The scientific and clinical basis for the treatment of Parkinson disease (2009)

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ARTICLE

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ABSTRACT

Parkinson disease (PD) is an age-related neurodegenerative disorder that affects as many as 1–2% of persons aged 60 years and older. With the aging of the population, the frequency of PD is expected to increase dramatically in the coming decades. Current therapy is largely based on a dopamine replacement strategy, primarily using the dopamine precursor levodopa. However, chronic treatment is associated with the development of motor complications, and the disease is inexorably progressive. Further, advancing disease is associated with the emergence of features such as freezing, falling, and dementia which are not adequately controlled with dopaminergic therapies. Indeed, it is now appreciated that these nondopaminergic features are common and the major source of disability for patients with advanced disease. Many different therapeutic agents and treatment strategies have been evaluated over the past several years to try and address these unmet medical needs, and many promising approaches are currently being tested in the laboratory and in the clinic. As a result, there are now many new therapies and strategic approaches available for the treatment of the different stages of PD, with which the treating physician must be familiar in order to provide patients with optimal care. This monograph provides an overview of the management of PD patients, with an emphasis on pathophysiology, and the results of recent clinical trials. It is intended to provide physicians with an understanding of the different treatment options that are available for managing the different stages of the disease and the scientific rationale of the different approaches. **NEUROLOGY 2009;72 (Suppl 4):S1–S136**

INTRODUCTION Parkinson disease (PD) is named in honor of James Parkinson, whose monograph entitled "An Essay on the Shaking Palsy," written in 1817, provided an enduring description of the clinical features of this disorder.[1] PD is the second most common neurodegenerative disorder, with an average age at onset of about 60 years. An estimated 5 million people throughout the world have PD, with 1 million individuals each in the United States and in Europe with the disorder. PD affects approximately 0.3% of the population and 1% to 2% of those older than 60 years.[2] With the aging of the population and the substantial increase in the number of at-risk individuals older than 60 years, it is anticipated that the prevalence of PD will increase dramatically in the coming decades.[3]

The cardinal clinical manifestations of PD are resting tremor, rigidity, bradykinesia, and gait dysfunction (table 1). It is now appreciated that PD is also associated with many nonmotor features, includ-

Table 1 Classic motor features of PD

Cardinal features	Additional features
Resting tremor	Micrographia
Rigidity	Masked facies
Bradykinesia	Decreased blinking
Gait disturbance/postural instability	Freezing
	Flexed posture

PD = Parkinson disease.

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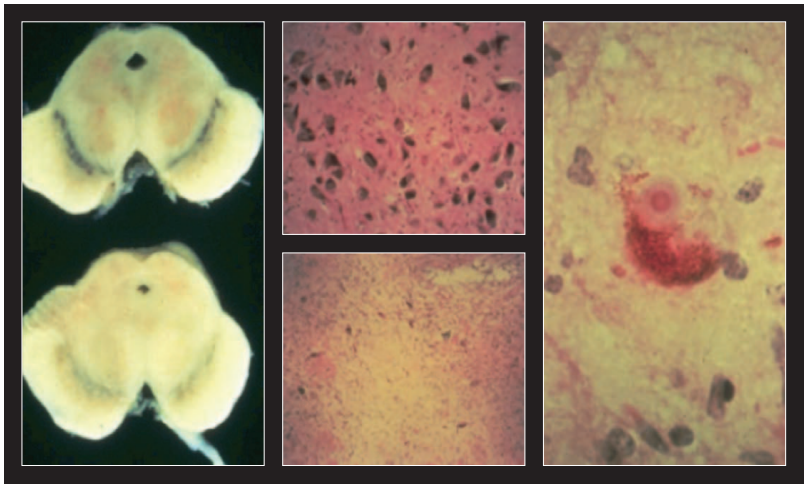
Figure 1 Classic pathology of PD.



The left panel illustrates the marked reduction in neuromelanin pigment in the substantia nigra pars compacta (SNc) in a patient with PD (bottom) compared with a normal individual (top). The middle panel illustrates the marked reduction in dopaminergic neurons in the SNc of a patient with PD (bottom) compared with a normal individual (top). The right panel depicts a surviving dopamine neuron containing a Lewy body using hematoxylin and eosin (H&E) stain. Note that the Lewy body has a dense core (representing proteinaceous material) surrounded by a pale halo (comprised of α-synuclein and neurofilaments). Courtesy of Dr. Dan Perl.

ing autonomic dysfunction, pain and sensory disturbances, mood disorders, sleep impairment, and dementia (see discussion in the nondopaminergic and nonmotor features section, page S70).

Pathologically, PD is characterized by degeneration of dopaminergic neurons in the substantia nigra pars compacta (SNc) coupled with intracytoplasmic proteinaceous inclusions known as Lewy bodies (figure 1). It is also now appreciated that PD is associated with extensive nondopaminergic pathology, which involves cholinergic neurons of the nucleus basalis of Meynert, norepinephrine neurons of the locus coeruleus, serotonin neurons in the midline raphe, as well as neurons in the cerebral cortex, brainstem, spinal cord, and peripheral autonomic nervous system.[4] Indeed, recent studies suggest that nondopaminergic pathology, particularly in the dorsal motor nucleus and olfactory regions, precedes the onset of dopaminergic pathology in the SNc.[5]

The introduction of levodopa in the late 1960s represented a major therapeutic advance in the management of PD.[6] Levodopa treatment provides meaningful benefit to most patients with PD, and is associated with improvement in activities of daily living, independence, employability, and survival. However, long-term treatment with levodopa is complicated by the development of adverse events (AEs) that include motor fluctuations, dyskinesias, and neuropsychiatric complications.[7,8] Additional medical and surgical therapies that have been developed for PD to date have focused primarily on treating or preventing levodopa-related motor complications, and do not provide benefits that are superior to what can be achieved with levodopa. Because of these advances, motor complications seem to represent less of a problem today than they did in the past. The nondopaminergic features of the disease (e.g., freezing, falling, and dementia) are not well controlled with dopaminergic therapies and now represent the major source of disability for most patients with advanced PD.[9] Thus, despite levodopa treatment and the considerable success that has been achieved in treating motor complications, patients with PD still experience severe disability. This has spurred an intensive effort to develop "neuroprotective" or "disease-modifying" treatments that can slow, stop, or reverse disease progression. This effort has been aided by the identification of a number of gene mutations that are associated with the development of familial and even sporadic cases of PD. In recent years, there has been an explosion of laboratory studies aimed at better defining the molecular basis of cell death in PD, and identifying novel targets for potential symptomatic and neuroprotective interventions.[10-12] Physicians who treat the patients with PD must now, more than ever, assimilate an enormous body of scientific and clinical information to optimally manage patients with this complex disorder.

In 1994,[13] 1998,[14], and 2001,[15] groups of movement disorder experts published an algorithm (decision tree) for the management of PD, with the intent of considering treatment options and providing therapeutic recommendations for practicing physicians who treat patients with PD. These monographs reviewed the available therapies, the scientific rationale for choosing them, and the decision-making processes involved in selecting treatment for an individual patient. Alternative treatment strategies were considered and areas of controversy identified. It is 7 years since the most recent of these publications, and in this time considerable new information relevant to the treatment of PD has become available. Thus, we believe it is timely to publish an updated, comprehensive review of PD therapy and the underlying scientific basis for considering the various treatment alternatives. From the laboratory perspective, there have been advances in identifying the cause of PD, the pathogenesis of how nerve cells die, the pathophysiology of the normal and dopamine-depleted basal ganglia, and the physiologic and molecular basis of levodopa-related motor complications. New gene mutations have been identified in patients with familial PD, as well as in individuals with typical sporadic PD. Increasingly, evidence indicates that there are many different causes of PD,[16] and, indeed, that sporadic PD might be the result of a complex interaction among multiple genetic and environmental factors that may vary in different individuals. New information has become available on the

mechanism responsible for levodopa-induced motor complications and the potential value of therapies that provide more continuous dopaminergic stimulation (CDS). Clinically, many new therapeutic interventions have been studied, and several of these are now on the market and available for the treatment of patients with PD. Specifically, there is new information with respect to the role of rasagiline, dopamine agonists and catechol-*O*-methyltransferase (COMT) inhibitors in early treatment; new agents that treat motor complications; the role of deep brain stimulation (DBS); infusion therapies; putative neuroprotective agents; and novel trial designs that attempt to sort out confounding symptomatic from disease-modifying effects. In addition, experimental studies suggest potential therapeutic benefits from stimulation of novel surgical targets, as well as from cell-based and gene delivery approaches. Furthermore, the importance of nonmotor and nondopaminergic features of the disease has become apparent. Indeed, it is possible that olfactory impairment, REM behavior disorder (RBD), and constipation might be early features of PD that antecede the onset of the classic motor features of the disease. These developments have expanded our knowledge, provided new treatment options, and improved our ability to treat patients with PD in different stages of the disorder.

We have revised our previous algorithm (decision tree) to take this new information into account. We continue to consider the advantages and disadvantages of various therapeutic agents, to highlight clinical controversies, and to provide our personal opinions. Where material in the 2001 supplement remains current and applicable, it was not changed. Where new information has become available, particularly from prospective, double-blind, controlled clinical trials, it has been incorporated and our treatment approaches modified accordingly. This monograph is designed to aid physicians in identifying and selecting treatment options for patients in various stages of PD and in the management of the various problems that can ensue. This monograph builds on the evidence-based medicine guidelines provided by organizations, such as the Movement Disorder Society and the American Academy of Neurology.[17-19] We try to evaluate the results of current studies in light of existing scientific information and to describe how this body of information can be used to make informed decisions. We recognize that physicians are often called upon to institute therapies despite a lack of adequate clinical and scientific information. We also recognize that the treatment of PD is highly individual and that the physician must use his or her best judgment and consider the wishes of the patient in making therapeutic decisions. In many instances, there may be alternative approaches that are equally valid, and an effort has been made to point these out. This monograph is not intended to represent a single way of treating PD, but rather to point out many different treatment options and the strengths and weaknesses of the underlying clinical data and scientific rationale. It is our hope that this publication will be of use to clinicians, managed care organizations, and other healthcare providers as they try to incorporate a large body of clinical and scientific information into the difficult and complex decision-making processes involved in caring for patients with PD.

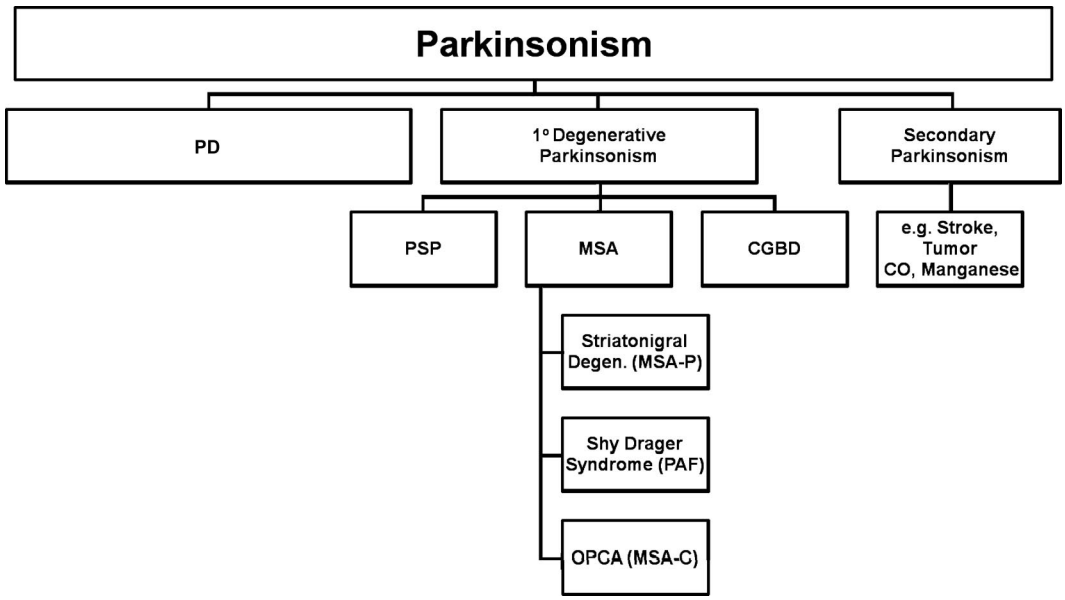
MANAGEMENT OF PD

Diagnosis. The differential diagnosis of PD is listed in table 2.[20] PD is the most common form of parkinsonism, accounting for about 75% of cases seen in the office of a movement disorder specialist. Historically, PD was diagnosed based on the presence of two of three cardinal features—tremor, rigidity, and bradykinesia—and pathologically by degeneration of dopaminergic neurons in the SNc coupled with the presence of Lewy bodies. However, studies performed at the London Brain Bank found that in 100 consecutive cases diagnosed as having PD in life, the diagnosis was not confirmed at autopsy in 24%.[21] A retrospective analysis of this population found that the clinical features that were most likely to accurately predict PD pathology were parkinsonism associated with resting tremor, asymmetry, and good response to levodopa.[22] Similar observations were made based on MRI studies.[23] In a subsequent study of 73 consecutive patients diagnosed as having PD by neurologists using these criteria, postmortem confirmation of the clinical diagnosis was made in all but one (98.6%) case.[24] Thus, a diagnosis of PD can be made with a high level of confidence in a patient with parkinsonism who has resting tremor, prominent asymmetry, and good response to levodopa.

Each patient with PD does not necessarily manifest all of these features. An estimated 30% of patients with PD do not have resting tremor. Patients with a tremor-dominant form of PD tend to have a relatively benign course, whereas those who present with an akinetic-rigid form of the disease have more rapid progression and are more likely to ultimately be diagnosed as having atypical parkinsonism.[25] There are also occasional examples of pathologically confirmed cases of PD that were misdiagnosed as having an atypical form of parkinsonism during life.[21]

Recent studies have emphasized that PD is associated with a variety of nonmotor features and that pathology is widespread and extends beyond the nigrostriatal system. Of particular interest are studies suggesting that nonmotor features of PD may antedate the development of the classic motor features of

Table 2 Differential diagnosis of PD



PD = Parkinson disease; MSA-P = multiple system atrophy-parkinsonian; MSA-C = multiple system atrophy-parkinsonian cerebellar.

the disorder. Thus, individuals with a combination of constipation, RBD, and anosmia may not only be at increased risk for developing PD, they may already have an early form of the disease.[26] On the basis of these findings, it is likely that cases will be diagnosed at earlier stages in the future and that current diagnostic criteria will need to be further amended.

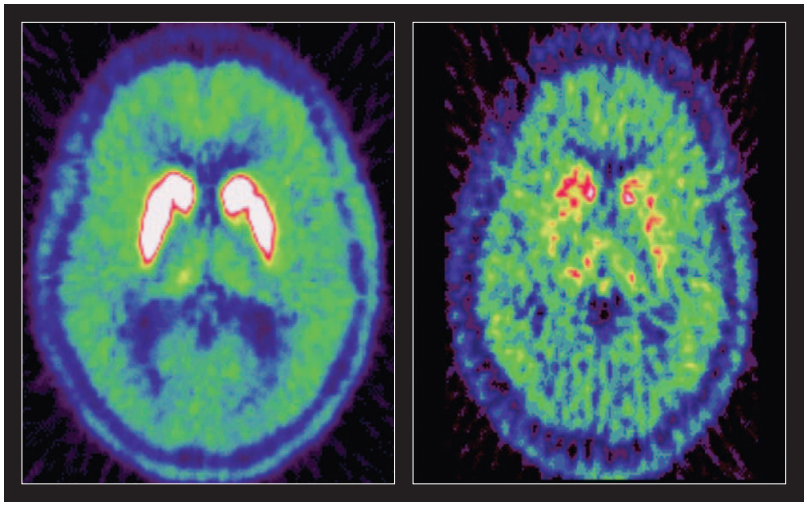
Clinical diagnostic accuracy is less precise for patients with atypical parkinsonism than for those with PD. Although it is usually possible to identify that a patient has an atypical parkinsonism, it may be difficult to diagnose the precise subtype. The clinical features that best predict that a patient has an atypical parkinsonism are early onset of prominent speech and gait dysfunction, postural instability, axial greater than appendicular rigidity, absence of resting tremor, prominent autonomic dysfunction, and poor or unsustained response to levodopa. The presence of prominent and symptomatic orthostatic hypotension or concomitant cerebellar signs should raise the possibility of multiple system atrophy (MSA).[27] Although features may overlap, recent nomenclature favors dividing MSA into those with predominant parkinsonian (MSA-P) or cerebellar (MSA-C) features. Pathologically, MSA is characterized by striatal and/or cerebellar degeneration associated with α-synuclein deposits in glial cells (glial cytoplasmic inclusions). Progressive supranuclear palsy (PSP) is characterized by features of an atypical parkinsonism, with impairment in vertical eye movements, particularly down gaze, hyperextension of the neck, and early falling.[28] Slowing of vertical saccades or the presence of a prominent stare with marked reduction in blink rate may be early features and should raise suspicion that a patient with atypical parkinsonism might have PSP. Some patients with PSP may strongly resemble patients with PD in the early stages of their illness and have a positive response to levodopa. Pathologically, PSP is characterized by degeneration in the SNc, other brainstem regions, and the pallidum, coupled with prominent tau-positive neurofibrillary tangles. Subgroups of PSP have been defined that have prominent Lewy bodies in the SNc.[29] Some have argued that this is a separate condition referred to as PSP–Parkinson, in contrast to the more classic form of the illness, which is referred to as PSP–Richardson. Atypical parkinsonism in the presence of asymmetric focal rigidity and cortical features, such as myoclonus, apraxia, or alien limb phenomenon, should raise the possibility of corticobasal ganglionic degeneration.[30] Parkinsonism can also be a feature of a variety of other conditions, including Huntington disease (particularly young-onset Westphal variant), Hallervorden-Spatz disease, Wilson disease, and dopa-responsive dystonia. A discussion of these conditions is beyond the scope of this monograph, but it is important to consider these conditions in the differential diagnosis of an atypical parkinsonism.

Some clinicians use a "levodopa challenge" to try and differentiate PD from atypical parkinsonism. We find this not to be particularly helpful because patients with PD with mild clinical features may not show much of a benefit from levodopa, whereas pa-

tients with atypical parkinsonism may show some benefit from the drug, particularly in the early stages of the disease. Furthermore, animal studies suggest that even a single dose of levodopa might prime the dopamine-depleted basal ganglia for the subsequent development of dyskinesia.[31] On the basis of these considerations, most experts recommend against performing this procedure as a diagnostic test.[32]

Secondary forms of PD can also occur. Drug-induced parkinsonism is the most common secondary cause and can closely resemble PD. Diagnosis can usually be made by taking a careful history and evaluating the effects of drug withdrawal. Neuroleptic agents used in the management of psychiatric disorders are the most common cause of secondary parkinsonism. It is important to appreciate that some neuroleptic agents are used primarily to treat nonpsychiatric problems, such as emesis (e.g., prochlorperazine [Compazine] and promethazine [Phenergan]) and other gastrointestinal disorders (e.g., metoclopramide [Reglan]). Other drugs that have been reported to induce or worsen parkinsonism include dopamine uptake inhibitors such as reserpine or tetrabenazine, selective serotonin reuptake inhibitors (SSRIs), lithium, valproic acid, calcium channel blockers such as cinnarizine and flunarizine, antiarrhythmics such as amiodarone, cholinergics, chemotherapeutics, amphotericin B, and estrogens. Other causes of secondary parkinsonism include infarcts, hemorrhages, tumors in the basal ganglia, hydrocephalus, infections such as HIV disease and influenza, and toxins such as manganese and carbon monoxide. These should be considered in the differential diagnosis, but are usually relatively easy to separate from PD based on clinical and laboratory criteria.

Figure 2 **[F-18]-fluorodopa (FD)-PET study in a normal individual (left panel) and a patient with PD (right panel).**



Note that in PD, there is a marked reduction in striatal FD uptake, which tends to be asymmetric and most prominent in the posterior putamen. Courtesy of Dr. Donald Calne.

