” and sudden “on-off”) and/or dyskinesia within 5 years after beginning treatment.\(^5,6\)

Some clinicians prefer to avoid levodopa as the initial treatment because of concerns that levodopa may exacerbate loss of dopaminergic neurons and/or accelerate the development of motor fluctuations; they prefer to use selegiline, amantadine hydrochloride, an anticholinergic drug, or a dopaminergic agonist. Follow-up in the Deprenyl and Tocopherol Antioxidative Therapy of Parkinsonism study revealed that patients treated early with selegiline were more likely to develop dyskinesias but less likely to develop freezing of gait. Amantadine has been demonstrated to have a modest but statistically significant improvement in the clinical assessments of PD. Side effects of amantadine can include peripheral edema, livedo reticularis, rash, and confusion. Anticholinergic drugs have their most substantial benefit in reduction of tremor and modest benefit in bradykinesia and rigidity, but peripheral and central side effects, particularly memory impairment and confusion, limit their use typically to younger patients with prominent tremor.

Two prospective, randomized, double-blind studies assessed the long-term outcome in patients with early PD initially treated with ropinirole or pramipexole,\(^8\) as compared with the outcome in patients treated with levodopa. In both studies, open-label levodopa could be added after the initial period of titration of levodopa or agonist if the response to the assigned treatment was no longer satisfactory. Results of both studies demonstrated that levodopa was significantly more effective in reducing the score on the UPDRS than was the agonist. Rasic et al\(^9\) reported that after 5 years, 20% of the subjects initially assigned to ropinirole developed dyskinesia, while 45% of the subjects assigned to levodopa developed dyskinesia. The Parkinson Study Group\(^8\) reported that 10% of patients initially randomized to pramipexole developed dyskinesia, while 31% of patients initially assigned to carbidopa-levodopa developed dyskinesia. Also, patients treated with pramipexole first were less likely to develop any of the 3 motor complications: wearing off, on-off, or dyskinesia.

A number of conclusions can be drawn from these 2 studies. First, treatment with a dopaminergic agonist or levodopa ameliorated the symptoms of PD to a level that the patient and investigator considered satisfactory. Second, both dopaminergic agonists and levodopa were typically well tolerated, but side effects, such as nausea or hallucinations, were not uncommon and were generally more common with the agonists than with levodopa. Subsequent meta-analysis has indicated that sudden sleepiness appears to be more common with the new agonists. Third, in both studies, levodopa reduced the score on the UPDRS more than did the agonist. Fourth, initial use of a dopaminergic agonist resulted in a reduced development of dyskinesia. The fourth conclusion is somewhat controversial because the groups were not comparable for the effect of therapy (patients treated with levodopa showed greater improvement in UPDRS scores), and the question has been raised whether patients treated with an agonist would have had a greater risk of dyskinesia if they had had improvement equivalent to that of the patients treated with levodopa.

Studies have been performed to evaluate whether initial treatment with controlled-release formulations of levodopa could lessen the development of motor fluctuations (eg, wearing off or on-off), but they have not
demonstrated a decrease in the development of fluctuations. Thus, there is no reason to use controlled-release levodopa for the initial treatment of PD.12

Because no treatment has been proved to slow the progression of PD, there is no compelling reason to begin using this medication until the patient’s disability warrants it. Levels of disability that warrant medication vary among patients with PD; for example, the level of acceptable slowness may differ between patients with PD who are working and those who are retired. Although selegiline, amantadine, and anticholinergic drugs can ameliorate the disability in early PD, the benefit is typically modest, and most patients soon need treatment with levodopa or a dopaminergic agonist. Use of an agonist as the initial treatment will reduce but not eliminate the incidence of dyskinesia, and this benefit should be weighed against the greater reduction in symptoms and signs of PD and lower cost of levodopa. Both dopaminergic agonists and levodopa are acceptable and appropriate initial treatments for PD.

WHAT SHOULD BE DONE FOR PATIENTS WHO HAVE BEGUN TO HAVE MOTOR FLUCTUATIONS AND/OR DYSKINESIA?