Finally, one must consider psychogenic forms of parkinsonism.[33] Such cases may represent as many as 5% of patients seen in the practice of a movement disorder specialist and may be difficult to diagnose. Psychogenic tremor is the most common feature of psychogenic parkinsonism and is characterized by variable frequency (tremor with multiple frequencies), distractibility (tremor is more prominent when the patient focuses on the tremor and diminishes or disappears when the patient is distracted whereas the opposite is true with organic tremor), and entrainment (in which the tremor frequency in the affected limb changes to match or entrain with a series of different frequencies in the opposite limb).[34] These features can often be recognized at the bedside and documented with accelerometry. Not all patients with psychogenic parkinsonism have overt psychiatric disease or even detectable psychopathology. Factors that point toward psychogenic parkinsonism include sudden onset of the movement disorder and concomitant evidence of associated psychogenic features, including give-way weakness, astasia-abasia, nonanatomic sensory deficits, and a history of litigation. Psychogenic problems may be associated with somatization and reflect a conversion disorder or frank malingering. It should also be borne in mind that some patients can have psychogenic parkinsonism superimposed on an organic disease such as PD.[35]

Imaging. Neuroimaging studies can occasionally be helpful in making a diagnosis of PD but are generally not required. Positron emission tomography (PET) and single photon emission (SPECT) can be used to provide an index of the integrity of the nigrostriatal dopamine system. Striatal uptake of [18F]-fluorodopa (FD),[36-39] ligands that bind to the dopamine transporter (DAT), such as beta-carbomethoxy-3 beta-(4-iodophenyl)tropane (β-CIT)[40] and TRODAT,[41,42] and ligands that bind to the vesicular monoamine transporter, such as [11C]-dihydrotetrabenazine,[43] can each be used to estimate the number of remaining dopamine terminals and nigral neurons. With each of these techniques, patients with PD demonstrate a significant and asymmetric reduction of tracer uptake in the striatum, particularly in the posterior portion of the putamen (figure 2). Neuroimaging has also been used to try and assess disease severity and the rate of PD progression.[39,44] The severity of change in striatal FD uptake on PET has been reported to correlate with the number of SNc dopamine neurons in monkeys lesioned with the neurotoxic compound 1-methyl-4-phenyl-1,2,3,6-tetrahydropyridine (MPTP), whose effects mimic PD,[45] and in patients with PD,[46] but only small numbers of patients or animals have been studied. Correlation between imaging measures and Unified

PD Rating Scale (UPDRS) motor scores are most reliable in untreated patients or in those with advanced PD, in whom the confounding symptomatic effect of antiparkinson drugs is absent or minimized.[47] Longitudinal studies using both FD-PET and β-CIT-SPECT to estimate the rate of disease progression show a loss of signal between 5% and 10% per year, suggesting that dopamine loss began about 5 years before symptom onset.[39,44]

Imaging of the dopamine system has also been used in trying to assess the effects of putative neuroprotective agents on disease progression as determined by the rate of decline of an imaging biomarker of nigrostriatal function.[48] However, the possibility of confounding pharmacologic or regulatory effects of the study intervention on the imaging end point limits the value of these studies,[49] and they are not currently recommended for use as primary end points in neuroprotective studies.[50] Interestingly, about 10% of patients who participate in neuroprotection trials have scans without evidence of dopamine dysfunction (SWEDDS). These patients raise the important question of whether a patient with PD can have normal dopaminergic function on imaging studies, which would be surprising because evidence suggests that at least 60% of dopamine neurons and terminals are lost by the time the earliest clinical features of PD emerge. Follow-up studies, to date, have not shown clinical worsening or deterioration in dopaminergic function in any patient with scans without evidence of dopamine dysfunction. We, therefore, believe it is likely that these patients do not have PD and were misdiagnosed. In this regard, it should be noted that these studies require enrollment of untreated patients at the earliest stages of the illness, when it may be difficult to be certain of the diagnosis. Thus, it has not been established that a patient with PD can have normal dopaminergic function on an imaging scan, and normal striatal uptake on FD-PET or β-CIT-SPECT should suggest an alternate diagnosis.

Although dopamine imaging approaches have proven useful in distinguishing patients with PD from age-matched controls, and from individuals with disorders in which the dopamine system is not affected, they have not been shown to reliably differentiate PD from atypical parkinsonism. In MSA and PSP, dopamine depletion is decreased equally in both the putamen and caudate nucleus, in contrast to the preferential involvement of the posterior putamen found in PD. However, PSP could not be separated from PD in a blinded study using SPECT measures of DAT binding.[51] Similarly, neither FD-PET nor volumetric MRI differentiates MSA from PD.[52] Imaging of postsynaptic striatal D2 receptors using ligands such as raclopride tends to be normal or up-regulated in PD, but slightly reduced in atypical parkinsonism, reflecting the respective sparing and damage to the striatum in these conditions. Although these changes are subtle, MSA-P could be differentiated from PD based on postsynaptic D2 receptor density.[52] Patients with MSA-P and PD have also been reported to have different patterns of glucose metabolism within the basal ganglia network on [18F]-fluorodeoxyglucose-PET.[53] These studies demonstrate a relative increase in metabolic activity in the internal globus pallidus (GPi) and decrease in activity in the thalamus in PD, with the opposite pattern seen in MSA.

On balance, imaging of the dopamine system is useful for identifying dopamine depletion in patients with early PD, but has not been established to be useful for differentiating PD from atypical parkinsonism. It is also expensive and not widely available for routine clinical use. A recent consensus panel argued against relying on dopamine imaging studies to differentiate PD from atypical parkinsonism or as a primary end point in clinical trials.[50]

Other imaging techniques have also been explored in an attempt to provide an objective method for diagnosing PD. Hyperechogenicity in the SNc on transcranial sonography has been reported to be more prominent in patients with PD than in controls,[54,55] but has not demonstrated sufficient reliability for use in clinical diagnosis of an individual patient. Interestingly, a hyperechogenic signal abnormality in the SNc is observed in 9% of the healthy population,[55] about the same proportion as reported to have incidental Lewy bodies at postmortem. It will be interesting to determine if this change is a marker of individuals who are at increased risk for developing PD.

MRI studies can be useful in evaluating patients with possible MSA. T2-weighted images in patients with MSA can demonstrate one or more findings of high-signal abnormality in the external capsule, low signal change (representing iron accumulation) in the posterior putamen, and cerebellar atrophy.[56,57] Although these changes may help support the diagnosis of MSA in an individual patient, their absence does not exclude the diagnosis. Conversely, MRI studies showing atrophy of the putamen and cerebellum are relatively reliable in diagnosing olivopontocerebellar atrophy (MSA-C). Bilateral high-signal abnormalities in the GPi and substantia nigra pars reticularis (SNr) on T1-weighted MRI are an indication of manganese accumulation and can be seen in patients with liver failure, manganese injection, or occupational exposure.[58]

Cardiac metaiodobenzylguanidine (MIBG) SPECT imaging of the heart provides a measure of cardiac sym-

pathetic innervation and may be useful in differentiating PD from MSA.[59] MIBG-SPECT is consistently abnormal in patients with PD and consistently normal in those with MSA or PSP.[60] Cardiac denervation can be observed at an early stage in PD and can be independent of any clinical features of autonomic dysfunction.[61] These observations suggest that MIBG-SPECT may be useful in the early diagnosis of PD and in differentiating PD from atypical parkinsonism.

With the development of the Pittsburgh Compound-B ([(11)C]-PIB), which binds to β-amyloid and can be used as a PET ligand for measuring plaque load in patients with Alzheimer disease (AD),[62] an intense effort has been directed toward developing a similar ligand that binds to α-synuclein and can be used for imaging in PD. Although this concept has attracted considerable commercial attention, it has proved to be a technical challenge because, unlike β-amyloid, α-synuclein is localized primarily within the cell, and labeling this molecule would require development of a positron-emitting compound that is soluble, enters the brain, enters nerve cells, binds to α-synuclein, and is nontoxic. Laboratory evidence shows that [(11)C]-PIB can bind to β-amyloid fibrils in Lewy bodies,[63] but preliminary studies in patients with early PD show no differences from controls.[64] The ability to image α-synuclein may permit an early diagnosis of PD, differentiation from other forms of parkinsonism, and detection of PD pathology before the emergence of the classic motor features of the disease. This would also be of enormous value in defining the natural pattern and rate of progression of PD and would permit the early identification of patients for disease-modifying therapies should they become a reality. This development is anxiously awaited.

Genetic testing. Genetic testing might have value in identifying patients with PD who carry a known mutation and individuals at risk for developing PD. Several different gene mutations have been linked to PD,[65] but most occur in small numbers of familial cases and are not likely to be useful for screening in the general population, where most cases are thought to occur sporadically. However, it is now appreciated that mutations in the leucine-rich repeat kinase 2 (*LRRK2*) gene, which were described in individuals with autosomal dominant PD, are also present in patients with a late-onset, sporadic form of the disease who do not have a positive family history and have classic neuropathology at postmortem.[66] Indeed, high percentages of Ashkenazi Jews and North African Arabs who have PD carry this mutation.[67,68] On the basis of these findings, investigators have now begun to test the validity and potential usefulness of *LRRK2* mutation test for diagnosing PD.[69] Although the test seems to be diagnostic in those with PD, it remains uncertain how predictive the test will be in asymptomatic individuals as many with this mutation do not develop PD and its penetrance rate is currently unknown. Mutations in the galactocerebrosidase gene found in Gaucher disease are also associated with a high risk of PD, particularly in Ashkenazi Jewish patients, and could be used for screening in appropriate individuals.[70] Genetic studies are also focusing on multigene markers that may be associated with an increased susceptibility for developing PD.[71] These studies are aimed at identifying gene expression signals in the blood that could eventually be used as trait or state biomarkers of PD. In any consideration of genetic testing, it is important to ensure that informed consent has been obtained, and that appropriate counseling and support services are available.

Diagnostic challenges. The challenges that occasionally arise in diagnosing PD in an individual case may reflect the pathologic heterogeneity of the disorder and the fact that PD may not be a single disease. The notion that PD represents a single nosologic disease entity characterized pathologically by the presence of Lewy bodies in the substantia nigra is now being challenged.[16] Several different gene mutations have now been associated with familial forms of PD.[65] Furthermore, the majority of PD cases occur sporadically, where the cause has not been established and there is no certainty that these are due to a single cause. Epidemiologic studies suggest that environmental factors likely play a major role,[72] but mutations in the LRRK2 gene have been described in patients with classic clinical and pathologic features of the disease who do not have a positive family history and who are indistinguishable from patients with sporadic PD.[66] It is, thus, possible that sporadic cases are related to a combination of genetic and environmental factors, which may vary in different individuals. Thus, genetic factors may contribute to, or underlie, even late-onset cases that are thought to be sporadic in origin and require an environmental trigger to be expressed. The pathologic picture of PD is equally complex. Lewy body pathology can be seen in several conditions other than PD (e.g., infantile neuroaxonal dystrophy, Hallervorden-Spatz syndrome, subacute sclerosing panencephalitis, and Down syndrome). Some patients with classic clinical features of the disease do not show typical PD pathology,[73] and as many as 30% of aged individuals who did not have neurologic abnormalities during life have incidental Lewy bodies at postmortem.[74] Furthermore, patients with PD from the same family and with the same LRRK2 gene mutation have been shown to have different pathologies, with some showing typical PD pathology with Lewy bodies, some having no Lewy bodies, and others having tau

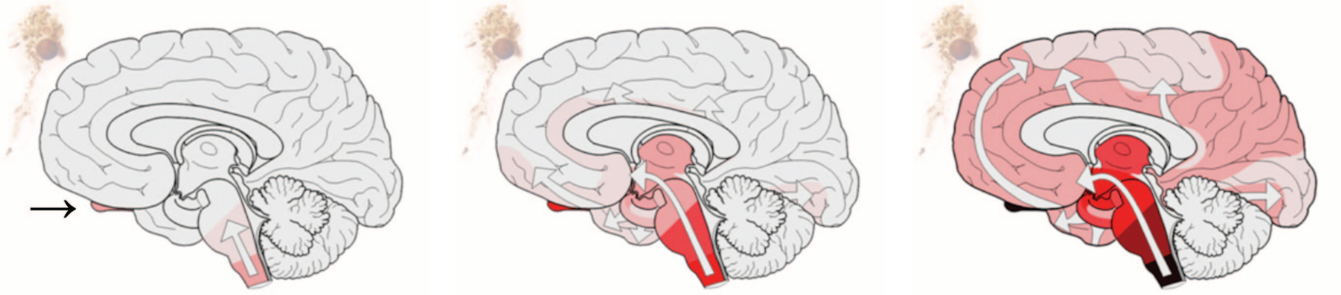
inclusions.[75] It is, therefore, hard to argue that PD is a single condition with a singular etiology and pathology. The significance of the Lewy body is also being questioned. Although Lewy bodies were once considered to be toxic and a contributing cause of cell death, it is now argued that Lewy bodies are a variant of an aggresome and represent a protective response to attempt to facilitate the clearance of high levels of misfolded proteins.[76] These challenges to our traditional ways of thinking about PD have fueled the search for a common mechanism of neurodegeneration that might underlie many potential causes of PD and represent a target for a therapy that would be applicable to patients with different forms of the disorder.[77]

Preclinical diagnosis of PD. Recent studies suggest that it may now be possible to identify PD in its nascent form, when the cardinal manifestations are minimal or even absent. PET studies suggest that neuronal dysfunction likely begins well before the cardinal motor manifestations of the disease are detectable.[78] Furthermore, PD is now appreciated to be associated with widespread nondopaminergic neuropathologic abnormalities, which appear to develop before the onset of the classic dopaminergic features of the disease. Pathologic studies by Braak et al.,[5] based on autopsies performed on a large series of individuals, suggest that α-synuclein accumulation in the SNc is a relatively late pathologic development in the course of PD, occurring only after changes have already developed in the lower brainstem and olfactory regions. The Braak staging of brain pathology in PD is provided in figure 3. Clinical studies similarly suggest that olfactory changes, constipation, and RBD are risk factors for the emergence of the more classic motor features of the disease.[26] For example, the prospective longitudinal Honolulu Heart Study showed that constipation increased the risk of developing PD by as much as 4.5-fold.[79] RBD is frequently associated with dopaminergic changes on PET imaging even when patients have no parkinsonian features,[80] and as many as 50% of patients with RBD go on to develop PD.[81,82]

The anterior olfactory region is a common and early site of pathology in PD, and anosmia is frequently found in patients with PD in all stages of the disease.[83] Studies in asymptomatic first-degree relatives of patients with PD found that the presence of anosmia markedly increased the risk that a subject would have reduced β-CIT uptake on SPECT and would ultimately be diagnosed with PD. A prospective study showed that 10% of hyposmic first-degree family members and almost half of the asymptomatic relatives of patients with PD who had hyposmia and an abnormal dopaminergic scan developed PD within 2 years, whereas PD did not develop in any of the relatives without anosmia during this same time period.[84] Indeed, it has been proposed that these features may represent more than risk factors. Their frequent appearance in patients who later develop the classic motor features of PD coupled with corresponding pathologic changes which seem to antedate degeneration of dopamine neurons, raises the possibility that they may actually represent an early phase of the disease process itself.[26]

Identifying PD before the onset of motor dysfunction might permit a putative disease-modifying therapy to be initiated at a stage when the agent might be more effective and have a greater impact on the natural outcome of the disease. We have proposed the term "Parkinson Associated Risk Syndrome," or "PARS," to describe individuals who have identifiable markers that place them at a high risk for developing PD or who might actually have an early stage of the disease.[85] These markers include olfactory loss, gastrointestinal dysfunction, RBD, abnormalities in striatal or cardiac dopamine neuroimaging, neuropsychological profiles, and genetic factors. Studies are currently under way to deter-

Figure 3 **Staging of α-synuclein pathology thought to be associated with the evolution of PD, based on work by Braak et al.[5]**



This hypothesis suggests that pathologic changes are first noted in the olfactory region and lower brainstem, and only later extend to involve dopamine neurons in the SNc (Courtesy of Heiko Braak).

mine the feasibility of screening large numbers of individuals to detect those at a high risk for developing PD for participation in neuroprotective trials. Indeed, it may be essential to introduce a neuroprotective therapy at an early stage, before the development of irreversible neurodegenerative changes.

PHARMACOLOGIC TREATMENT OF PD

Neuroprotection. Neuroprotection or disease modification in PD can be defined as an intervention that protects or rescues vulnerable neurons and thereby slows, stops, or reverses disease progression. At present, no agent has been conclusively demonstrated to have a neuroprotective or disease-modifying effect in PD, although there are many promising candidate agents based on laboratory studies. Several of these agents have shown positive results in clinical trials, but they cannot be unequivocally determined to be neuroprotective as confounding effects cannot be excluded.[86] Thus, the decision to use a putative neuroprotective agent in a given individual is based on a combination of available scientific data, physician judgment, and patient philosophy. If it is decided to use such an agent, it makes sense to introduce it at the time of diagnosis. Indeed, if a therapy could be established to slow or prevent disease progression, it would heighten the need to identify at-risk individuals so that the disease-modifying therapy could be initiated even before the development of the classic motor features of the disease.

Etiopathogenesis of PD. In an attempt to define a neuroprotective therapy for PD, understanding the cause of cell death would be of enormous value. Ideally, it would be best to identify a single etiology or pathogenic mechanism that could be targeted by a specific intervention. However, it now seems that many different etiologic factors may be capable of causing PD. Indeed, multiple factors may contribute to the development of PD in a given individual. Considerable evidence supports a role for both genetic and environmental factors in the etiology of PD.

Approximately 5% to 10% of patients with PD have a familial pattern of inheritance, and to date, linkage has been reported with 11 different genes, with several specific gene mutations having been identified (table 3).[65,87] Familial PD has been described in association with mutations in *α-synuclein*,[88] ubiquitin carboxy-terminal hydrolase L1 (*UCH-L1*),[89] *parkin*,[90] *DJ-1*,[91] PTEN-induced kinase 1 (*PINK1*),[92] *LRRK2*,[75,93] and, more recently, in the genes encoding for Omi/HtrA2[94] and ATP13A2.[95] Most gene mutations have been observed in small numbers of familial cases and do not seem to account for the large majority of individuals in whom PD occurs sporadically. Epidemiologic studies suggest that genetic factors are not likely to play a major role in the majority of cases that occur sporadically,[72]

Table 3 Gene mutations and familial PD

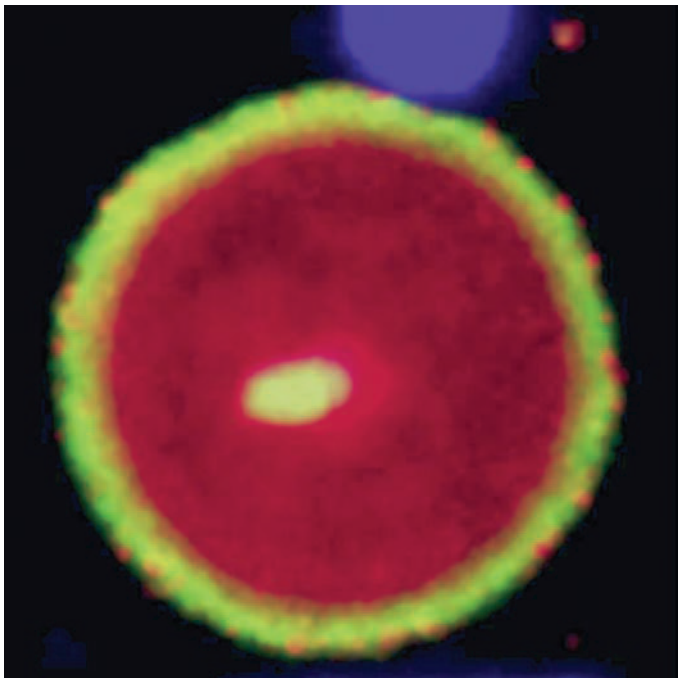
Name	Chromosome	Locus	Gene
Park 1	Chr 4	4q21-23	*α-synuclein*
	Chr 4	4q21-23	*dupl/trip*
Park 2	Chr 6	6q23-27	*parkin*
Park 3	Chr 2	2p13	Unknown
Park 4	Chr 4	4p15	Unknown
Park 5	Chr 4	4q14-15	*UCH-L1*
Park 6	Chr 1	1p35-36	*PINK1*
Park 7	Chr 1	1p36	*DJ-1*
Park 8	Chr 1	12p11	*LRRK2*
Park 9	Chr 1	1p36	Unknown
Park 10	Chr 1	1p32	Unknown
Park 11	Chr 1	2q36-37	Unknown

PD = Parkinson disease.

although no single environmental factor has yet been established to cause PD. Furthermore, there are now reports of patients with sporadic PD who have typical clinical and pathologic features with no family history and were found to have LRRK2 mutations.[66] Indeed, it is estimated that LRRK2 mutations account for 2% to 3% of patients with "sporadic" PD in white populations, and as many as 30% to 40% of cases in Ashkenazi Jews and North African Arabs.[67,68] It is indeed possible that most cases of sporadic PD will turn out to result from a combination of different genetic susceptibility and environmental factors, but this has not been established, and the full extent of the role played by genetic and environmental factors in the etiology of PD is not yet known.

The first mutation identified in PD was in the *α-synuclein* gene located on chromosome 4q21-q23, resulting in a substitution of an alanine for a threonine at position 53 (A53T).[86] A30P and E46K mutations were subsequently identified in PD families, confirming the relevance of these mutations to the development of PD. More recently, PD has been described in patients with duplication[96] and triplication[97] of the wild-type *α-synuclein* gene, showing that overexpression of the normal protein can also cause the disease. Patients with α-synuclein mutations have an autosomal dominant inheritance pattern and a relatively young-onset form of PD. At postmortem, α-synuclein pathology is prominent, but is confined primarily to neurites rather than localized within cell bodies in the form of discrete Lewy bodies. α-Synuclein is a soluble, natively unfolded protein, which is prone to oligomerize and form insoluble aggregates. This raises the possibility that critical mutations or excess levels of wild-type protein cause this protein to misfold, accumulate within the cell, and induce cell death. The finding that α-synuclein is a

Figure 4 Lewy body in a residual dopamine neuron stained for ubiquitinated proteins (red) and α-synuclein (yellow).



Note that α-synuclein accumulates in a peripheral location, suggesting that this may occur late in the process. The cell nucleus is stained blue. Courtesy of Dr. Kevin McNaught.

key component of Lewy bodies in patients with sporadic PD[98] suggests that accumulation of this protein may somehow be related to the cause of cell death in sporadic PD as well (figure 4). Indeed, overexpression of both mutant and wild-type α-synuclein can induce motor changes and degeneration of dopamine neurons in drosophila.[99] It is noteworthy, though, that overexpression of mutant α-synuclein does not lead to PD pathology in transgenic mice, possibly because of species differences in metabolism of the α-synuclein protein.[100] Greater success in replicating PD pathology and behavioral effects has been accomplished with gene delivery of α-synuclein to mesencephalic dopaminergic regions in both rodents and primates.[101]

Mutations have also been described in the gene on the long arm of chromosome 6 that encodes for the protein parkin.[90] These patients have an autosomal recessive, young-onset form of PD and typically have disease onset before the age of 40 years. Clinically, they demonstrate the classic motor features of the disease, but frequently experience diurnal fluctuations with intermittent periods of improvement and worsening. They are exquisitely sensitive to levodopa and are particularly prone to develop motor complications. Pathology demonstrates severe neuronal degeneration confined to the SNc and locus coeruleus, typically without Lewy bodies. Parkin has been demonstrated to be an ubiquitin ligase, and mutant forms of parkin lose this activity.[102] Ubiquitin ligases attach ubiquitin to misfolded proteins to signal for their transport to the proteasome for degradation. Thus, parkin mutations might lead to cell death as a consequence of impaired clearance of unwanted proteins.

Mutations in the UCH-L1 protein have been described in two siblings,[89] and there is some question as to whether this mutation is a real cause of PD. It is of interest, though, because the enzyme is responsible for cleaving ubiquitin from ubiquitinated proteins, which permits their entry into the proteasome for degradation. Mutations in *UCH-L1* interfere with this function and cause protein accumulation, inclusion body formation, and cell death in laboratory models.[103]

Mutations in *DJ-1*[91] and *PINK1*[92] are associated with an autosomal recessive, young-onset form of PD that has been linked to mitochondrial dysfunction (see discussion later). *LRRK2* mutations[75,93] are associated with a wide range of PD phenotypes, including young-onset PD, a clinical picture typical of sporadic PD, and a syndrome characteristic of dementia with Lewy bodies (DLB). Interestingly, patients in the same family and with the same *LRRK2* mutation may demonstrate pleomorphic clinical presentations and pathologies.[75] This gene mutation has attracted considerable attention because it is emerging as the most common cause of familial PD and also because it can be identified in patients with seemingly sporadic PD who do not have a positive family history.[66] The precise mechanism whereby *LRRK2* mutations cause PD remains unknown, but recent studies indicate that LRRK2 has kinase[104] and GTPase[105] activities, and that mutations are associated with reduced GTP hydrolysis and altered kinase activity.[105] These observations suggest that cell death may relate to altered phosphorylation of target proteins.

Despite these observations, it is by no means clear that the majority of cases that occur sporadically are genetic in origin. A large epidemiologic study suggests that genetic factors do not play a role in patients with PD beginning after the age of 50 years, who comprise the bulk of cases.[72] This study used the US National Research Council World War II Veteran Twin Registry maintained by the National Academy of Sciences to assess concordance of PD in monozygotic and dizygotic twins. For patients with PD onset before the age of 50 years, concordance for PD was significantly greater in monozygotic than dizygotic twins, consistent with the notion that genes play a major role in these patients. However, for patients with PD with onset after the age of 50 years, the concordance rate was not different in the two groups, suggesting that environmental factors are likely to be more important in cases of sporadic PD. Furthermore, a high-resolution whole-genome association

study genotyped 198,345 uniformly spaced and informative single-nucleotide polymorphisms (SNPs) in 443 sibling pairs discordant for PD and identified 13 SNPs that seemed to be associated with PD.[106] However, these 13 SNPs were not found to be significantly associated with PD in a comparison of 5,526 PD cases and 6,682 controls.[107] Most recently, genome-wide genotyping was performed in a cohort of 267 patients with PD and 270 neurologically normal controls using more than 408,000 unique SNPs.[108] Two hundred twenty million genotypes were performed in the 537 individuals, and no significant associations were detected between genetic variations and PD. The authors concluded that PD is not primarily a genetic disease and that environmental factors must be the major determinant.

Epidemiologic studies have suggested that a variety of environmental factors might be risk factors for developing PD; the most consistent findings have been rural living, and exposure to well water, pesticides, herbicides, and wood pulp mills.[109-111] Cases of acute, transient PD-like syndromes have also been reported in association with infectious agents.[112] The finding that a PD-like syndrome developed in addicts who injected themselves with the synthetic meperidine derivative MPTP provided support for the environmental hypothesis,[113] but subsequent studies have failed to identify any link between exposure to this class of compounds and sporadic PD. Chronic administration of the pesticide rotenone and the proteasome inhibitors PSI and epoxomicin have also been reported to selectively damage nigral dopaminergic neurons and to induce a PD-like syndrome in rodents.[114,115] To date, however, no toxic or environmental agent has been definitively established to be a cause of sporadic PD. Interestingly, there is an inverse relationship between the risk of developing PD and coffee and caffeine consumption and smoking,[116,117] although the mechanism responsible for how these might lower the risk is unknown, and the possibility that these might reflect confounding symptomatic effects associated with these agents has not been excluded. Thus, the cause of the large majority of PD cases is currently unknown, and it remains uncertain whether they are even due to a single cause. The possibility of a complex interaction among multiple genes and proteins that may vary in different individuals has attracted considerable interest. The "double hit hypothesis" suggests that patients might develop PD if they are exposed to a particular toxin and carry a susceptibility gene. This hypothesis suggests that a gene defect or exposure to the environmental toxin alone is not sufficient to induce clinical PD.

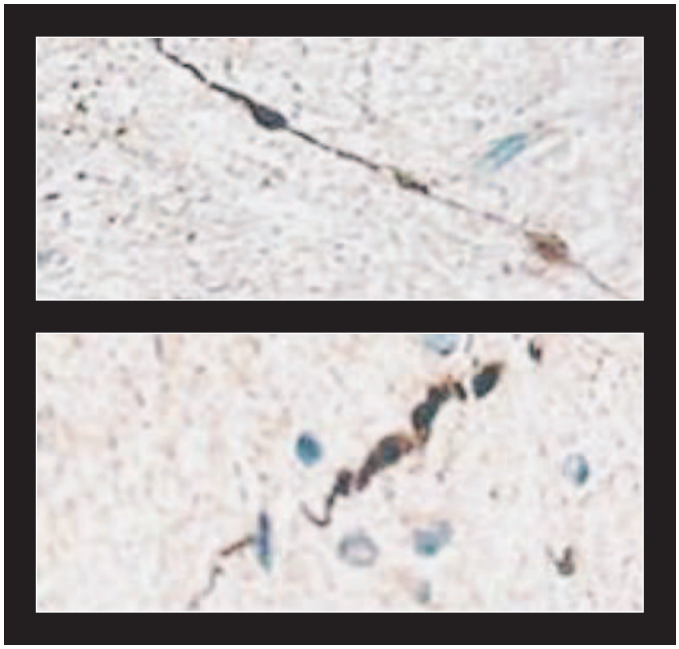
In efforts to define targets for neuroprotective therapies, most interest has focused on efforts to block pathogenic factors that contribute to cell death. Factors that have been implicated include oxidative stress, mitochondrial dysfunction, excitotoxicity, and inflammation[10,11,118,119] (detailed reviews of each of these factors can be found in Ref. 119). Each of these pathogenic factors represents a potential target for a neuroprotective therapy. However, after more than a decade of intensive research, it remains uncertain whether any one or more of these factors is a primary cause of cell degeneration, is secondary and only contributes to the pathogenic process, or is merely an epiphenomenon and of no pathologic significance. It is possible that cell death occurs as a consequence of a complex interaction between a network of pathogenic factors that vary in different individuals and in which no single factor is of critical importance in all patients. Alternatively, cell death may occur by way of a different process that is currently not defined. Obviously, resolving these issues is of great importance in developing a neuroprotective therapy.

Regardless of the etiology and pathogenic mechanism responsible for the neurodegenerative process, there is considerable evidence indicating that cell death in PD occurs by way of a signal-mediated apoptotic process.[120,121] Apoptosis is a form of cell death that is characterized by chromatin clumping and fragmentation of DNA, with a relative absence of inflammation. Apoptosis was initially described in embryonic and developmental stages, and thought to represent a means of eliminating unnecessary neurons. However, apoptosis is now known to occur in response to a number of PD-related toxins and to occur in a variety of neurodegenerative diseases, including PD. Apoptosis is commonly associated with mitochondrial dysfunction and involves a sequence of events that include a fall in mitochondrial membrane potential, opening of the mitochondrial permeability pore, release of apoptosis-initiating factors such as holocytochrome c into the cytosol, and activation of caspases with consequent fragmentation of DNA and cell death.[122] Nigral neurons may be at particular risk for undergoing apoptosis because free radical species derived from the oxidative metabolism of dopamine can promote mitochondrial damage and opening of the mitochondrial pore. This propensity to undergo apoptosis may be increased by the oxidative stress and mitochondrial defects that have been described in the SNc in PD.[123,124] Signals that mediate apoptosis provide targets for the development of antiapoptotic agents that might be neuroprotective in PD regardless of the specific etiology or pathogenesis of the cell death process. Mitochondrial damage due to calcium cytotoxicity has attracted recent attention, with the observation that, with aging, dopamine neurons convert from using sodium channels to 1.3 L-type calcium channels to maintain their pacemaker activity. This process permits increased

calcium to enter the cell and increases the risk of excitotoxic damage. Calcium channel blockers reverse this process and protect dopamine neurons in in vitro studies.[125] In this regard, it is interesting that the laterally placed SNc dopamine neurons, which are most vulnerable to degeneration in PD, are relatively deficient in the calcium-binding protein calbindin, in comparison with neurons in the ventral tegmental area, which are relatively spared.[126]

Attention has also focused on the possibility that cell death in PD might result from proteolytic stress due to impairment in the capacity of affected cells to clear misfolded and other unwanted proteins. Genetic or environmental factors could lead to increased production of mutant or damaged proteins and/or diminished clearance due to impairment of the ubiquitin-proteasome or autophagy systems. Under these circumstances, abnormal proteins could accumulate, oligomerize, aggregate, and impair critical cell functions leading to apoptosis. The idea that PD might be related to proteolytic stress is not surprising, as the disease is characterized by the presence of Lewy bodies and Lewy neurites, which are primarily comprised of abnormal protein aggregates. The major system for clearing unwanted proteins from eukaryocytic cells is the ubiquitin-proteasome system.[127] Here, unwanted proteins are tagged with chains of ubiquitin that signal for their proteasomal degradation. Abnormal proteins can also be cleared by lysosomes through a process known as autophagy.[128] Alternatively, proteins can be segregated in aggresomal inclusions that facilitate their degradation. It has been proposed that Lewy bodies are variants of aggresomes and, in this respect, are thought to be protective rather than toxic, as has been considered historically.[129]

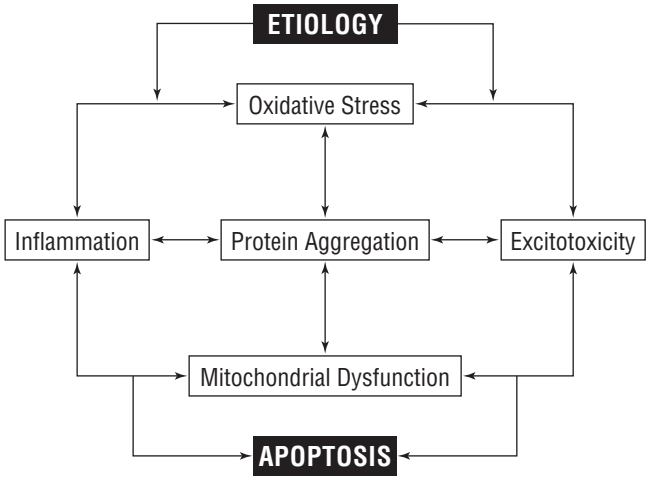
Figure 5 **Lewy neurites stained for ubiquitin protein complex in a patient with PD. Courtesy of Dr. Kevin McNaught.**



The possibility that cell death in PD relates to proteolytic stress is supported by recent genetic and pathologic findings.[130] Mutations or excess levels of wild-type α-synuclein are prone to misfold.[131] This, in turn, can promote self-aggregation of the protein, aggregation of other wild-type proteins, and inhibition of proteasomal function, further restricting protein clearance.[132] Test tube studies indicate that dopamine promotes the formation of toxic α-synuclein protofibrils, perhaps explaining the specific vulnerability of SNc neurons.[133] Parkin is an ubiquitin ligase that attaches ubiquitin to substrate proteins, which signal for their transport to the proteasome for degradation.[127] Mutations in parkin could impede this process and result in the accumulation of misfolded proteins. Indeed, increased levels of nonubiquitinated protein substrates of parkin accumulate in the SNc of patients with PD who carry this mutation.[134] UCH-L1 is an enzyme that cleaves ubiquitin from protein adducts. Mutations in UCH-L1 that are associated with familial PD can prevent deubiquitination of proteins and thereby prevent their entrance into the proteasome.[89] Furthermore, this mutation could limit the availability of ubiquitin monomers necessary for the clearance of additional misfolded proteins. Inhibition of UCH-L1 causes degeneration of cultured dopamine neurons coupled with the formation of inclusions that stain for α-synuclein and ubiquitin.[103] In addition, there is evidence of proteasomal dysfunction in patients with sporadic PD.[135] First, PD is associated with massive accumulation of ubiquitinated proteins in nerve terminals and cell bodies (figure 5). In addition, there is decreased expression of proteasomal alpha subunits and reduced activity of each of the proteasomal enzymes in the SNc of patients with PD.[135] In the laboratory, proteasome inhibitors induce a selective degeneration of dopamine neurons coupled with the formation of inclusion bodies that stain positively for α-synuclein and ubiquitin.[103,136] Furthermore, systemic administration of proteasome inhibitors has been reported to cause a model of PD in rats that replicates both the dopaminergic and nondopaminergic pathology of PD.[115] Although this potentially represents an extremely important model of PD, several investigators have not been able to replicate these results,[137,138] although others have reproduced key features of the model.[139-141] The reason for these differing results remains unknown.

The concept that proteolytic stress contributes to cell death in PD suggests novel targets for putative neuroprotective therapies. Heat shock proteins (especially HSP70) are chaperones that promote both the refolding and the degradation of misfolded proteins.

Figure 6 **Schematic illustration of factors that might be involved in the pathogenesis of cell death.**



This flowchart attempts to demonstrate that multiple factors may contribute to the cascade of events leading to cell death in patients with PD and that different factors might be more important in different individuals. Adapted from Olanow.[10]

HSPs have been shown to protect against dopamine nerve cell death induced by overexpression of α-synuclein.[142,143] Similar results can be seen with drugs such as geldanamycin, which block inhibition and promote upregulation of endogenous HSP70.[144,145] It has also been observed that a nontranscriptional increase in phosphorylated p53 mediates cell death after proteasome inhibition, and this can be prevented by p53 inhibitors such as pifithrin-α or by RNA inhibition.[146] This may be particularly relevant to PD, because p53 expression has been shown to be increased in the SNc of patients with PD.[146]

Mitochondrial dysfunction was also implicated in cell death with the discovery that there is a selective defect in activity of complex I of the respiratory chain in SNc neurons in PD.[124] Genetic studies suggest that mitochondrial dysfunction may play a key role in cell death in PD.[147] Mutations in *PINK1* encode a putative serine/threonine kinase with a mitochondrial targeting sequence. Knockout of the *PINK1* homologue in drosophila leads to morphologic changes in mitochondria, with dopamine cell loss.[148,149] Defects in the *parkin* gene induced by knockout or by RNA interference also lead to alterations in mitochondrial morphology with dopamine neuronal degeneration and enhance the degree of mitochondrial damage seen with *PINK1* mutations.[149,150] Overexpression of wild-type parkin restores mitochondrial morphology in *PINK1* mutant drosophila, suggesting that PINK1 and parkin act in a common pathway that is critical for normal mitochondrial function.[150] Evidence also suggests that DJ-1 acts as a sensor of oxidative stress in mitochondria, and that this function is lost when the protein is mutated.[91] LRRK2 is bound to the outer membrane of the mitochondria, and immunoprecipitation studies demonstrate an interaction with parkin, again suggesting there may be a common pathway for cell death that involves mitochondria.[151]

Although neither the cause nor the pathogenesis of cell death in PD is known, studies using mutations known to be associated with the development of PD provide potential insights into how cell death in PD might occur and targets for putative neuroprotective therapies (see review in Ref. 12). It is hoped that these different mutations cause cell death through a common pathway whose identification could provide an enormous step forward in defining relevant targets for neuroprotective therapies in PD. The situation may, however, be more complex. It is possible that cell death results from an interactive network of pathogenic factors in which no one component is essential and where the initiating pathogenic factor may vary in different individuals (figure 6). Indeed, laboratory studies demonstrate that oxidative stress can damage mitochondria and proteasomes,[152–154] mitochondrial dysfunction leads to oxidative stress and proteasomal damage,[155,156] and proteasomal dysfunction causes oxidative stress and mitochondrial dysfunction.[155,157,158] Furthermore, it has been shown that oxidative stress and proteasome inhibition act synergistically to promote protein misfolding.[154,159] These observations have important therapeutic implications and raise the possibility that a cocktail of agents directed against multiple different pathogenic processes may be necessary to achieve neuroprotection in PD.

Clinical trials of putative neuroprotective agents. On the basis of the current concepts of the pathogenesis of cell death in PD, it has been postulated that interference with one or more of these factors might block the cascade of events leading to neurodegeneration and provide a disease-modifying effect. Many potentially promising approaches have not yet been tested in patients with PD. For example, there is evidence of inflammatory change in the SNc in PD, and retrospective epidemiologic studies suggest that exposure to nonsteroidal anti-inflammatory drugs reduce the risk of developing PD.[160-162] Additionally, clinical trials testing approaches designed to prevent or reverse proteolytic stress have not yet been performed in patients with PD. However, several putative neuroprotective agents have been tested in placebo-controlled clinical trials. A partial list of possible targets and candidate neuroprotective agents is listed in table 4.[86] Some clinical trials had negative outcomes despite promising theoretical or preclinical evidence. These include the antioxidant vitamin E,[163] the glutamate release inhibitor riluzole,[164] the antiapoptotic agents TCH346[165] and CEP-1437,[166] and the neuroimmunophilins which are thought to act via a possible trophic mechanism.[167] Conversely, some putative neuroprotective agents have

Table 4	Candidate approaches to neuroprotection
Antioxidants	
	Free radical scavengers (vitamin E, glutathione, spin trap agents)
	Iron chelators
Antiexcitatory	
	Excitatory amino acid antagonists
	Glutamate release inhibitors (e.g., riluzole)
	Glutamate reuptake enhancers, nitric oxide synthesis inhibitors
	Poly(ADP-ribose) polymerase inhibitors
Calcium channel blockers	
Mitochondrial bioenergetics	
	Creatine, coenzyme Q10, ginkgo biloba, nicotinamide, carnitine
Anti-inflammatory agents	
	Nonsteroidal anti-inflammatory agents (e.g., minocycline, COX-2 inhibitors)
	Steroids
Antiapoptotic agents	
	Desmethylselegiline, TCH346, caspase inhibitors
	Agents that maintain closure of mitochondrial pore (e.g., cyclosporine)
Agents that prevent protein accumulation and aggregation	
	Heat shock proteins
	Geldanamycin
	Gene therapies that restore defective components of the ubiquitin-proteasome system
Trophic factors	
	Glial cell line-derived neurotrophic factor
	Neurturin
Cell-based strategies	
	Human fetal nigral transplantation
	Porcine fetal nigral transplantation
	Retinal pigment epithelial cells
	Dopamine neurons derived from stem cells

demonstrated significant benefits compared with controls, but still could not be unequivocally deemed to be neuroprotective because of the possibility of confounding symptomatic or pharmacologic effects. Although it is not possible to claim with certainty that any of these drugs are neuroprotective, many are routinely used by physicians based on the hope that they might slow disease progression. These agents, and the relevant clinical trials, are considered below.

Selegiline. Selegiline (Deprenyl, Eldepryl) is a selective, irreversible inhibitor of monoamine oxidase-B (MAO-B). Selegiline was the first drug to be tested as a putative neuroprotective therapy in patients with PD based on its capacity to protect dopamine neurons by inhibiting the MAO-B oxidation of MPTP[168,169] and blocking the formation of free radicals derived from the oxidative metabolism of dopamine.[123] Selegiline has been shown to protect dopamine neurons in vitro and in vivo from a variety of toxins.[170] Interestingly, neuroprotection seen in the laboratory with selegiline does not seem to depend on MAO-B inhibition, but rather on a propargyl ring that is incorporated within its molecular structure.[171-173] Furthermore, protection in model systems seems to be dependent on its principle metabolite desmethylselegiline (DMS) rather than on the parent compound.[174,175] It is now thought that DMS and other propargylamines act by binding to glyceraldehyde-phosphate dehydrogenase (GAPDH), an intermediary in glycogen metabolism.[173,176,177] GAPDH normally exists in a tetrameric form, bound to RNA stem loops. Under conditions of mitochondrial stress, nicotinamide adenine dinucleotide releases GAPDH from its binding site into the cytosol, where it translocates to the cell nucleus and blocks transcriptionally mediated upregulation of antiapoptotic and antioxidant molecules, such as Bcl-2, superoxide dismutase, and glutathione. Propargylamines such as DMS bind to a channel in the GAPDH tetramer and maintain it as a dimer, in which form it does not translocate to the nucleus, thereby permitting the compensatory upregulation of protective molecules to take place.

Several double-blind, placebo-controlled studies have tested selegiline in untreated patients with PD and demonstrated that the drug delays the emergence of motor dysfunction and disability compared with placebo.[163,178-180] In the Deprenyl and Tocopherol Antioxidative Therapy of Parkinsonism (DATATOP) study, selegiline delayed the development of disability necessitating the introduction of levodopa therapy in patients with PD,[163,179] consistent with the drug having a neuroprotective effect. However, posthoc analysis showed that selegiline has symptomatic effects that could have accounted for some, if not all, of these benefits.[181] In the Sinemet-Deprenyl-Parlodel (Sindepar) study, selegiline was again shown to be superior to placebo in untreated patients with PD.[180] Here, the primary end point was the change in UPDRS score between untreated baseline and a final visit that occurred after 12 months of selegiline treatment and 2 months of drug withdrawal. However, it is now known that selegiline and other antiparkinsonian drugs can have long-duration pharmacodynamic effects that can last for months,[182] and it is not certain that the duration of the washout period used in this study was sufficiently long. Clinical follow-up of the patients with DATATOP makes it clear that selegiline therapy does not halt disease progression.[183,184] However, long-term follow-up studies suggest that patients randomized to early treatment with selegiline have better long-term outcomes, with improved UPDRS scores and reduced freezing of

gait.[185-187] It is, thus, not possible to state conclusively that selegiline has a neuroprotective effect in PD, but this possibility has not been excluded.