Controlled-release formulations of levodopa reduce the number of doses needed, but, surprisingly, the increase in the on time with controlled-release levodopa is relatively modest.13 Dopaminergic agonists are often added to levodopa to treat PD, and results from a number of studies have demonstrated improvement. Addition of bromocriptine mesylate, pramipexole, or placebo in patients treated with levodopa who had motor fluctuations has been studied, and both bromocriptine and pramipexole significantly improved scores on the UPDRS part II (activities of daily living) and part III (motor score), as compared with placebo; pramipexole, but not bromocriptine, caused a significant reduction in the time spent in the off state.14 The agonists initially introduced, bromocriptine and pergolide mesylate, are ergot derivatives and rarely are associated with fibrosis, such as in the pleura or heart. The more recently introduced agonists, such as pramipexole and ropinirole, appear not to have this side effect and are used more commonly.

In the periphery, levodopa is metabolized by aromatic–amino acid–decarboxylase and catechol-O-methyltransferase (COMT). Two COMT inhibitors, entacapone and tolcapone, are currently marketed. Results of some studies have indicated that addition of tolcapone in patients receiving levodopa who have fluctuations can decrease the percentage of off time by 2 to 3 hours. However, approximately 3% to 4% of patients treated with tolcapone developed abnormalities in liver function tests, and 3 deaths from liver failure occurred. The hepatotoxicity led to a ban of tolcapone in the European Union and to stringent controls of its use in the United States. In patients with wearing off, addition of entacapone caused a 5% increase in the on time of approximately 1 hour and reduction in levodopa dose by approximately 12%.15 The COMT inhibitors can be beneficial in patients with PD with wearing off.

Results of the study by Metman et al16 and other more recent studies showed that treatment with amantadine (up to 300 or 400 mg/d) reduced dyskinesia induced by intravenous or oral levodopa or as measured as cumulative dyskinesias recorded in diaries. Selegiline has been found to improve motor function in patients receiving levodopa, but the improvement has typically been modest.

In patients with wearing off, addition of a dopaminergic agonist, controlled-release levodopa, or a COMT inhibitor can reduce off time. In patients with dyskinesia, addition of amantadine can substantially reduce dyskinesia.

WHAT IS THE ROLE OF SURGERY IN THE TREATMENT OF PD, AND WHICH SURGICAL TREATMENT IS BEST?

Three regions in the brain have been targeted for surgical intervention in PD: the thalamus, globus pallidus interna (GPi), and subthalamic nucleus (STN). Ablative procedures (eg, thalamotomy or pallidotomy) were initially used but have recently been largely supplanted by deep brain stimulation (DBS). A number of excellent reviews, such as the one by Lang,17 provide a more detailed discussion.

Thalamotomy and DBS of the thalamus can both markedly reduce tremor in the contralateral arm but have little effect on rigidity and bradykinesia; DBS has been reported to have fewer adverse effects and result in greater functional improvement. However, bilateral thalamotomy and DBS lead to impairment in speech and swallowing and should be avoided.

In the 1990s, there was a renewal of interest and activity in pallidotomy and later advancing to DBS. Most of the reports on pallidotomy for PD have not been prospective, randomized, or blinded. However, de Bie et al18 conducted a prospective randomized trial of unilateral pallidotomy vs medical therapy and found significant benefit as assessed with the motor portion of the UPDRS during a clinically defined off period and with measures of activities of daily living and dyskinesia. Vitek et al19 recently confirmed this finding. Patients undergoing unilateral pallidotomy may experience major persistent adverse events, and bilateral pallidotomy is also often accompanied by serious adverse events, most frequently impairments of speech and cognition.17

Deep brain stimulation of the GPi or STN has largely supplanted unilateral pallidotomy because of the ability to manipulate the circuitry bilaterally and a reduced likelihood of permanent adverse events. The Deep-Brain Stimulation for Parkinson’s Disease Study Group20 performed a study in which 18 centers enrolled 143 patients with PD and implanted bilateral electrodes in either the STN (n=96) or GPi (n=38) in 134 patients, according to the experience and preference of the investigators at each site. After 3 months, the patients were assessed with the motor portion of the UPDRS after overnight discontinuation of medication and stimulation. Significant improvement was reported in both groups of patients—STN stimulation (49%) and GPi stimulation (37%). Home diaries indicated increase in the on time
without dyskinesia. However, 7 intracranial hemorrhages and 2 infections requiring removal of electrodes occurred in the 143 patients.

The data suggest that in patients with advanced PD that cannot be managed satisfactorily with medication, DBS of either the GPI or STN can improve motor function and reduce dyskinesia. As with pallidotomy, there is the risk of intracranial hemorrhage and neuropsychological changes and the additional risks of infection and hardware failure. The superior site for DBS—GPI or STN—remains uncertain, but the Department of Veterans Affairs (Washington, DC) and National Institute of Neurological Disorders and Stroke (Bethesda, Md) are performing a prospective randomized trial to address this question.