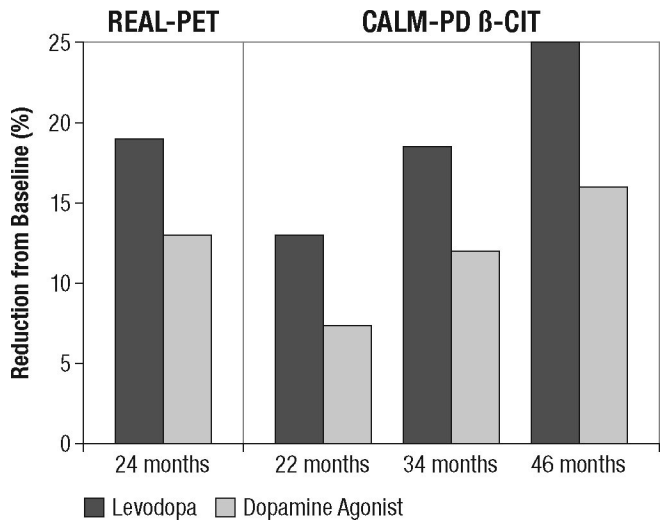
TCH346 (CGP3466B) is another propargylamine that has been studied in PD for its putative neuroprotective effects. In the laboratory, TCH346 provided powerful antiapoptotic effects similar to selegiline and DMS.[188-190] The drug does not inhibit MAO-B and therefore was anticipated to avoid the confounding symptomatic effects that were seen with selegiline. However, in a placebo-controlled, double-blind trial in untreated patients with PD, in which time to disability requiring levodopa was the primary end point, no benefit was observed with any of the three doses of TCH346 that were tested.[165]

Coenzyme Q10. Coenzyme Q10 is a cofactor for complex I, which acts as a bioenergetic and an antioxidant. It has been tested as a putative neuroprotective agent in PD based on laboratory studies showing that it protects dopamine neurons in PD models.[191] In a pilot study, patients were randomized to one of three doses of coenzyme Q10 or placebo.[192] The primary end point in this study was the change from baseline to final visit in UPDRS score. Patients receiving the highest dose (1,200 mg/day) showed a modest benefit compared with placebo. However, the study was underpowered and there was evidence of a possible confounding symptomatic effect. Coenzyme Q10 was not rejected as being futile in the NIH Exploratory Trials in PD study (NET-PD)[193] (see discussion later) and symptomatic effects were not detected in a double-blind study, although 300 mg/day was the highest dose tested.[194] Thus, the only possibility that coenzyme Q10 is neuroprotective cannot be excluded. A large-scale, double-blind trial is currently under way that will hopefully clarify the role of coenzyme Q10 in the treatment of PD. Despite the uncertainty over the role of coenzyme Q10 in PD, many physicians prescribe the drug because it is well tolerated at a dose of 1,200 mg, but it is not manufactured by traditional pharmaceutical companies and is not regulated by the US Food and Drug Administration (FDA).

Dopamine agonists. Dopamine agonists have been studied for putative neuroprotective effects in PD, based on their capacity to protect dopamine neurons from a variety of toxins.[195,196] Indeed, the dopamine agonist pramipexole has been reported to protect dopamine neurons in MPTP-lesioned primates.[197] Several possible mechanisms of action have been proposed, but most interest has focused on the potential of these drugs to block apoptosis. One set of studies demonstrated that dopamine agonists provide variable protective effects for dopaminergic cells against hydrogen peroxide toxicity through activation of a D2-receptor–mediated signaling pathway, which is linked to a PI-3 kinase (PI3-K)/AKT signaling pathway.[198,199] AKT has emerged as a focal point in signal transduction pathways, and has been shown to be important in mediating protective responses by inhibiting proapoptotic and activating antiapoptotic molecules.[200] More recently, studies have implicated the phosphorylation and inactivation of GSK-3β as being a key factor in neuroprotection induced by dopamine agonists.[200a] Interestingly, all D2 dopamine agonists tested had similar effects on activating G-proteins (thought to be responsible for the motor effects of D2 receptor stimulation), but individual agonists have different capacities to activate the PI-3K/AKT signaling pathway and to protect cultured dopamine neurons from oxidative stress.[198] This raises the exciting possibility that dopamine agonists that activate the same receptor and have similar motor effects may nonetheless have an individual intracellular signaling fingerprint and different potentials to activate other functional pathways within the cell. It should be appreciated that some studies have demonstrated that dopamine agonists can also protect dopamine neurons through mechanisms independent of the dopamine receptor.[201]

Clinical trials have attempted to test the capacity of dopamine agonists to provide disease-modifying effects in PD. To avoid a confounding symptomatic effect that would be anticipated with this class of agent, studies used a surrogate neuroimaging biomarker of nigrostriatal function as the primary end point. In the Requip as Early Therapy vs L-dopa-PET (REAL-PET) study, ropinirole was compared with levodopa using the rate of decline in striatal FD-PET as the primary end point.[202] In the Comparison of the Agonist Pramipexole vs Levodopa on Motor Complications of Parkinson Disease (CALM-PD) study, pramipexole was compared with levodopa using striatal β-CIT uptake on SPECT as the primary outcome measure.[203] In each of these studies, patients randomized to initial treatment with the dopamine agonist ropinirole or pramipexole had a reduced rate of decline in the imaging biomarker compared with those started on levodopa (figure 7). Because there was no placebo group, it could not be determined if this difference was due to a dopamine agonist–induced protective effect or to a levodopa-induced toxic effect. The picture is further confounded because patients treated with levodopa had better clinical outcomes, although it could be argued that this could be readily explained by the more prominent symptomatic effect of levodopa. It has also been suggested that the study interventions may have different regulatory or pharmacologic effects on the biomarker, that is, levodopa may induce greater internalization or downregulation of the biomarker than the

Figure 7 **Percent reduction in striatal uptake of imaging biomarker of dopaminergic function in the REAL-PET[202] and the CALM-PD β-CIT[203] studies.**



Note that in each of these trials, patients randomized to levodopa had a greater reduction than did those randomized to the dopamine agonist.

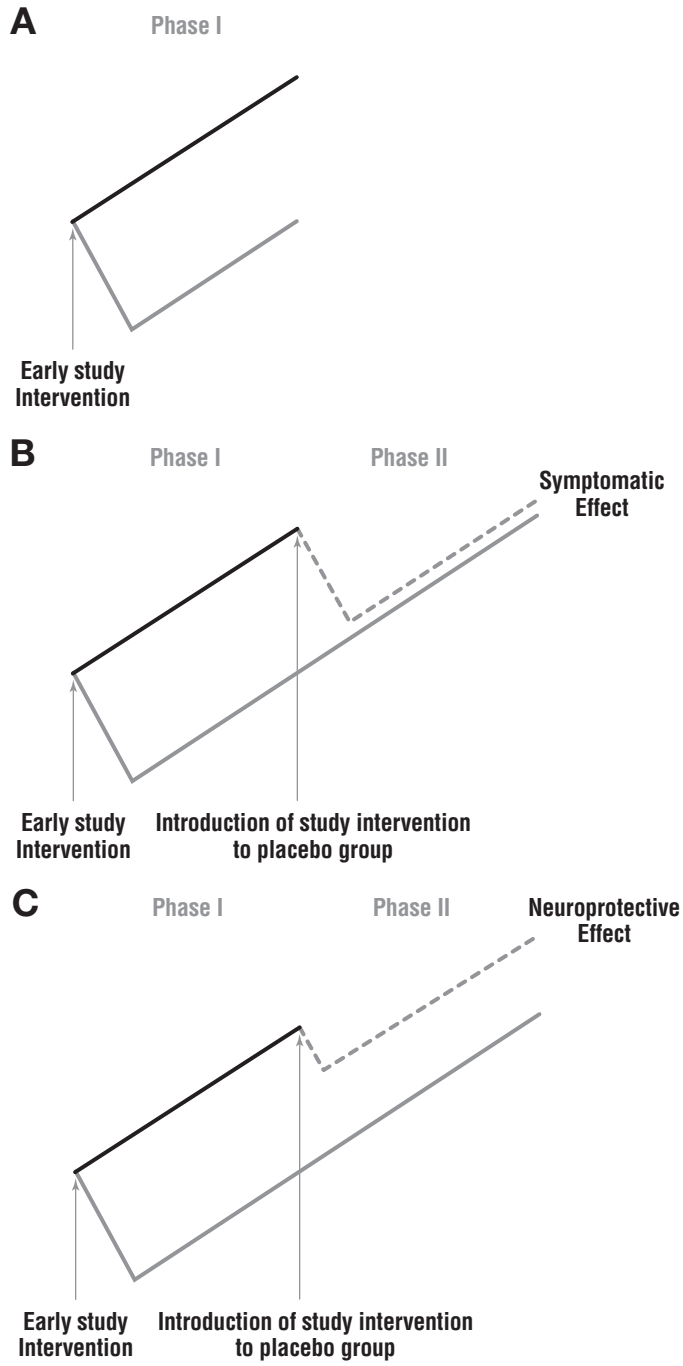
dopamine agonist, thereby accounting for reduced uptake and creating the false impression that there is a greater loss of dopaminergic neurons in levodopa-treated patients.[49] The Investigating Effects of Short-term Treatment With Pramipexole or Levodopa on β-CIT and SPECT Imaging in Early PD (INSPECT) study tried to resolve this issue by comparing the change in DAT binding between baseline and 12 weeks in patients randomly assigned to treatment with pramipexole, levodopa, or placebo. The study found no evidence of any short-term pharmacologic effect to account for the differences between levodopa and the dopamine agonists in the two clinical trials,[204] although a later occurring pharmacologic effect cannot be excluded. Although it still cannot be said with certainty that dopamine agonists have neuroprotective effects, this possibility has by no means been ruled out.

Rasagiline. Rasagiline (Azilect) is another selective, irreversible MAO-B inhibitor that has recently been approved for the treatment of PD. It also incorporates a propargyl ring within its molecular structure, and has been shown to provide protective effects for dopamine neurons in a wide variety of in vitro and in vivo model systems.[119,205,206] Rasagiline has also been shown to have antiapoptotic effects, and to act by binding to GAPDH, preserving mitochondrial membrane potential, and preventing activation of the caspase system.[207,208] Protection in model systems might also relate to the capacity of the drug to induce upregulation of trophic factors, such as brain-derived neurotrophic factor and glial cell line-derived neurotrophic factor, and to activate the PI3K/AKT signaling pathway.[209] Recent studies have demonstrated that the rasagiline metabolite aminoindan exerts protective effects that might also contribute to the benefits provided by rasagiline.[210]

To test for a possible neuroprotective effect in patients with PD, a novel study design, the "delayed start," was used in an attempt to avoid the confounding symptomatic effects seen with other clinical trial designs[211] (figure 8). The delayed-start study is conducted in two stages. In the first stage (approximately 6 to 9 months), drug-naïve patients are randomized to initiate therapy with the active study intervention or placebo. In the second stage (approximately 6 to 9 months), patients in both study groups receive treatment with the active study intervention. Differences between the study drug and placebo at the end of the first stage could be due to symptomatic or neuroprotective effects. However, benefits seen at the end of the second stage, when all patients are receiving the same medication, are not readily explained by a straightforward symptomatic effect and must somehow be due to the early initiation of the treatment intervention. The Rasagiline Mesylate [TVP-1012] in Early Monotherapy for PD Outpatients (TEMPO) study used this study design as an add-on to a 6-month efficacy trial,[212] and showed that benefits associated with early rasagiline treatment could not be equaled with the later introduction of the same drug[213] (figure 9). These results are consistent with rasagiline having a neuroprotective effect, although there are alternate explanations. It could be that early administration of a symptomatic drug prevents the loss of compensatory mechanisms, which having been lost cannot be restored. It is also possible that maladapted compensatory mechanisms might occur as a consequence of dopamine depletion and may be prevented by the early introduction of a dopaminergic therapy.

More recently, rasagiline has been tested in a large, prospective, multicenter trial using a delayed start design—the Effect of Rasagiline Mesylate in Early PD patients (ADAGIO) study—to further assess its potential effects on disease progression. Both 1 and 2 mg/day doses were tested. The primary endpoint included 3 hierarchal analyses which had to be met by the early start group in order to declare the study positive: a) superiority compared to placebo in rate of deterioration in UPDRS between weeks 12–36, b) superiority to delayed start in change between final visit at week 72 and baseline, and c) non-inferiority to delayed start in rate of deterioration between weeks 48–72.[213a] Rasagiline 1 mg/day met all 3 primary endpoints consistent with the possibility that the drug has a disease modifying effect.[213b] Rasagiline 2 mg/day failed to meet all 3 endpoints, possibly because the stronger symptomatic effect of the drug masked an underlying disease modifying effect. Long term extension studies are being planned. A delayed-start study design is also being used to test the

Figure 8 Schematic representation of a delayed-start study.



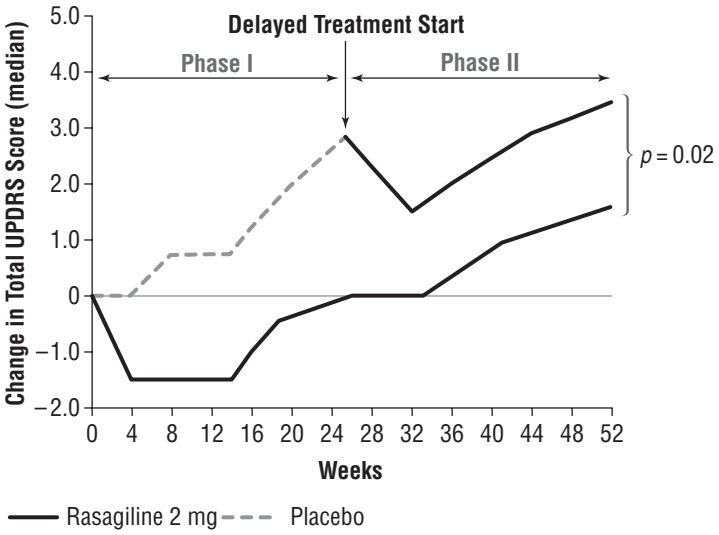
In the first phase, patients are randomized to early start with the active intervention or placebo (top panel, A). Differences between the groups at this time point could be due to symptomatic or neuroprotective effects. If this difference disappears during the second phase, when both groups are receiving the same treatment, this suggests that the differences in phase I were due to a symptomatic effect (middle panel, B). If, however, the differences persist at the end of phase II and the slopes do not converge, this is consistent with the intervention having a disease-modifying or neuroprotective effect (bottom panel, C).

potential disease-modifying effects of the dopamine agonist pramipexole in the Assessment of Potential Im**P**act of P**R**amipexole **O**n **U**nderlying **D**isease (PROUD) study.

Another approach to operationally defining neuroprotection is being used in the NET-PD study. Here, promising agents are screened in a "futility analysis," looking at change from baseline to 6 months in UPDRS score compared with placebo.[214] In contrast to traditional studies, the null hypothesis is that the drug is effective. If there is no difference between placebo and the study drug, the null hypothesis is rejected and the agent is considered to be futile. The intention is to reject agents that are not superior to placebo and to evaluate in more detail only those agents that have not been found to be futile. This approach has been used in stroke and cancer, but is somewhat problematic in PD because of the potential confounding symptomatic effect of study interventions. Among the agents tested so far, creatine has been selected for further study.[215] It is certainly possible that creatine could have confounding symptomatic effects, because it is known to enhance muscle strength and may improve a person's sense of well-being. A 2-year, prospective, double-blind trial showed that creatine did have some effect on mood and levodopa dose, although it had no effect on UPDRS scores or DAT binding on SPECT.[216] To try to get around short-term symptomatic effects, the NIH study will use the "long-term simple" study design. Here, patients are randomized to study intervention or placebo, treated with whatever additional medications are deemed necessary by the study investigator, and followed up for a relatively long period of time (approximately 5 years). The primary outcome measure is a composite end point that incorporates traditional motor features, as well as measures of gait, postural instability, freezing, dementia, and quality of life. Long-term benefits in cognitive function, gait, and quality of life in this outcome-oriented study would be welcome regardless of the responsible mechanism. Although the design is interesting, these are long and expensive studies that may not be practical for the pharmaceutical industry, where drugs have a limited patent life.

At present, no drug has been conclusively demonstrated to be neuroprotective in PD and none has received regulatory approval for this indication. The list of agents that look promising in the laboratory and that might provide neuroprotective effects in PD is daunting[217] (gene- and cell-based therapies will be considered in the experimental surgical approach section, page S66), and we are left with the challenge of determining how we will obtain the resources (patients and funds) to study so many promising therapeutic opportunities. It is disturbing that many agents that seem so promising in the laboratory cannot be determined to have a disease-modifying effect in clinical trials, even if they are shown to be superior to placebo. This failure could be related to targeting the wrong etiopathogenic mechanism, lack of a relevant animal model that reflects the etiopathogenesis and progressive course of PD, difficulty in calculat-

Figure 9 **The results of the TEMPO study,[212] which demonstrated that benefits seen at the end of phase I are still present at the end of phase II, when both groups of patients are receiving rasagiline 2 mg/day.**



These results are not readily explained by a symptomatic effect of the drug and are consistent with the agent having a disease-modifying effect. Adapted with permission Arch Neurol 59(12):1937–1973. Copyright © 2002 American Medical Association. All rights reserved.

ing the correct dose to use in a clinical trial, and lack of an outcome measure that accurately reflects the underlying disease state.[218] Hopefully, this situation is about to change. Molecular studies based on mutations associated with PD are already helping to delineate the mechanism responsible for cell death and should lead to the discovery of novel targets for the development of neuroprotective agents.[11,12] Transgenic animals that carry mutations known to be associated with PD are likely to be more relevant models for testing putative neuroprotective agents than are those that have traditionally been used (e.g., MPTP, 6-hydroxydopamine [6-OHDA]) and that may have little relevance to PD. In addition, transgenic models are likely to be progressive, which would permit testing of an intervention during the course of the disease process as it would be used in PD. Interestingly, this has not been as easy to achieve as was hoped, and no transgenic animal that has been developed to date precisely replicates the behavioral features or the dopaminergic and nondopaminergic pathology of PD.[219] New trial designs, such as the delayed-start and the long-term simple studies, may allow us to determine if a drug has influenced the course of PD without necessarily having to define its precise mechanism of action or demonstrating what specific effect it has on neuronal survival. A determination that early treatment provides a better long-term outcome, or that an intervention delays the emergence of disability related to nondopaminergic features such as falling and dementia, would be a welcome addition to the PD armamentarium. Such a drug would also likely receive regulatory approval with a label describing the benefits of the drug independent of its possible mechanism of action. Finally, we must consider that our failure to delineate a neuroprotective therapy for PD may be because we have been looking in the wrong direction and have not yet identified agents capable of providing protective effects in PD. As indicated above, it is also possible that cell death occurs by way of a network of events and that a cocktail of agents directed against multiple mechanisms will be necessary to achieve neuroprotection.

Pharmacologic agents used in the symptomatic treatment of PD. ***Levodopa.*** Levodopa is the most effective drug for the symptomatic treatment of PD and the gold standard against which new therapies must be measured. Indeed, no other medical or surgical therapy currently available has been shown to provide antiparkinsonian benefits superior to what can be achieved with levodopa. Virtually all patients with PD experience clinically meaningful benefits with levodopa treatment, with improvements in activities of daily living, quality of life, independence, and employability. Benefits are usually seen in all stages of the disease and can be particularly noteworthy in patients with early PD, in whom the drug can control virtually all of the classic motor features. Importantly, levodopa treatment is associated with decreased morbidity and mortality compared with treatment in the prelevodopa era,[220] although patients with PD continue to have mortality rates higher than age-matched controls.[221]

Levodopa is routinely administered in combination with a decarboxylase inhibitor, to prevent its peripheral conversion to dopamine and the development of side effects such as nausea, vomiting, and orthostatic hypotension due to stimulation of dopamine receptors in the area postrema that are not protected by the blood-brain barrier. In the United States, levodopa is combined with the decarboxylase inhibitor carbidopa and marketed as Sinemet. Dosage strengths of 10/100, 25/100, and 25/250 mg are available, with the first number representing the dose of carbidopa and the second number representing the dose of levodopa. In Europe, levodopa is combined with the decarboxylase inhibitor benserazide and sold under the trade name of Madopar; it is available in doses of 25/100 and 50/200 mg, as well as in a 25/100 mg water-dispersible tablet. Parcopa is an orally dissolving form of levodopa/carbidopa that requires no liquid intake and may be useful for patients with swallowing difficulties.[222] A combination of carbidopa/levodopa and the COMT inhibitor entacapone (Stalevo) is available and marketed in formulations containing 50, 75, 100, 150, and 200 mg of levodopa. A liquid preparation of levodopa can be

made from regular formulations of the agent by adding the drug to water in the presence of ascorbic acid; the preparation has to be freshly made and cannot be stored, however, and it has not been established to provide more rapid absorption than can be achieved with multiple oral doses of standard formulations of levodopa.[223] Sustained-release formulations of Sinemet (Sinemet CR) in doses of 25/100 and 50/200 mg, and Madopar (Madopar HBS) in doses of 50/200 mg, are available. A formulation that combines immediate- and controlled-release forms of levodopa in a single tablet (Vadova) has recently been approved in some countries. Methyl ester formulations of levodopa are also available in some countries and offer a possible advantage over traditional levodopa, in that they are more rapidly and predictably absorbed. This prodrug of levodopa has greater gastric solubility, rapid transit into the small intestine, and is rapidly hydrolyzed to form levodopa before absorption. The pharmacokinetic profile of these prodrugs suggests that they might provide more rapid and more predictable "on" episodes in fluctuating patients with PD who experience "delayed-on" or "no-on" responses (see later).[224] A gel preparation of levodopa (Duodopa) has been used for intraintestinal infusion of the agent and is available in many countries in Europe.[225] Parenteral forms of levodopa may be particularly valuable in the management of patients with PD who undergo surgery and cannot take medications orally.