WHAT CAN BE DONE FOR PATIENTS WITH COGNITIVE COMPROMISE AND/OR HALLUCINATIONS?

The prevalence of dementia in patients with PD is approximately 25% and increases with advancing disease; approximately 15% develop hallucinations. Aarsland et al23 reported that treatment with donepezil modestly but statistically significantly improved the score on the Mini-Mental State Examination in patients with PD with cognitive impairment.

Typical antipsychotic drugs cause worsening of parkinsonian features and should be avoided in patients with PD. Clozapine has been shown to improve drug-induced psychosis significantly in patients with PD without worsening of parkinsonism. However, patients receiving clozapine can develop agranulocytosis, as well as seizures and myocarditis, and the complete blood cell count must be monitored closely.

Other atypical antipsychotic drugs have been studied in PD. However, olanzapine worsens parkinsonism. Risperidone has recently been reported to be associated with an increase in the incidence of stroke when used in elderly patients with dementia. Although controlled prospective studies of quetiapine for the treatment of psychosis in PD have not been reported, it has been described as reducing psychosis in patients with PD without worsening parkinsonism.

ARE NEW TREATMENTS ON THE HORIZON FOR PD?

Transplantation of fetal mesencephalic cells in patients with PD has been studied in 2 prospective, randomized sham operation-controlled trials by Freed et al22 and Olanow et al23 in patients with PD. Results of [18F]fluorodopa positron emission tomography in these patients indicated that the implanted cells survived and were biochemically functional. In both studies, the primary analysis indicated that the procedure did not lead to functional improvement in patients who had fetal dopaminergic cells implanted. Some of the patients with transplanted cells developed disabling dyskinesia that could not be controlled with medication adjustment.

In the past decade, extensive research has been directed to the development of therapies to induce regeneration of the nigrostriatal dopaminergic system in PD. Much of the work has focused on trophic factors, with the most promising being glial cell line–derived neurotrophic factors (GDNF). Nutt et al24 conducted a multicenter, randomized, double-blind, placebo-controlled, sequential cohort study to compare the effects of monthly intracerebroventricular administration of placebo and escalating doses of GDNF in 50 subjects with PD. The total score and the score on the motor portion of the UPDRS during clinically defined on and off periods did not improve with GDNF. Common adverse events included nausea, anorexia, vomiting, weight loss, paresthesia, and hyponatremia. Nutt et al24 hypothesized that GDNF did not improve parkinsonism, possibly because it did not reach the target tissues, the putamen and substantia nigra pars compacta. The results of their study underscore the need for delivery of the trophic factor to the appropriate target (eg, the striatum) and for delivery of the trophic factor in a controlled fashion. Results of a recent pilot study suggest that direct infusion into the putamen may be beneficial.

Neuroimmunophilin ligands (eg, GPI-1046) have also been reported to promote regeneration of the injured nigrostriatal dopaminergic system, but this finding is controversial. Neuroimmunophilin ligand-A (GPI-1485) has been studied in patients with PD in 1 trial, but the results were disappointing.23 Neuroimmunophilin ligands are still considered deserving of further study in PD,20 and an additional trial is under way.

Research in PD has recently elucidated a number of processes that appear to contribute to degeneration and to identify interventions in these processes. These pathogenic mechanisms include mitochondrial dysfunction, oxidative stress, impaired protein degradation, abnormal protein aggregation, inflammation, and apoptosis. An encouraging development has been the National Institute of Neurological Disorders and Stroke Neuroprotection Exploratory Trials in PD, which has the mandate to identify agents with the potential to slow the progression of PD and then conduct clinical trials with the most promising agents.26 Neurologists should encourage patients with PD to consider participating in clinical trials supported both by federal agencies, such as National Institute of Neurological Disorders and Stroke and the Department of Veterans Affairs, and pharmaceutical firms because only through prospective, randomized placebo-controlled trials will neurologists and patients develop better treatments for PD.

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Dr Shults is a coinventor in a pending patent application for use of coenzyme Q10 in neurodegenerative diseases. The application is jointly owned by Enzymatic Therapy, Inc, Green Bay, Wis (owner of Vitaline Corp, Ashland, Ore), and The Regents of the University of California.

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