Levodopa is absorbed in the small bowel by active transport through the large neutral amino acid (LNAA) pathway, and can be impaired by alterations in gastrointestinal motility and by dietary LNAAs, such as phenylalanine, leucine, and valine, which compete with levodopa for absorption through the LNAA.[226] Similar absorption problems can occur with Parcopa, which is absorbed through the intestine even though it dissolves in the mouth.[227]

Acute side effects associated with levodopa include nausea, vomiting, and hypotension. Levodopa is generally started at a low dose to minimize these risks. Patients are then gradually titrated to an effective dose over weeks or months. Traditionally, levodopa has been initiated two or three times daily using the lowest effective dose, although there have been no studies designed to determine the optimal way to administer the drug (see discussion later under levodopa-induced motor complications, page S22). In the early stages of the disease, motor control can usually be accomplished with a total daily dose of 300 to 400 mg/day. In some patients, larger dosages may be required to achieve a therapeutic benefit and levodopa doses of 1,000 mg/d or higher must be administered for several weeks or months before a patient can be said to be nonresponsive. Patients with PD who fail to respond to high doses of levodopa (>1,200 mg) probably have an atypical parkinsonism rather than PD and are unlikely to respond to other dopaminergic drugs.[228] Sustained-release formulations of levodopa are not as well absorbed as regular formulations, and doses 20% to 30% higher may be necessary to achieve the same clinical effect. It is usually best to administer levodopa when the patient has an empty stomach, to facilitate absorption and avoid competition with dietary proteins, even though many pharmacists label for levodopa to be taken with meals. A practical approach is to dose levodopa 1 hour before or 1 hour after eating.

Decarboxylase inhibitors such as carbidopa are typically administered in a dose of 75 mg/d, to inhibit decarboxylase activity and prevent dopamine-related side effects. If a patient is on a small dose of Sinemet or Madopar, it may not contain enough of the decarboxylase inhibitor to adequately inhibit the decarboxylase enzyme, and in some individuals it may be necessary to provide additional doses of carbidopa (Lodosyn), which is available in 25 mg tablets. Occasionally, patients require as much as 300 mg of supplemental carbidopa to prevent levodopa-induced nausea or vomiting. Supplemental carbidopa can usually be discontinued when higher doses of Sinemet are used or after the patient has developed tolerance to the nausea and vomiting. The peripheral dopamine-receptor antagonist domperidone, in doses of 10 to 20 mg administered 30 minutes before each levodopa dose, can be effective in preventing nausea and vomiting, but this drug is not yet available in the United States. Trimethobenzamide hydrochloride (Tigan) 200 mg TID can be used in its stead but is not generally as effective. With the use of these strategies (extra carbidopa or addition of an antiemetic), it is rare for a patient with PD to be unable to tolerate levodopa because of acute side effects. If, however, orthostatic hypotension is prominent and does not attenuate over time, or respond to carbidopa or domperidone, the possibility that the patient might have MSA rather than PD should be considered.

Chronic levodopa therapy is associated with motor complications, such as dyskinesias and motor fluctuations, in the majority of patients[7] (see levodopa-induced motor complications, page S22, for a detailed discussion). These can represent a source of disability for some patients and limit the ability to fully use levodopa to control parkinsonian features. Patients with PD can also experience fluctuations in such nonmotor symptoms as mood, cognition, autonomic disturbances, pain, and sensory function.[229] Levodopa may also be associated with neuropsychiatric side effects, including cognitive impairment, confusion, and psycho-

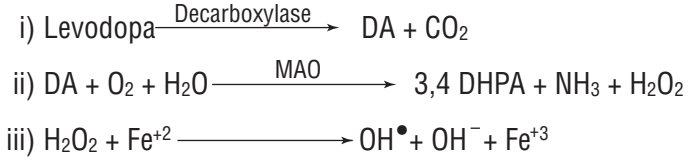
sis. Importantly, many PD features are not satisfactorily controlled by, or do not respond to, levodopa. These include freezing episodes, postural instability with falling, autonomic dysfunction, mood disorders, pain and sensory disturbances, and dementia. A more complete discussion of these problems and their management is provided below. Levodopa treatment can also be associated with a dopamine dysregulation syndrome in which patients compulsively take extra doses of levodopa in an addictive fashion. They may also experience punding, which consists of repetitive, complex, nonproductive behaviors such as purposeless arranging and rearranging of objects.[230] Although levodopa has been associated with impulse control disorders (ICDs) such as hypersexuality and pathologic gambling, these behaviors have primarily been reported to be associated with dopamine agonists (see later).

It is fascinating to consider that 40 years after the introduction of levodopa, there is a paucity of information on how to maximize benefits and minimize side effects with this drug.[231] There is also little scientific evidence to support the anecdotal treatment regimens that are routinely used. The recent Earlier vs Later Levodopa Therapy in PD (ELLDOPA) study was the first double-blind, placebo-controlled trial to assess the safety and efficacy of different doses of levodopa.[232] Not surprisingly, higher doses of levodopa provide greater clinical benefit but also pose a greater risk of inducing motor complications. Insight into the organization of the basal ganglia in normal and pathologic states suggests that the intermittent, pulsatile manner in which we routinely administer levodopa does not replace brain dopamine in a physiologic manner and likely contributes to the risk of developing motor complications.[233] Considerable effort has been directed toward better understanding the role of dopamine in normal basal ganglia function[224,234] and how levodopa can be administered to patients with PD to simulate physiologic brain dopamine levels as closely as possible (discussed in detail below).

Levodopa toxicity. There has long been a theoretical concern that levodopa might accelerate neuronal degeneration in PD because of the potential of the drug to generate free radicals through its oxidative metabolism[235] (figure 10). In the laboratory, levodopa has been shown to be toxic to cultured dopaminergic neurons, but the relevance to PD is not clear. Toxicity is seen with concentrations that are substantially higher than used in the treatment of patients with PD and low concentrations are actually protective, possibly because they induce upregulation of Bcl-2 and glutathione.[236] Levodopa has not been shown to be toxic to dopamine neurons in normal animals or humans,[237,238] and does not increase neuronal degeneration in dopamine-lesioned animals.[239] It is possible that the situation may be different in PD, in which there is oxidative stress and compromised defense mechanisms in the SNc. To examine this possibility, levodopa was administered to rodent pups in combination with buthionine sulfoximine, an inhibitor of the synthesis of glutathione, the principle antioxidant in the brain. Although levodopa increased toxicity associated with oxidative stress in vitro, no toxicity to dopamine neurons was observed in rodents despite the presence of severe oxidative stress.[240] One possible explanation for the disparity between the in vitro and in vivo findings could be that cultured dopamine neurons lack critical antioxidant defense mechanisms, such as ascorbate, which are present in the intact and even the PD brain and have been shown to be able to prevent levodopa-induced toxicity.[240]

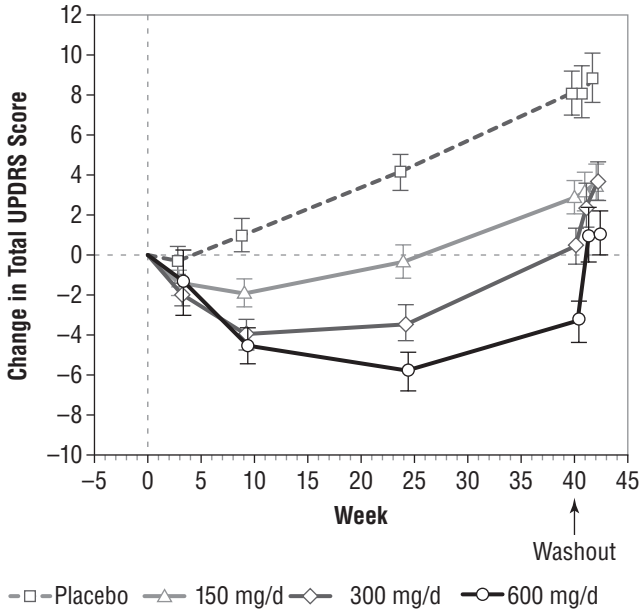
To address the potential toxicity of levodopa in patients with PD, the NIH sponsored the ELLDOPA trial.[232] In this prospective, double-blind study, untreated patients with early PD who did not require antiparkinsonian therapy were randomly assigned to one of three doses of carbidopa/levodopa (12.5 mg/50 mg TID, 25 mg/100 mg TID, or 50 mg/200 mg TID) or placebo. Patients were treated with the study drug for 9 months, withdrawn from treatment over 3 days, and examined again 1 and 2 weeks after drug withdrawal. Levodopa treatment provided significantly improved UPDRS scores compared with placebo, with a clear dose–response effect (figure 11). Washout of study drug for up to 2 weeks led to deterioration in benefit for each of the levodopa treatment groups, but none deteriorated to the level of the placebo group, arguing against any toxic effect of the drug. Interestingly, there was also a dose–response effect with respect to motor complications, with dyskinesias developing in

Figure 10 **Equations illustrating how the conversion of levodopa to dopamine can lead to the formation of oxidizing species and cytotoxic free radicals.**



i) Levodopa is decarboxylated to form dopamine (DA). ii) Dopamine is oxidized by monoamine oxidase (MAO) to yield hydrogen peroxide (H_2O_2). iii) Under normal circumstances, H_2O_2 is detoxified by glutathione (data not shown). However, H_2O_2 that is not cleared by glutathione can react with ferrous iron to generate the highly reactive and cytotoxic hydroxyl ($OH^{\bullet}$) radical according to the Fenton reaction. In addition, levodopa can undergo spontaneous auto-oxidation to yieldreactive oxygen species. Reproduced with permission from Olanow and Koller.[14]

Figure 11 **The ELLDOPA study[232] demonstrated that levodopa provides a dose-related improvement in Unified PD Rating Scale (UPDRS) scores, and that benefit vs placebo persists even after 2 weeks of washout.**



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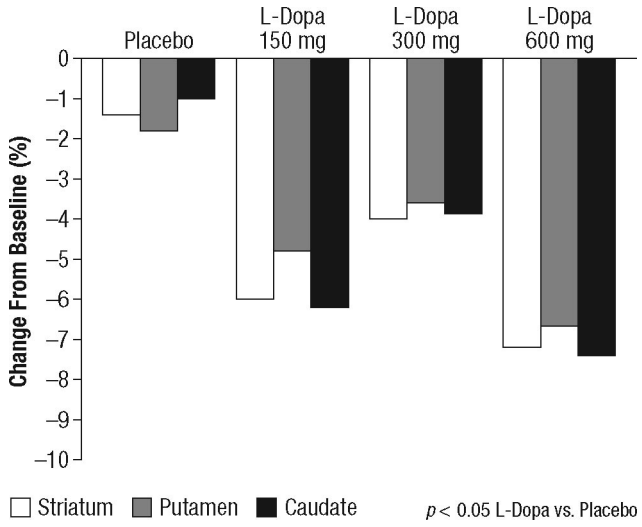
16.5% of patients and "wearing off" in 28% of patients in the levodopa 600 mg/day group after just 9 months of treatment. The clinical results of this study do not demonstrate any adverse effect of levodopa on PD progression, and even suggest that the drug might have a protective effect that slows short-term progression of the disease. Alternatively, it is possible that benefits were observed because the drug can provide long-duration symptomatic benefits, which endure for more than 2 weeks after its withdrawal. Indeed, levodopa washout studies suggest that benefits can persist for weeks to months.[182,241] Benefits observed with levodopa treatment could also relate to preventing decompensation as a result of the early administration of a symptomatic drug (see Figure 8). In any event, the clinical results certainly do not provide any evidence to suggest that levodopa is toxic or accelerates the development of disability in patients with PD.

Figure 12 **Change in striatal β-CIT uptake between baseline and 40 weeks in the ELLDOPA study.[232]**



Note that there was a significant reduction in levodopa-treated patients compared with placebo-treated patients.

The problem, however, is more intriguing. As part of the ELLDOPA trial, a subset of patients underwent β-CIT-SPECT studies at baseline and at final treatment visit (40 weeks), to determine the effects of levodopa on striatal DAT binding, a surrogate measure of nigrostriatal function. Despite significant improvement in UPDRS scores, levodopa was associated with significant worsening in the rate of decline of striatal binding compared with placebo ($p = 0.036$; figure 12). In contrast to the clinical findings, the SPECT studies suggest that levodopa might accelerate degeneration of dopamine neurons. However, it is also possible that levodopa induces downregulation of the DAT, and that the increased rate of decline in DAT binding is due to a regulatory or pharmacologic effect of the drug rather than to any toxicity.[49] The INSPECT study examined the rate of decline in striatal β-CIT binding after just 12 weeks of levodopa treatment. No change in comparison with placebo was detected.[204] This study provides no evidence of any short-term regulatory effect of levodopa on DATs but does not exclude the possibility of levodopa toxicity.

The ELLDOPA study thus raises more questions than it answers: 1) Is levodopa protective and should it be started early? Or, is there sufficient concern that levodopa is toxic that clinicians should delay or avoid the introduction of the drug? 2) Why is there a decline in striatal binding of β-CIT to DAT in levodopa-treated patients when they are doing better clinically? 3) How long does the long-duration symptomatic benefit of levodopa last in patients with early PD? 4) If higher doses of levodopa are more beneficial, is the risk of dopaminergic side effects (dyskinesias and wearing-off) a reasonable trade-off for early patients? Although there are no definite answers to these questions, the general view of experts is that there is not sufficient evidence to consider levodopa toxic in PD, and that levodopa should not be withheld unless further information to the contrary becomes available. Rather, we advocate that levodopa should be used in patients with PD when it is deemed necessary, taking into account the efficacy

Table 5	Motor complications of levodopa therapy
Motor fluctuations	
End of dose ("wearing-off ")	
Unpredictable motor fluctuations ("on-off " phenomenon)	
Dose failures and "delayed-on"	
Dyskinesia	
Early AM dystonia	
Peak-dose dyskinesia	
Diphasic dyskinesia (D-I-D syndrome)	

D-I-D = dyskinesia-improvement-dyskinesia.
Adapted with permission from Olanow et al.[15]

and AE profile of the drug in relation to the individual patient.[235,242]

Levodopa-induced motor complications. Chronic levodopa treatment is frequently associated with the development of motor complications.[7,243,244] These can be divided into two major subgroups, motor fluctuations and dyskinesia, as illustrated in table 5. Motor fluctuations consist of alterations between periods when patients respond to levodopa and experience relatively good mobility and motor function ("on" periods), and periods when the medication does not satisfactorily control motor disability and the response is suboptimal ("off" periods). During the early stages of PD, the clinical response after a single levodopa dose is stable and long lasting (>4 hours), despite the drug's relatively short plasma half-life of approximately 60 to 90 minutes.[245] Indeed, benefits are frequently maintained even if one or multiple doses are missed (the "long-duration response"). With advancing PD, patients begin to experience the wearing-off effect, in which the motor benefit after a dose of levodopa is reduced in duration and lasts less than 4 hours (the "short-duration response"). Over time, the duration of benefit after a single dose of levodopa progressively shortens and begins to approximate the plasma half-life of the drug, even though there is no change in levodopa plasma pharmacokinetics.[246-249] Eventually, patients may begin to experience rapid and unpredictable fluctuations between "on" and "off" states known as the "on-off" phenomenon.[250] In the advanced state, some doses may take longer to become effective (delayed-on), and some may not be effective at all (no-on).

The short-duration response is a measure of the duration of benefit after a single dose of levodopa.[251] The duration of the motor response is a function of the duration of levodopa therapy and disease severity, becoming progressively shorter with advancing PD.[252] The latency from the time of levodopa administration to the onset of motor improvement is typically about 30 to 90 minutes with the standard formulation and 60 to 180 minutes with the controlled-release formulation. Patients with delayed gastric emptying may experience a delay in achieving a motor response, as levodopa is absorbed exclusively in the small intestine. Caffeine may shorten the time to maximum concentration and increase the magnitude of the response.[253] To tailor therapy to an individual patient, the clinician should be aware of the magnitude and duration of the motor response after a dose of levodopa/carbidopa, and the relationship between "on" and "off" periods and dyskinesias. This can sometimes be determined from the patient history but occasionally may require monitoring of the patient during several dosing cycles.

The long-duration response is the time from complete withdrawal of levodopa until parkinsonian deterioration is maximal.[251] The long-duration response is an important component of motor fluctuations, as it determines the baseline function upon which "on" and "off" fluctuations occur. The long-duration response is difficult to assess in a routine clinical setting, however, as it involves taking patients off medication for a sustained period of time (usually 1 to 2 weeks, but possibly longer[182,246]). This is not routinely performed or recommended, as it can be associated with severe worsening of parkinsonism and the development of a neuroleptic malignant-like syndrome.

Levodopa-induced dyskinesias are involuntary movements that are most often seen in association with the peak plasma levodopa concentration and the maximal clinical response (peak-dose dyskinesias). Movements are typically choreiform or dance-like in character, but may involve dystonia, myoclonus, or other movement disorders. Virtually any part of the body may be involved, including the head, neck, torso, limbs, and respiratory muscles. Dyskinesias may be mild and of greater concern to the family than to the patient, or severe and a source of considerable disability to the patient. They have been viewed as a disruption in the ability of the basal ganglia to automatically select and execute normal motor tasks.[254]

Dyskinesias can also occur as the patient begins to turn "on" and again as they begin to turn "off," but not at the time of the peak levodopa effect. This is known as diphasic dyskinesia or the dyskinesia-improvement-dyskinesia (D-I-D) syndrome.[255] Movements tend to be stereotypic, rhythmic, and asymmetric; to primarily affect the lower limbs; and to be associated with parkinsonism in other body regions. They may also involve dystonic contractions. Diphasic dyskinesias are thus associated with relatively low doses of levodopa and, in contrast to peak-dose dyskinesias, tend to improve with higher doses of levodopa.

Dystonia can be seen as a feature of untreated PD as well as a consequence of levodopa, particularly as an early manifestation of dyskinesia that is later followed by more classic choreiform movements. It is important to distinguish between dystonia that occurs in "off" periods and is a function of too little levodopa, and dystonia that occurs in "on" periods and is a function of too much levodopa. When dyskinesia manifests itself as dystonia, it tends to involve the distal extremities. Drugs such as anticholinergics can also induce dyskinesias,[256,257] but these typically involve oro-facial-lingual muscles and resemble tardive dyskinesias.

Levodopa-induced dyskinesias and motor fluctuations tend to develop at about the same time, and may be related to a similar mechanism (see discussion later). Motor fluctuations can usually be reversed by increasing the dose of levodopa, but this often leads to worsening of dyskinesia. In contrast, dyskinesias tend to disappear with the reduction or elimination of levodopa, but this is usually associated with deterioration in parkinsonism. Most patients with PD prefer to be "on" with dyskinesia rather than "off," but in some patients the dyskinesia can be more disabling than the parkinsonism, particularly when respiratory muscles are involved.

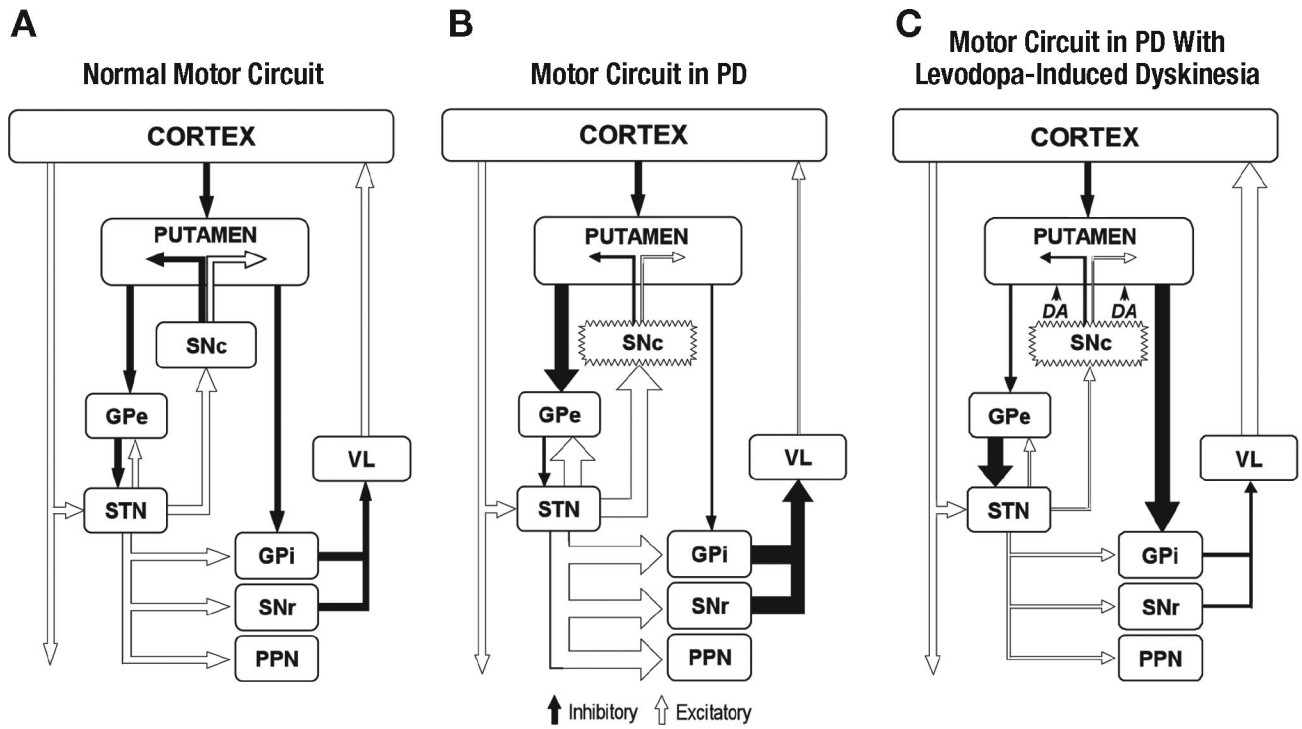
When patients first begin to experience motor complications and/or dyskinesias, they have a relatively wide "therapeutic window," and it is usually possible to find a dose of levodopa that controls parkinsonian features and does not induce obvious or at least troublesome dyskinesias. With advancing disease, there is a "narrowing" of this therapeutic window, and it becomes increasingly difficult to find a dose of levodopa that is both effective and does not cause dyskinesia. In the extreme, patients may cycle between "on" periods, which are complicated by dyskinesias, and "off" periods, in which they are akinetic and severely parkinsonian. At this stage, levodopa-induced motor complications can be extremely difficult to control and represent a major source of disability for the patient. Eventually, it may become impossible to delineate a dose of levodopa that provides motor benefit without inducing dyskinesia.

Motor complications occur in as many as 90% of patients with PD who have received levodopa for 5 to 10 years.[258] They are particularly common in patients with young-onset PD (aged 21 to 39 years), occurring in virtually 100% of these individuals,[259,260] and are less likely to develop or to be troublesome in patients with PD whose symptoms begin after the age of 70 years. This difference may be related to the greater plasticity of the younger brain, and its increased ability to generate both beneficial and maladaptive compensatory responses to dopamine depletion and dopaminergic therapy. Indeed, patients with PD who develop disabling levodopa-induced motor fluctuations tend to have experienced a stronger therapeutic response than those without motor complications.[261] In a community-based study, motor complications were also found to be associated with the use of high doses of levodopa.[262] Indeed, it is generally felt that severe dyskinesias are less prevalent today compared with a decade ago, because of the tendency to use lower doses of levodopa. In the DATATOP study, 46% to 49% of patients experienced motor fluctuations, and 21% to 31% had dyskinesia after a mean duration of levodopa treatment of 20.5 months.[163] The ELLDOPA study confirmed that motor complications are more common in patients receiving higher doses of levodopa. This study also illustrated that motor complications can develop relatively early in the course of therapy; in the 600 mg/day group, dyskinesias were seen in 16% of patients and motor fluctuations in 20% after just 9 months of levodopa therapy.[232] The long-term significance of early motor complications remains to be determined, although we believe that patients with early dyskinesias are more likely to develop severe dyskinesias down the road than patients who do not develop dyskinesias in their first few years of therapy. Long-term studies suggest that while motor complications are common, disability in patients with advanced PD is related primarily to nondopaminergic features such as falling and dementia.[9]

Mechanism responsible for levodopa-induced motor complications. Understanding the mechanism responsible for the development of levodopa-induced motor complications is essential for developing therapeutic strategies to reduce the risk of their occurrence. Much of our current approach for treating levodopa-induced motor complications is derived from the classic model of the basal ganglia (figure 13).[263,264] The model suggests that the input region of the basal ganglia (the striatum) communicates with the output region, composed of the GPi and the SNr, by way of direct and indirect striatopallidal pathways. Nerve cells in the direct pathway inhibit, and those in the indirect pathway excite, basal ganglia output neurons, thereby influencing the basal ganglia's effect on the thalamocortical and brainstem motor regions. Dopamine exerts a dual action on medium spiny striatal neurons (MSNs), activating D1 receptors on MSNs in the direct pathway and inhibiting D2 receptors on MSNs that participate in the indirect pathway. The classic model predicts that parkinsonian motor features are related to increased neuronal firing frequency of basal ganglia output neurons, whereas levodopa-induced dyskinesias are associated with decreased firing of these neurons.

In the PD state, the model suggests that dopamine depletion leads to increased neuronal firing ac-

Figure 13 Schematic representation of the classic model of the basal ganglia, illustrating the direct and indirect pathways connecting the striatum and the globus pallidus, and the modulatory effects of dopaminergic neurons on each of these systems.



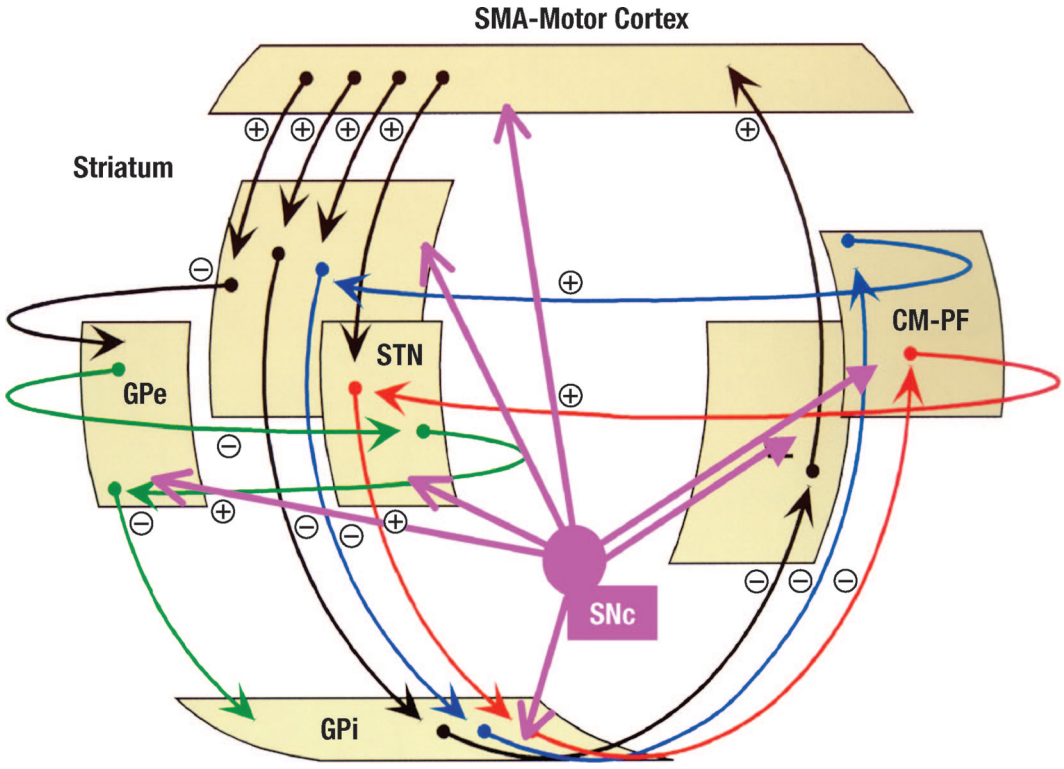
Excitatory fibers are shown in black and inhibitory fibers in white. The model predicts that neuronal firing in the STN and GPi are increased in the parkinsonian state, leading to excessive inhibition of brainstem and thalamocortical neurons with the development of parkinsonian motor features. In contrast, the model proposes that dyskinesia is related to decreased firing in the STN and GPi, with reduced inhibition of thalamic and cortical motor regions. SNc = substantia nigra pars compacta; GPe = external globus pallidus; STN = subthalamic nucleus; VL = ventralis lateralis; Gpi = internal globus pallidus; SNr = substantia nigra pars reticularis; PPN = pedunculopontine nucleus; DA = dopamine. Reproduced from Obeso et al.[265]

tivity in excitatory neurons of the subthalamic nucleus (STN) and reduced firing in the inhibitory striatopallidal neurons that make up the direct pathway. These changes combine to result in excessive firing of GPi and SNr neurons, with consequent overinhibition of the thalamus, reduced activation of cortical motor regions, and resultant parkinsonian motor features. This concept is supported by neurophysiologic studies in patients with PD and MPTP monkeys showing increased neuronal firing rates in the GPi and STN.[263,264] These observations formed the basis for modern surgical treatments for PD, which are aimed at reducing overactive neuronal activity in these structures.

The classic model of the basal ganglia has served us less well when it comes to understanding the origin of levodopa-induced motor complications and, more specifically, levodopa-induced dyskinesias.[265] The classic model hypothesizes that the effects of excess dopamine on the direct and indirect pathways would result in decreased firing in pallidal output neurons, reduced inhibition of the thalamus, excessive activation of cortical and brainstem motor areas, and consequent dyskinesia (figure 13). In support of this concept, microelectrode recordings in parkinsonian monkeys and patients with PD have found that the acute administration of a dopaminergic therapy is associated with a dramatic reduction in GPi firing frequency coupled with the onset of dyskinesia.[266,267] However, the model does not explain the effects of pallidotomy. The model predicts that pallidotomy should be associated with the development of dyskinesia. However, pallidotomy is consistently associated with the amelioration, not the induction, of dyskinesia.[268,269]

It is now appreciated that the basal ganglia are more complex than had been appreciated and are comprised of a complex network of neurons with many feedback and feed forward loops. Furthermore, it is clear that encoded information is transmitted by way of multiple neurophysiologic parameters, rather than the linear frequency-dependent system depicted by the classic model.[270,271] Dopamine innervation is now known to extend throughout the entire basal ganglia system, as well as to the thalamus and cortex, and is not restricted to the nigrostriatal system.[272] In addition, it is now appreciated that physiologic information in basal ganglia output neurons is conveyed by more than just firing frequency (e.g., pauses, bursts, synchrony). It is likely that it is the disruption of an abnormal neuronal firing pattern that accounts for the bene-

Figure 14 A modern view of the basal ganglia illustrating that it is organized as a complex network rather than in the linear manner portrayed in the classic model.



Note that the basal ganglia network is stabilized by multiple feedback and feed forward loops, and by the modulatory effects of dopamine, which extends throughout the basal ganglia system, thalamus, and cerebral cortex, and is not confined to the striatum. SMA = supplementary motor area; GPe = external globus palidus; STN = subthalamic nucleus; CM-PF = centre médian-parafascicular; SNc = substantia nigra pars compacta; Gpi = internal globus pallidus. Modified from Obeso et al.[270] with permission from Elsevier.

ficial effects of pallidotomy on dyskinesia. A more modern schema of the basal ganglia illustrating some of these features is provided in figure 14.

A clear picture of the role of dopamine in the normal basal ganglia and the factors responsible for the origin of motor complications have begun to emerge.[270,271] Historically, it was noted that the duration of motor benefit after cessation of a levodopa infusion progressively decreased with increasing disease severity, despite all groups having comparable plasma levodopa pharmacokinetics.[248,249] These findings gave rise to the notion that motor fluctuations in patients with advanced PD are associated with a decreased capacity to store dopamine because of the loss of dopaminergic terminals. However, similar findings were observed with apomorphine, which is not stored in dopaminergic terminals[273,274]; these findings cannot be explained by the "storage hypothesis." Furthermore, shortening of the duration of the motor response occurs with repeated doses of levodopa in 6-OHDA-lesioned rodents with stable brain lesions whose capacity to store dopamine has presumably not changed.[275] These findings suggest that there must be a postsynaptic component to the development of motor complications. It is now apparent that motor complications are related, at least in part, to abnormal pulsatile stimulation of dopamine receptors, with consequent dysregulation of genes and proteins in striatal neurons leading to altered neuronal firing patterns in basal ganglia output neurons.[276]

Under normal circumstances, striatal dopamine is maintained at a relatively constant level, and there is continuous stimulation of striatal dopamine receptors.[277] SNc dopaminergic neurons normally fire in both a tonic (continuous) and phasic (intermittent bursts) manner.[278,279] Under normal circumstances, approximately half of the SNc dopamine neurons fire tonically, in a continuous but random manner, independent of movement. Firing of individual SNc dopamine neurons is regulated by GPi–SNc inhibitory neurons.[280] Tonic firing leads to continuous dopamine release, with activation of extrasynaptic D1 receptors by way of volume transmission. Phasic or burst firing of dopamine neurons is glutamate mediated and occurs in response to anticipation of reward or novel stimuli.[281,282] Burst firing releases large quantities of dopamine, which activate D1 and D2

receptors located within the synapse. Neurons that undergo burst firing, however, contain large numbers of DATs and have a robust dopamine reuptake capacity. Thus, striatal dopamine levels remain relatively constant in the physiologic state,[283-285] independent of the SNc neuronal firing rate.[286] The constant firing of SNc dopamine neurons, stable striatal dopamine levels, and continuous activation of striatal dopamine receptors are essential for normal basal ganglia function.

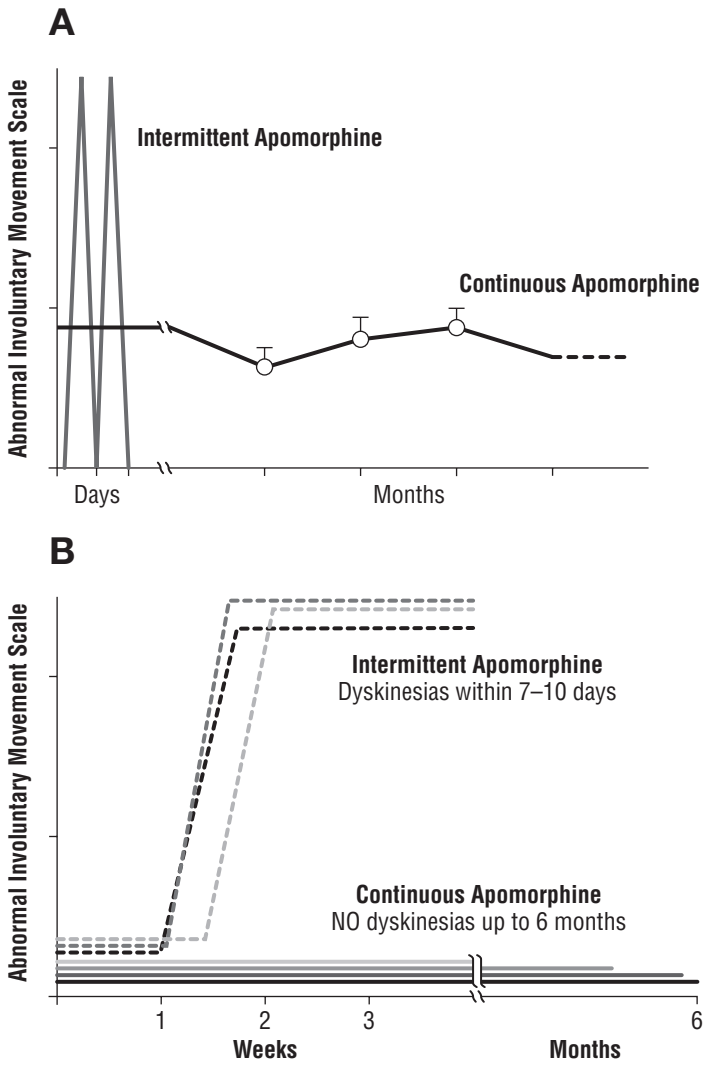
Under physiologic conditions, dopamine acts presynaptically to modulate the glutamate-mediated excitability of striatal neurons (in both up and down directions) and to influence plasticity (long-term potentiation and long-term depression). Dopamine also acts postsynaptically to inhibit excitation in the indirect pathway and to activate the inhibitory effects of the direct pathway. In these and other ways, dopamine acts to stabilize the basal ganglia network.

This is not the case in PD, where there is prominent dopamine depletion and striatal dopamine levels are dependent on the peripheral availability of levodopa. In this situation, replacement of striatal dopamine with intermittent (and discontinuous) doses of standard formulations of levodopa does not restore basal ganglia function to normal. Here, fluctuations in levodopa plasma concentration caused by the short half-life of the drug are directly translated to the striatum, and individual doses of levodopa induce large oscillations in striatal dopamine levels.[283] Indeed, PET studies in fluctuating patients with PD show evidence of oscillating synaptic dopamine levels after individual doses of levodopa.[287] Under these circumstances, striatal dopamine receptors are exposed to intermittently high and low concentrations of dopamine after each dose of levodopa. This nonphysiologic, discontinuous, or pulsatile stimulation of dopamine receptors leads to a variety of molecular and physiologic changes that are associated with the development of motor complications. These include a) alterations in levels of expression in striatal neurons of a variety of genes including preprodynorphin, delta fos-b, delta c-fos, and preproenkephalin, which have been observed in striatal neurons of dyskinetic rodents, primates, and patients with PD[288-290]; and b) changes in neuronal firing pattern (e.g., frequency, bursts, pauses, synchronization) in basal ganglia output neurons.[266,269,291] More recently, it has been shown that levodopa treatment and the development of dyskinesia are associated with alterations in plasticity,[292] and with translocation of NR2B subunits of the NMDA receptor from a synaptic to an extrasynaptic location.[293] Interestingly, manipulations of the NR2B subunit can either induce or eliminate dyskinesia in rodents.[293] Furthermore, levodopa impairs depotentiation of striatal neurons, which might contribute to the persistence of undesired behaviors such as dyskinesia.[294] These studies illustrate that the intermittent manner in which we administer levodopa therapy does not normalize the parkinsonian brain, but rather destabilizes the already unstable basal ganglia.

Two factors are known to promote pulsatile stimulation of the dopamine receptor: a) the degree of loss of striatal dopaminergic terminals, with a consequent loss in their capacity to buffer fluctuations in striatal dopamine; and b) intermittent doses of a dopaminergic agent with a short half-life, such as levodopa. There is considerable experimental evidence supporting the notion that pulsatile stimulation of striatal dopamine receptors contributes to the induction of levodopa-induced motor complications. Levodopa induces shortening of the motor response (wearing-off) in parkinsonian rodents when it is given intermittently but not when it is administered continuously.[295] Short-acting dopaminergic agents such as levodopa are more prone to induce dyskinesia in MPTP-treated monkeys than are long-acting dopaminergic agents such as bromocriptine and ropinirole.[296,297] Of particular importance is the observation that the same short-acting dopaminergic agent that induces dyskinesia when administered in a pulsatile manner does not induce dyskinesia when administered continuously.[298,299] For example, intermittent doses of the short-acting dopamine agonist apomorphine induce severe dyskinesia in MPTP primates, whereas continuous infusion of the same agent does not[299] (figure 15). These different patterns (pulsatile and continuous) of dopamine receptor stimulation are likely to elicit different functional responses, because they activate different signal transduction pathways in postsynaptic neurons.[300] These examples serve to illustrate that the same dose of the same molecule can induce, or not induce, dyskinesia, depending on the mode of administration.

In the final analysis, motor complications likely relate to miscoded information being relayed from basal ganglia output neurons to brainstem and cortical motor regions. It is the elimination of this abnormal neuronal firing pattern that presumably accounts for the antidyskinetic effect of pallidotomy and DBS. On the basis of these considerations, it has been hypothesized that therapies that deliver levodopa or other dopaminergic agents in a more continuous manner will provide antiparkinsonian effects with a reduced risk of causing motor complications.[233,301,302] This concept has become known as CDS. Indeed, multiple clinical trials have demonstrated that long-acting dopamine agonists induce less dyskinesia and wearing-off in patients with PD than does levodopa, and continuous infusion of levodopa or a dopamine agonist

Figure 15 The top panel illustrates the plasma concentrations with intermittent vs continuous doses of apomorphine.



The bottom panel illustrates that intermittent doses of apomorphine are associated with severe dyskinesia, whereas continuous apomorphine is associated with a relative absence of dyskinesia, even over 6 months of follow-up. Reprinted from Bibbiani et al.[299] with permission from Elsevier.

Table 6 Levodopa: Advantages and disadvantages

Advantages
Most efficacious antiparkinsonian drug
Virtually all PD patients respond
Improves disability, and prolongs capacity to maintain employment and independent activities of daily living
Reduces mortality rate
Disadvantages
Motor complications
Dyskinesias: choreiform movements, dystonia
Motor fluctuations
Neuropsychiatric problems: confusion, psychosis, punding
Sedation
Does not treat the so-called nondopaminergic features of PD (e.g., freezing, postural instability, autonomic dysfunction, dementia)

PD = Parkinson disease.
Adapted with permission from Olanow and Koller.[14]

can reduce established motor complications in patients with advanced PD.

It should also be appreciated that other factors have been implicated in the pathophysiology of levodopa-induced motor complications. There has long been interest in the possibility that dyskinesia might relate to the pattern of stimulation of dopamine receptor subtypes, and agents that specifically activate D2 receptors are thought to be less likely to induce dyskinesias than are D1 agonists. However, dyskinesias can be induced with selective, short-acting D1 or D2 receptor agonists in both MPTP monkeys and patients with PD.[303,304] Interest has also focused on the possible role of the D3 receptor in the origin of dyskinesias, as partial but not full D3 agonists have been reported to provide motor benefits without dyskinesias in MPTP monkeys.[305] It is also possible that some characteristic of the levodopa molecule makes it particularly prone to inducing dyskinesias.[306] Nonetheless, in all studies performed to date, continuous administration of a short-acting dopaminergic agent results in less dyskinesia than pulsatile administration of the same agent. We therefore believe that CDS-based approaches offer the best near-term opportunity for developing pharmaceutical agents that might prevent or reverse motor complications in patients with PD. A summary of the advantages and disadvantages of levodopa is listed in table 6.

Dopamine agonists. Dopamine agonists are a class of drugs with diverse physical and chemical properties. They share the capacity to directly stimulate dopamine receptors, presumably because they incorporate a dopamine-like moiety within their molecular configuration. Dopamine agonists have drawn particular interest as a treatment for PD because of their potential to provide antiparkinsonian effects with a reduction in the motor complications associated with levodopa. They have been used in the treatment of PD since the early 1970s,[228] historically used as adjuncts to levodopa in patients who had begun to experience motor complications. Today, dopamine agonists are also used as early symptomatic therapy to reduce the risk of developing the motor complications associated with levodopa therapy.

Dopamine agonists offer several theoretical advantages over levodopa.[307] First, they act directly on striatal dopamine receptors and do not require metabolic conversion to an active product to exert their pharmacologic effect. They thus act independently

of degenerating dopaminergic neurons. They can also be designed to stimulate specific subsets of dopamine receptors, thereby theoretically providing an opportunity to obtain specific receptor-mediated benefits with reduced AEs. Second, dietary plasma amino acids do not compete with dopamine agonists for absorption from the gut and transport into the brain. Third, dopamine agonists currently on the market have a longer half-life than immediate-release formulations of levodopa and therefore may provide more sustained stimulation of striatal dopamine receptors and reduced dyskinesia. Finally, they do not undergo oxidative metabolism and do not generate free radicals. Indeed, as discussed earlier, there is evidence suggesting they may have neuroprotective effects in PD (see section on neuroprotection, page S9).

The first group of dopamine agonists used in the treatment of PD were ergot derivatives. The most widely used among these were bromocriptine (Parlodel), pergolide (Permax), and cabergoline (Cabsar, Dostinex). Numerous studies have demonstrated the effectiveness of these agents in PD as adjuncts to levodopa and shown that as monotherapy they are associated with a reduced risk of inducing dyskinesia compared with levodopa.[308–311] However, their use has markedly declined due to the risk of AEs and the introduction of nonergot dopamine agonists. Although Frank ergotism is rare,[312] cardiac dysfunction with valvular thickening and fibrosis has now been reported with pergolide and cabergoline, presumably because they activate the 5HT2b receptor.[313-315] As a consequence, pergolide has been voluntarily withdrawn from the market, and the use of cabergoline has markedly declined. Patients still receiving these drugs must be carefully monitored for the development of cardiac valve dysfunction. Lisuride is a short-acting ergot dopamine agonist that is currently being studied/used in patients with advanced PD using either patch or infusion delivery methods. Even though lisuride is an ergot, it has not been associated with cardiac valvulopathy, presumably because it is an agonist at two related serotonin receptors (5-HT_{2A} and 5-HT_{2C}) but an antagonist at the 5-HT_{2B} receptor.[316]

In the past decade, nonergot dopamine agonists have largely supplanted the ergot agonists as the dopamine agonists of choice for the treatment of PD. Pramipexole (Mirapex) and ropinirole (Requip) are the two most widely used drugs. More recently, rotigotine (Neupro) has been approved for the treatment of early PD in a transdermal (patch) delivery formulation, but has been voluntarily withdrawn from the market in the United States because of a tendency for the material to crystalize in the patch. As a group, the newer dopamine agonists have been more extensively studied than the older dopamine agonists, particularly in the early stages of PD. Apomorphine (Apokyn) is a short-acting dopamine agonist that is available in injectable form as a rescue drug for the management of "off" periods, and in some countries as an infusion therapy for the management of patients with advanced motor complications. The receptor profiles and clinically effective doses of available agonists are listed in table 7. It should be appreciated that the functional significance of the different dopamine receptors is not known.

Table 7 Dopamine agonist receptor profile and dose ranges

Dopamine agonist*	Receptor profile	Starting dose, mg/day	Usual dose range, mg/day
Bromocriptine	D1 (−), D2 (+)	1.25 BID or TID	7.5–40
Pergolide	D1(+), D2(+)	0.05 QD	0.75–6.0
Pramipexole	D2, D3	0.125 TID	0.75–3.0
Ropinirole	D2, D3	0.25 TID	9–24
Cabergoline	D2	0.25 QD	0.5–5
Rotigotine	D1, D2	2-mg patch	4–8
Lisuride	D2	0.2 QD	1–2
Apomorphine	D1, D2, D3	2.0	2–8

*Dopamine agonists should be introduced at a low dose and titrated gradually to optimal clinical benefit over the course of several weeks to months, to minimize adverse effects. Adapted with permission from Olanow et al.[15]

Bromocriptine was the first dopamine agonist to be approved as a treatment for PD. It is an ergot derivative that is a D2 receptor agonist and a weak D1 receptor antagonist. Several studies have demonstrated the capacity of bromocriptine, used as an adjunct to levodopa, to improve parkinsonian disability and reduce dyskinesia and motor fluctuations in patients with advanced PD.[317-319] Pergolide is also an ergot agent with D2 receptor agonist properties but differs from bromocriptine in that it is a weak agonist at the D1 receptor. A large, prospective, multicenter, double-blind, placebo-controlled trial in levodopa-treated patients demonstrated that the addition of pergolide improved motor and ADL scores, decreased "off" time, and provided a levodopa-sparing effect.[308] Similar results have been obtained with lisuride and cabergoline when used as adjuncts to levodopa.[320,321]

Double-blind, placebo-controlled studies have similarly demonstrated that pramipexole and ropinirole exert antiparkinsonian effects with levodopa sparing in patients with advanced PD.[322,323] In a 6-month, double-blind, controlled study, ropinirole treatment was associated with a reduction in "off" time of 3.7 hours, compared with 1.6 hours in the placebo group ($p < 0.001$).[323] Similarly, in a 32-week, placebo-controlled, double-blind study, pramipexole improved motor function by 25%, compared with 12% in the placebo group

($p < 0.001$), decreased "off" time (31% vs 7%; $p < 0.001$), and reduced the levodopa dose requirement (27% vs 5%; $p < 0.001$).[322]

Ropinirole is typically initiated at a dose of 0.25 mg TID and gradually increased to a total of 9 to 24 mg/d based on clinical response. Pramipexole is initiated at a dose of 0.125 mg TID and titrated up to a maximum dose of 4.5 mg/d.

High-dose dopamine agonists have been used with limited success as a substitute for levodopa in patients with complex motor fluctuations and severe dyskinesia.[324-326] This approach is associated with potentially serious side effects and has limited applicability for most patients with PD. Dopamine agonists administered via continuous infusion, however, have been demonstrated to reduce "off" time and dyskinesia in patients with advanced PD,[327] and warrant further investigation (see section on infusion therapies, page S64).

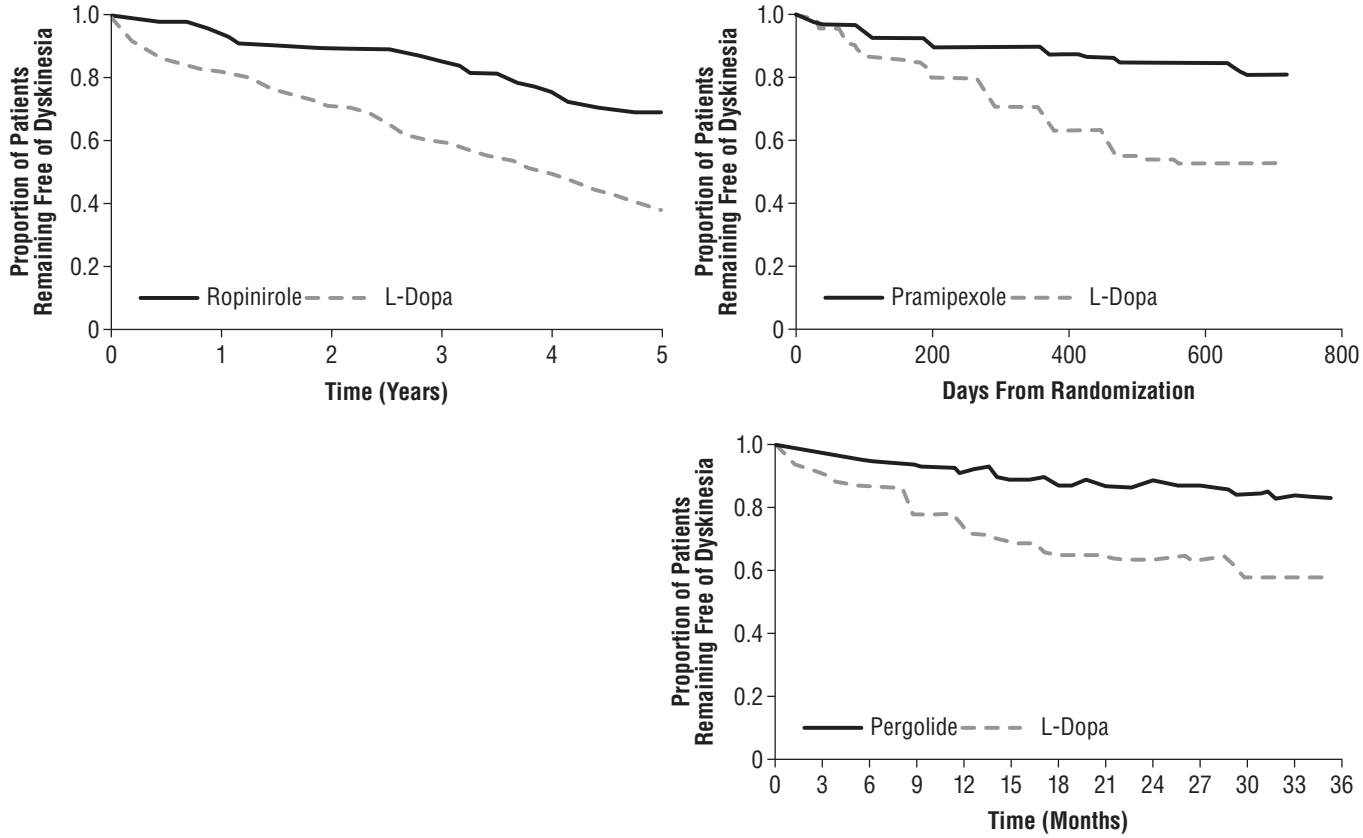
Despite the benefits obtainable with the adjunctive use of dopamine agonists, levodopa-related motor complications can be extremely difficult or even impossible to control (see section on management of motor complications, page S22). In fact, motor complications that are refractory to medical treatments are the major reason for surgical interventions in patients with PD. Accordingly, there has been considerable interest in the use of long-acting dopamine agonists as initial therapy based on their potential to provide CDS with a reduced risk of inducing motor complications.[302] In the laboratory, long-acting dopamine agonists such as bromocriptine and ropinirole are associated with a reduced risk of motor complications compared with levodopa and short-acting dopamine agonists such as quinpirole or CY-208.[296,297,303] Furthermore, the same short-acting dopamine agonist (e.g., U-91356A, apomorphine) induces dyskinesia when given intermittently but not when administered continuously.[298,299]

These observations have fueled interest in the notion that it may be better to initiate symptomatic therapy in PD with a relatively long-acting dopamine agonist rather than with levodopa. Well-designed clinical trials have now been performed in patients with early PD evaluating dopamine agonist monotherapies as initial treatment for PD. Prospective, double-blind studies clearly demonstrate the superiority of monotherapy with pramipexole, ropinirole, pergolide, or cabergoline compared with placebo with respect to motor efficacy.[311,328-331] Few studies have directly compared dopamine agonists with levodopa as monotherapy. A 6-month interim analysis of a 5-year, double-blind study demonstrated that patients randomized to receive treatment with ropinirole had clinical benefits that were only slightly inferior to those randomized to levodopa (44% vs 32% improvement).[332] Benefits were comparable for patients in Hoehn and Yahr stages I and II, with the superior efficacy of levodopa becoming evident in more advanced patients. Indeed, approximately 50% of patients with PD can be satisfactorily controlled with dopamine agonist monotherapy for 3 years and 30% can be maintained on agonist alone for up to 5 years before requiring levodopa supplementation.[333,334]

Several prospective, double-blind, multicenter studies have also been performed comparing the risk of developing motor complications in untreated patients with PD who are randomized to initial treatment with levodopa compared with ropinirole,[333] pramipexole,[334] cabergoline,[311] or pergolide.[310] The primary outcome measure for the pramipexole study was the time for the development of any motor complication (dyskinesias, wearing-off effects, or "on-off" fluctuations), whereas the time to onset of dyskinesia was the primary end point for the other studies. Each of these studies demonstrated a significant reduction in the risk for and frequency of developing motor complications in patients randomized to initial therapy with the dopamine agonist compared with levodopa, even when supplemental levodopa was required (figure 16).

The first of these studies to be reported was the 5-year, double-blind trial comparing ropinirole with levodopa in 268 untreated patients with PD.[333] Patients with early PD (average duration 2.5 years) who required dopaminergic treatment were randomized to begin therapy with either ropinirole or levodopa/carbidopa. Ropinirole was initiated at a dose of 0.25 mg TID and levodopa at a dose of 50 mg TID. The blinded "dose level" could be increased at weekly intervals until satisfactory control was achieved or side effects developed. The maximal daily dose that could be prescribed was 24 mg of ropinirole and 1200 mg of levodopa. If the investigator deemed PD features to be not adequately controlled by adjustment of the blinded study medication, supplementary open-label levodopa could be added to patients in either group at any time during the study. Sixty-six percent of patients in the ropinirole group and 36% in the levodopa group received open-label levodopa supplementation. After 5 years of treatment, patients in the ropinirole group were receiving a mean daily dose of 16.5 mg of ropinirole plus 427 mg of open-label levodopa, whereas those in the levodopa group were taking a mean dose of 753 mg of levodopa. Patients randomized to the ropinirole group had a significantly reduced risk of developing dyskinesia, regardless of whether or not they received open-label levodopa supplementation ($p < 0.001$). Dyskinesias developed in 40 of 88 patients (45%) in the levodopa group, compared with only 36 of 177 ropinirole-treated patients (20%) (OR = 3.9:1). When analysis

Figure 16 Survival analyses demonstrating time to develop dyskinesia in three separate trials.[310,333,334]

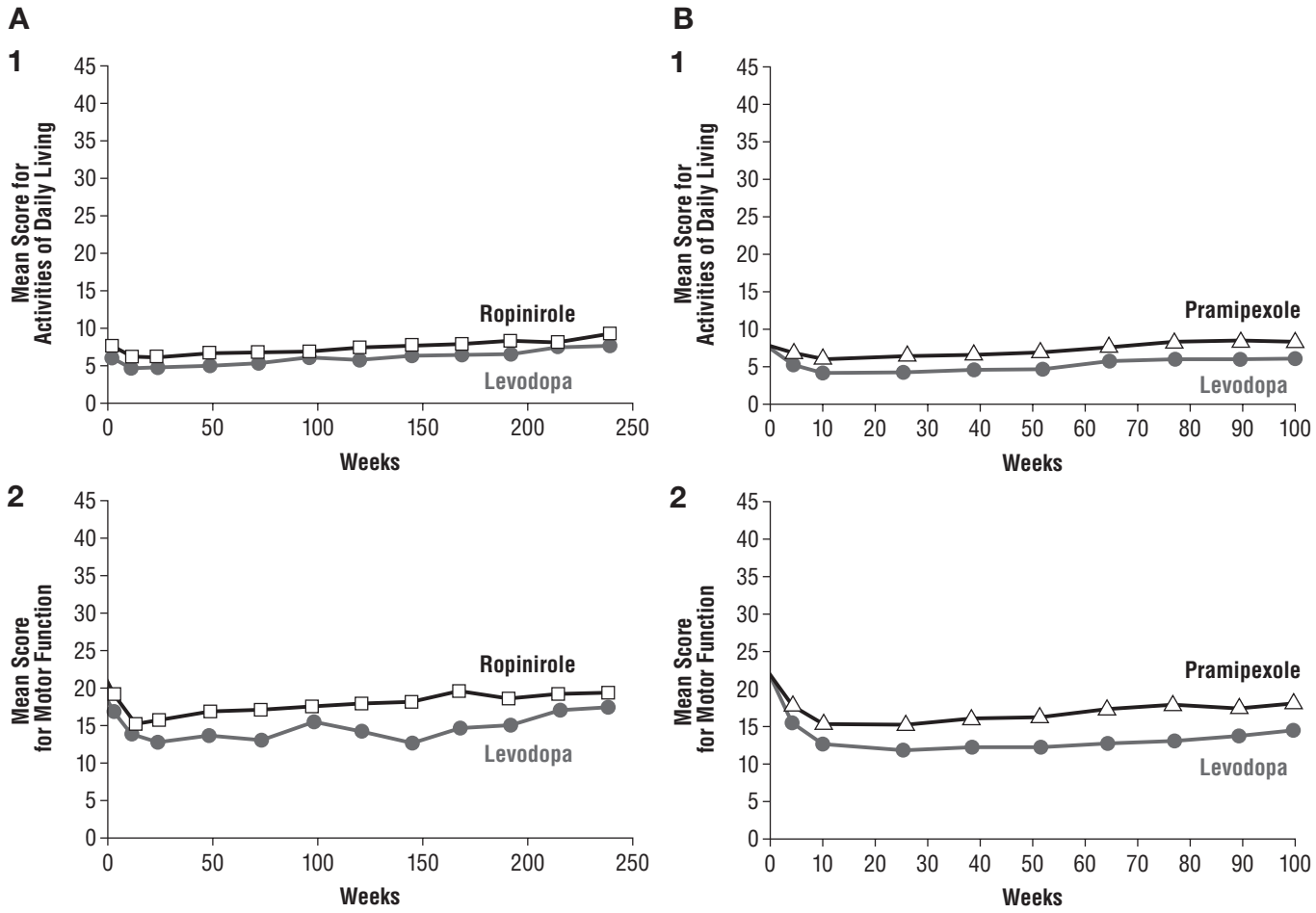


Note that randomization to the dopamine agonist ropinirole, pramipexole, or pergolide was associated with a reduced risk for developing dyskinesia, compared with levodopa, even though patients on dopamine agonists could receive supplemental treatment with levodopa when deemed necessary.

was restricted to patients who were able to remain on monotherapy and did not require open-label levodopa supplementation, only 5% of ropinirole-treated patients developed dyskinesia compared with 36% of those on levodopa monotherapy (OR = 15:1; $p < 0.001$). The risk for developing disabling dyskinesias was assessed as a secondary outcome, and yielded similar results in favor of ropinirole-treated patients. Open-label follow-up of these patients for up to 10 years noted that there continued to be reduced dyskinesia in patients originally randomized to ropinirole, although only relatively small numbers of patients were still being followed.[335]

CALM-PD was a prospective, double-blind study designed to evaluate the risk of developing motor complications in 301 untreated patients with early PD randomized to receive initial treatment with the dopamine agonist pramipexole vs levodopa/carbidopa.[334] Dosage adjustment was permitted during the titration phase, and patients in either group could receive supplemental open-label levodopa if deemed necessary. After approximately 2 years of treatment, patients in the pramipexole group were receiving a mean daily dose of 2.78 mg of pramipexole and 264 mg of supplemental levodopa whereas patients in the levodopa group received a mean daily levodopa dose of 509 mg. The primary end point was the time to the first occurrence of any of three motor complications: dyskinesia, wearing off, or "on-off" effects. The risk of developing a motor complication was greater in patients assigned to levodopa in comparison with those randomized to pramipexole ($p < 0.001$). Fifty-one percent of subjects randomized to initial treatment with levodopa reached the primary end point compared with only 28% of subjects randomized to begin therapy with pramipexole (hazard ratio 0.44, $p < 0.001$). In comparison with patients assigned to levodopa, pramipexole-treated patients had a reduced frequency of dyskinesia (10% vs 31%; $p < 0.001$), reduced wearing-off effects (24% vs 38%; $p = 0.009$), and reduced "on-off" effects (1% vs 5%; nonsignificant). These results persisted after 4 years of follow-up.[336] Again, motor complications (i.e., wearing-off or dyskinesia) occurred more commonly in the levodopa group than in the pramipexole group (74% vs 51.7%; $p < 0.001$). The most robust difference was in the rate of dyskinesia, which was present in 54% of patients in the levodopa group vs 24.5% in the pramipexole group ($p < 0.0001$). A subset of patients in this study underwent β-CIT SPECT studies, which

Figure 17 UPDRS activities of daily living and motor function scores of patients randomized to the dopamine agonist pramipexole or ropinirole vs levodopa.[333,334]



Note that patients randomized to initiate therapy with levodopa had superior benefits compared with those randomized to a dopamine agonist, even though they could receive supplemental levodopa when deemed necessary. Adapted with permission from A) Rascol O, Brooks DJ, Korczyn AD, De Deyn PP, Clarke CE, Lang AE. A five year study of the incidence of dyskinesia in patients with early Parkinson's disease who were treated with ropinirole or levodopa. N Engl J Med 2000;342:1484–1491. Copyright © 2000 Massachusetts Medical Society. All rights reserved and B) JAMA 284(15):1931–1938. Copyright © 2000 American Medical Association. All rights reserved.

demonstrated that patients in the pramipexole group had a slower decline in this surrogate biomarker of nigrostriatal function in comparison with levodopa[203] (see discussion under Neuroprotection).

Interestingly, in both the ropinirole and pramipexole vs levodopa studies, patients randomized to the levodopa group had small but significantly greater benefits on the motor and ADL subscales of the UPDRS at each visit (figure 17). It is hard to explain these findings because patients in both groups could have received supplemental open-label levodopa at any time point during the study if either the physician or the patient felt that additional treatment was necessary, and withdrawal rates in the different groups were similar. It is possible that the UPDRS does not completely capture all features related to parkinsonian disability, especially in early patients. In this regard, it is noteworthy that the dopamine agonist pramipexole has been shown to have antidepressant effects in double-blind, controlled studies,[337-339] and quality of life scores at 4 years in the CALM-PD study were comparable in the two groups, trending in favor of pramipexole therapy.[336] It has been suggested that the UPDRS scale is not particularly sensitive to changes that occur in patients with early PD.[340] A modified version of the UPDRS scale (MDS-UPDRS)[341] and a new nonmotor questionnaire[342,343] have recently been developed to capture additional aspects of PD that might benefit from early dopaminergic therapy that might not have been captured on the traditional UPDRS.[344] It is also possible that because levodopa provides greater symptomatic benefits than a dopamine agonist, it might thereby prevent decompensation in parkinsonian features that cannot be recaptured by later introduction of the medication.

An important subanalysis derived from these studies demonstrated that the latency until dyskinesia developed after the addition of levodopa was the same

whether levodopa was used as initial therapy or added as an adjunct to patients who had been initially randomized to receive either ropinirole or pramipexole.[345,346] Thus, dopamine agonists such as ropinirole and pramipexole do not seem to reduce the risk of dyskinesia once levodopa is added, but rather provide benefit with respect to dyskinesia by delaying the time until levodopa treatment is required and permitting lower doses of levodopa to be used. Long-term studies to assess the clinical significance of reduced early motor complications have not been performed, and while it seems intuitive, it has not been established that the onset of early dyskinesias necessarily increases the risk of later developing disabling dyskinesias. Furthermore, long-term studies indicate that while almost all patients eventually develop motor complications, the nondopaminergic features of the illness are the major sources of disability in advanced patients.[9]

Pramipexole is typically initiated at a dose of 0.25 mg and gradually titrated to 1.5 mg TID depending on patient's response. It should be noted that in dosing studies, the group receiving 0.5 mg TID had benefits comparable with those receiving higher doses, but with fewer side effects.[328] We, therefore, typically titrate patients to 0.5 mg TID and use higher doses on an individual basis rather than as part of a routine titration schedule. Ropinirole is initiated at a dose of 0.25 mg TID and titrated to 1 to 3 mg TID. This dose may be ineffective for many patients, and titration to higher doses (up to 24 mg/d) is generally necessary to see a benefit. Thus, pramipexole probably titrates to too high a level and ropinirole to too low a level. Physicians should titrate patients on an individual basis until the desired result is obtained. Given the side effect profile of these drugs, many physicians now prefer to use dopamine agonists at a relatively low dose and avoid higher doses which are associated with a greater risk of side effects (see side effects, page S33).

Similar results with respect to the risk of developing dyskinesia have been observed with cabergoline[311] and pergolide.[310] In both of these studies, the time to onset and the frequency of motor complications were significantly reduced in patients randomized to receive the dopamine agonist compared with levodopa. In the cabergoline study, 34% of patients randomized to receive levodopa developed motor complications over 3 to 5 years, compared with 22% of those who received the agonist ($p < 0.02$). The pergolide study differed in that levodopa "rescue" medication was not permitted. During the 3 years of the trial, the time to onset of dyskinesia and severity of motor complications were significantly better in patients randomized to pergolide. As in the ropinirole and pramipexole studies, patients randomized to initial therapy with levodopa also had slightly greater clinical improvement. Because of the risk of cardiac valve damage, use of pergolide and cabergoline has been markedly curtailed.

Each of these studies demonstrates that initiating PD treatment with a relatively long-acting dopamine agonist is associated with a reduced risk of developing motor complications compared with short-acting levodopa. Indeed, dyskinesias are primarily related to the introduction of levodopa, and rarely develop in patients who can be maintained on dopamine agonist monotherapy. However, as stated, the long-term significance of avoiding dyskinesias remains to be determined. The Sydney long-term study noted that although 95% of patients had motor complications after 15 years, disability was primarily related to the development of nondopaminergic features[9] (see discussion later).

A long-acting preparation of ropinirole (ropinirole 24-hour prolonged release) has now been approved in several countries. This is a once-daily preparation that uses Geomatrix technology (SkyePharma, London, UK) to allow for slower absorption of the drug from the gastrointestinal tract. This allows for less fluctuation in plasma drug levels and permits drug levels to be maintained during the waking day and to drop off during the night. This may lead to better compliance and more consistent symptom response throughout the day and perhaps better nighttime symptom control. In an adjunct study (EASE-PD), ropinirole 24 hours provided improvement in UPDRS motor and quality-of-life scores comparable with the immediate-release form of the drug and was well tolerated.[347] A long-acting formulation of pramipexole is currently in development.

Rotigotine is a new dopamine agonist that has been investigated in both early and advanced PD and is unique in that it is administered by transdermal or patch technology.[348] Rotigotine is a nonergot, lipid soluble aminotetralin derivative with a strong structural resemblance to dopamine.[349] The drug activates D_3, D_2, and D_1 dopamine receptors and has motor benefits in animal models of PD. It has a short half-life when administered by mouth due to extensive first-pass hepatic clearance.[350] As a transdermal patch formulation, however, rotigotine avoids first-pass hepatic metabolism and provides steady-state plasma levels with one patch application daily. Patch sizes (cm^2) with corresponding doses of rotigotine (mg) used in clinical trials were as follows: 10 cm^2, 4.5 mg; 20 cm^2, 9 mg; 30 cm^2, 13.5 mg; 40 cm^2, 18 mg; and 60 cm^2, 27 mg. Over the course of 24 hours, these deliver 2 mg, 4 mg, 6 mg, 8 mg, and 12 mg of active drug. These different reportings of dosage are confusing, and it is the latter nomenclature (mg delivered per 24 hours) that are used in the commercial product. In

clinical trials, rotigotine has been shown to be safe and well tolerated and to provide benefits in both monotherapy and levodopa add on studies,[351-356] although there have also been negative trials.[357]

A double-blind, placebo-controlled, parallel-group, dose-ranging study was performed in 242 patients with early PD randomized to receive rotigotine in patches containing 4.5 mg, 9 mg, 13.5 mg, or 18 mg/day (delivering 2, 4, 6, or 8 mg/day) or placebo.[352] Significant improvement was observed in UPDRS ADL and motor scores for patients given 6 mg/day (-4.83 points; $p < 0.001$) and 8 mg/d (-5.23 points; $p < 0.001$). Another placebo-controlled trial in 277 patients with early PD showed that patients titrated to receive up to 6 mg of rotigotine had significant improvement over placebo in total UPDRS score with a mean improvement of 3.98 points compared with a mean worsening of 1.31 points in placebo-treated patients ($p < 0.0001$).[353] In another monotherapy trial, patch rotigotine 8 mg/d improved motor and ADL scores compared with placebo, but was significantly inferior to ropinirole in this same trial.[354]

Several placebo-controlled trials have assessed rotigotine as an adjunct to levodopa in advanced PD. In one study, "off" time was reduced by a mean of 2.7 hours with the 40 cm^2 (8 mg delivered) patch ($p < 0.0001$ vs placebo), 2.1 hour with the 60 cm^2 (12 mg delivered) patch ($p = 0.003$ vs placebo), and 0.9 hours for the placebo group.[355] The rate of response (defined as patients with at least a 30% reduction in "off" time) was 57% with the 40 cm^2 (8 mg delivered) patch and 55% with the 60 cm^2 (12 mg delivered) patch, compared with 34% in the placebo group ($p < 0.001$ for both active treatment groups vs placebo). In a second levodopa adjunct study, rotigotine was not inferior to pramipexole in terms of change in absolute "off" time (although pramipexole had greater absolute benefit).[356] However, rotigotine was inferior to pramipexole with respect to responder rate. In yet another study, rotigotine patch in doses of 20, 40, or 60 cm^2 (delivering 4, 8, or 12 mg/d) provided no significant improvement in "off" time compared with placebo.[357]

Rotigotine patch was well tolerated in these trials and had a safety profile similar to other dopamine agonists, except for increased skin reactions at the site of the patch application. These were encountered in approximately 40% of individuals, but were rarely serious. Skin reactions can be minimized by changing the application site after each patch and ensuring that the skin is regularly cleaned. Transdermal delivery of rotigotine has been shown to provide constant plasma levels and should cause a negligible risk of developing dyskinesias, although this has not been formally tested in patients with PD. When the drug was administered continuously to the MPTP-lesioned monkey, motor benefits comparable with levodopa were seen with much less dyskinesia than with either levodopa or intermittent injections of rotigotine (personal observations, P. Jenner, C.W. Olanow, 2009).

The novelty of rotigotine is the transdermal delivery system and once-daily dosing. It is well established that patient compliance with medical therapy decreases with more frequent daily doses, even in patients with PD.[358,359] Transdermal delivery bypasses some of the obstacles associated with levodopa pharmacotherapy, including the adverse effects related to slowed gastrointestinal motility and competition with dietary proteins. This method of drug delivery will also allow treatment for patients with PD with dysphagia and for those in the perioperative period who cannot take medication by mouth.

The superior efficacy obtained with the 8-mg patch compared with the 12-mg patch, coupled with the apparent superior efficacy of ropinirole and pramipexole, raises the possibility that 24-hour continuous delivery of rotigotine has induced tolerance and limited the potential benefits of this drug. This is a particular concern with rotigotine as it activates D1 and D2 dopamine receptors. In animal models, continuous activation of the D1 receptor is prone to induce tolerance. Studies are currently planned to determine if higher rotigotine doses provide enhanced efficacy, and/or if the drug causes tolerance. Restricting use of the patch to the waking day might avoid the problem of tolerance, allow for enhanced efficacy, and diminish the risk of irritating skin reactions. Conversely, 24-hour delivery is likely to be of value in preventing early-AM dystonia and benefiting patients with nocturnal akinesia. Studies to assess the affect of the patch on these symptoms are currently under way.

It should be noted that rotigotine patches have recently been recalled in the United States because of the drug's potential to crystallize in the patch leading to erratic dosing. It is anticipated that the drug will be reintroduced once this issue has been resolved.

Side effects of dopamine agonists. The acute side effects of dopamine agonists are similar to those observed with levodopa and include nausea, vomiting, and postural hypotension. They tend to occur with the initiation of treatment and to abate as tolerance develops usually over the ensuing days to weeks. These side effects can be minimized by initiating treatment at a low dose and gradually titrating to the desired clinical response. The use of domperidone, where available, minimizes dopaminergic side effects and permits faster titration. Neuropsychiatric problems such as hallucinations occur more frequently with agonists than with levodopa and are particularly prone to oc-

cur in the elderly or in those with cognitive impairment. The ergot-derived dopamine agonists can be associated with a Raynaud's-like phenomena, erythromelalgia, and pulmonary or retroperitoneal fibrosis.[360] These events are relatively uncommon and are not seen with the nonergot dopamine agonists. As described above, valvular fibrosis may occur in as many as 30% of patients receiving ergot-based dopamine agonists and can lead to valvular dysfunction with the need for surgical repair in extreme cases.[313-316] This has resulted in withdrawal of pergolide from the market, and a marked reduction in the use of the other ergot agonists. When these agents are used, it is essential that patients be periodically monitored with echocardiography to detect valvular alterations.

Sedation with excess daytime sleepiness (EDS) and possible unwanted sleep episodes have been associated with the use of dopamine agonists. Sleep disturbances are common in PD, affecting as many as 80% to 90% of patients.[361,362] The importance of EDS is highlighted by the report of the cases of eight patients who were taking dopamine agonists and suddenly fell asleep while at the wheel of a motor vehicle.[363] The authors termed these episodes "sleep attacks" because they came on without apparent warning. It is now evident that EDS and unwanted sleep episodes are more common than was previously appreciated, and that they can be associated with any dopaminergic drug, including levodopa.[364,365] The notion that these episodes are sleep attacks has been questioned,[366] as such sudden onsets of sleep are not thought to occur under physiologic or pathologic conditions. The concept of a sleep attack has been abandoned in narcolepsy, and the term is not currently recognized by the American Academy of Sleep Medicine or the International Classification of Sleep Disorders.[367] Rather, it has been proposed that these sudden episodes of falling asleep likely represent an extreme form of somnolence related to the common sleep disturbances in PD coupled with the propensity of dopaminergic drugs to induce dose-related sedation.[366] Dopaminergic medications, and dopamine agonists in particular, are known to have dose-related sedative side effects.[308,328,333,334] Sudden episodes of sleepiness often go unnoticed because subjective estimates of sleepiness are often unreliable and patients may be amnestic for the drowsiness that antedates falling sleep. To detect sleepiness, it is preferable to use scales such as the Epworth sleepiness scale (ESS)[368] or the PD sleep scale (PDSS),[369] which assess the propensity to experience unintended sleep episodes and do not rely upon subjective estimates of sleepiness. The true prevalence of sleep attacks is difficult to estimate because most studies do not distinguish them from sleep episodes that occur in association with preexisting ambient drowsiness. Estimates have ranged from 3.8% to 32%, depending on the methodology and definition.[370-373] In one study, 100 consecutive patients with PD and age-matched controls were evaluated with the ESS. Seventy-six percent of patients had EDS and 24% had sleep levels comparable with patients with narcolepsy.[374] ESS scores were significantly increased compared with controls. Regardless of the underlying mechanism, physicians and patients should be aware of this potential problem, particularly in patients on dopamine agonists. Routine assessments of "sleepiness" should be performed on patients receiving dopaminergic medications. Management should include proper sleep hygiene, ruling out underlying sleep disorders, and using the lowest dose of a dopamine agonist that provides satisfactory clinical control.[375] Patients who have EDS should not drive until this problem has resolved and consideration given to lowering the dose of the dopamine agonist. See section on sleep disorders on page S89 for further discussion of this issue.

Other problems related to the use of dopamine agonists include weight gain (possibly related to overeating)[376] and edema (especially in the lower extremities).[377] In one study, leg swelling developed in 7% of pramipexole-treated patients within 1 year of treatment. A history of coronary artery disease increased the risk for developing edema in this study. More recently, attention has been focused on the association of dopamine agonist treatment with the development of a variety of ICDs, such as pathologic gambling, hypersexuality, and compulsive eating and shopping.[378] This has attracted considerable scientific interest because of the known relationship between dopamine and reward, and is discussed in more detail in the neuropsychiatric problems section, page S70. Although much remains to be learned about the role of dopamine agonists in the evolution of these problems, physicians should probe for the presence of these problems, as patients may be reluctant to report them, and advise patients of the potential that they might occur.

Apomorphine is a short-acting dopamine agonist that has been used primarily as a "rescue agent" for patients with advanced PD who experience disabling "off" periods. When administered parenterally, apomorphine provides rapid benefit that lasts around 45 to 60 minutes[379,380] and can be useful for the acute management of unpredictable or levodopa-unresponsive "off" episodes. Apomorphine is a lipophilic water-soluble compound that requires no active transport mechanism to reach the brain. Apomorphine has high in vitro binding affinity for D4 dopamine receptors, moderate affinity for D2, D3, and

D5 receptors, and low affinity for D1 receptors.[381] The drug is usually administered subcutaneously but can also be administered by IM, sublingual, rectal, oral, and transdermal routes.[382] In a two-phase, double-blind study, 29 levodopa-responsive subjects were randomized to receive treatment with subcutaneously injected apomorphine or placebo.[383] Subjects were pretreated for 3 days with trimethobenzamide 250 mg TID before their initial apomorphine dose. During the first (inpatient) phase of the study, patients were initiated on treatment with 2 mg apomorphine injections, and the dose increased by 2 mg at 2-hour intervals until patients either attained a "levodopa-equivalent response" or a dose of 10 mg was reached. In the second (outpatient) phase of the study, subjects were instructed to take apomorphine as needed for reversal of "off" episodes (up to 5 times per day) at the highest dose tolerated during the inpatient portion of the study. The mean effective dose per injection was 5.4 mg. The drug had a mean latency to onset of 22 ± 2.4 minutes. Approximately 95% of hypomobility episodes were successfully aborted with apomorphine, compared with 23% with placebo ($p < 0.001$). Total daily "off" time was reduced by a median of 2 hours in apomorphine-treated patients, whereas there was no change in the placebo group. The total time spent with dyskinesias did increase, but the magnitude of dyskinesias was not changed. Regular apomorphine use did not make subsequent doses less effective. Studies have also shown that chronic treatment does not adversely effect the time to onset of benefit after an apomorphine injection compared with apomorphine-naïve subjects.[384] Side effects of apomorphine are similar to other dopamine agonists but include yawning after injections. Local skin irritation and bruising is common but is rarely a serious problem and can be minimized by rotation of injection sites.

Few direct comparisons have been made between the different dopamine agonists. A double-blind crossover study demonstrated that pergolide and bromocriptine were of approximately equal efficacy as adjuncts to levodopa in patients with advanced PD.[385] In a double-blind direct comparison between ropinirole and bromocriptine in untreated patients with PD, ropinirole was shown to be superior (35% vs 28% improvement in UPDRS score; $p < 0.05$).[386] Ropinirole benefits were still noted at 3 years, but the number of patients who could be maintained on monotherapy was not significantly different in the two groups.[387] In another study in untreated patients with early PD, ropinirole was superior to rotigotine,[354] but these results may be partially explained by the fact that there were dose limitations for patients in the rotigotine group, although in this study the highest rotigotine dose did not provide superior benefits compared with lower doses. As an adjunct to levodopa, rotigotine was not inferior to pramipexole in measures of "off" time, but pramipexole provided enhanced benefits and responder rates were greater in the pramipexole group.[356] The possibility that continuous delivery of rotigotine induced tolerance and limited its maximal efficacy may explain these results and warrants further investigation.

As discussed in the section on neuroprotection, laboratory studies suggest that dopamine agonists may have neuroprotective effects in PD,[195,196] and clinical trials demonstrate that ropinirole and pramipexole are associated with a reduced rate of decline in an imaging biomarker of nigrostriatal function compared with levodopa.[202,203] Although these results are consistent with the drugs having a disease-modifying effect, this has by no means been established. Nonetheless, there are several theoretical mechanisms by which dopamine agonists might provide a protective effect in PD: a) reduction of the need for levodopa thereby minimizing the formation of levodopa-mediated oxidative metabolites; b) stimulation of D2 autoreceptors so as to decrease dopamine synthesis and metabolism and thereby reduce their oxidative byproducts[388]; c) agonist-mediated direct antioxidant effects; d) suppression of overactivity in STN neurons thereby reducing the risk of STN-mediated excitotoxicity in target structures[389]; and e) antiapoptotic effects through receptor-mediated activation of the PI3K/AKT pathway[198] and nondopaminergic pathways.[202] Interestingly, although all agonists seem to have comparable effects on receptor-coupled G proteins (which presumably relate to their capacity to provide motor benefits in PD), they have different effects on their capacity to activate the PI-3k/AKT pathway and to protect dopamine neurons.[198] This fascinating observation suggests that even though dopamine agonists may bind to the same receptor, they may activate different signaling pathways within the cell and thereby mediate different functional effects. This has recently been demonstrated with agonists for the serotonin receptor[390] and may be a valuable property to exploit in attempts to develop drugs that have desired (protective) effects, while avoiding undesired (adverse) effects. A delayed start study is now being conducted to compare the effect of early vs late treatment with pramipexole (the PROUD study) to try and further determine if it has disease-modifying effects.

In summary, dopamine agonists have been shown to have antiparkinsonian effects when used as an adjunct to levodopa in patients with advanced disease. It has also been demonstrated that initiating therapy with a dopamine agonist provides antiparkinsonian benefits with a reduced risk of developing motor complications compared with levodopa. However, dopamine agonists are less efficacious than levodopa

and levodopa supplementation is eventually required, which in turn increases the risk of developing motor complications. Indeed, two studies have now shown that the time to onset of motor complications from when levodopa is introduced is the same whether levodopa is used as initial therapy or as an adjunct to the dopamine agonist.[345,346] Thus, dopamine agonists primarily serve to delay the onset of motor complications by delaying the time until levodopa is required, but do not prevent motor complications once levodopa is introduced. In addition, side effects such as leg swelling, sedation, hallucinations, and ICDs are more commonly seen with dopamine agonists than with levodopa. To reduce the risk of adverse events, we prefer to use relatively low doses of dopamine agonists and to combine them with other dopaminergic agents when required. As with other dopaminergic therapies, dopamine agonists do not address the nondopaminergic features of PD such as falling, freezing, and dementia which themselves can represent a major source of disability for patients with PD. That dopamine agonists have disease-modifying effects is theoretically possible, but has not been established.

There are little data to help choose between the different dopamine agonists, and physicians generally use the agonist with which they have the most experience and are most comfortable. Because of the titration schedules that are used, pramipexole tends to provide efficacy in a shorter time period and may be preferable for patients with more severe disability, whereas ropinirole offers a slower titration schedule that may lead to fewer side effects and be preferable for more fragile patients. Rotigotine has shown efficacy inferior to that of both ropinirole and pramipexole, but offers the convenience of once-daily dosing. A new extended-release oral formulation of ropinirole also offers once-daily dosing. An extended-release formulation of pramipexole is in development. In deciding to initiate therapy with a dopamine agonist, it is important to consider the benefits as well as the side-effect profile. Acute side effects are generally overcome by slow titration, but physicians should be aware of sedation with EDS and the risk of ICDs and advise patients accordingly. A summary of the advantages and disadvantages of dopamine agonists is listed in table 8.

Table 8 Dopamine agonists: Advantages and disadvantages

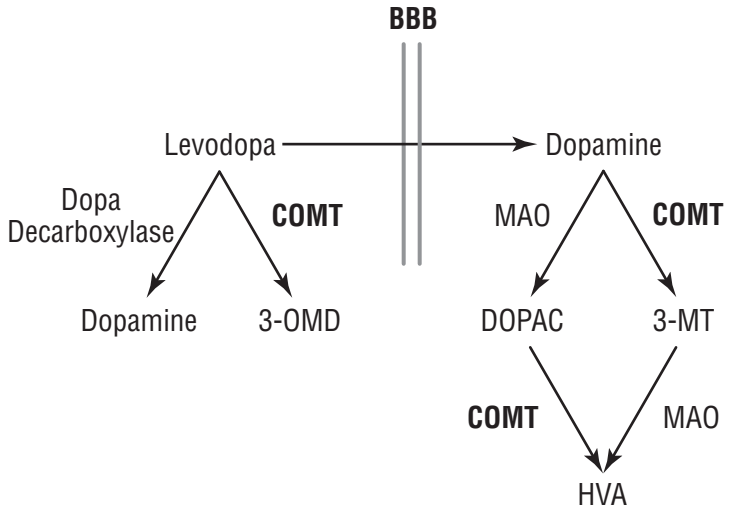
Advantages
Antiparkinsonian effects when used as monotherapy or as an adjunct to levodopa
Reduced risk of developing levodopa-related motor complications
Do not generate oxidative metabolites
Levodopa sparing effect
Potential neuroprotective benefits
Disadvantages
Dopaminergic side effects (nausea, vomiting, orthostatic hypotension)
Neuropsychiatric side effects (hallucinations, psychosis, and ICDs)
Excessive daytime sleepiness
Ergot-related side effects with some ergot-derived agonists (erythromelalgia, pulmonary fibrosis, cardiac valve fibrosis)
Swelling of legs and weight gain
Do not eliminate the need for levodopa
Do not treat nondopaminergic features of PD, such as freezing, postural instability, autonomic dysfunction, and dementia

PD = Parkinson disease; ICD = impulse control disorder. Adapted with permission from Olanow et al.[15]

COMT inhibitors. Levodopa is metabolized primarily by the aromatic L-amino acid decarboxylase (AADC) enzyme to form dopamine. For the past 30 years, levodopa has routinely been administered in combination with an aromatic AADC inhibitor to prevent the peripheral accumulation of dopamine. When levodopa is administered with a decarboxylase inhibitor, the drug is metabolized primarily by the COMT enzyme to form the inert metabolite 3-O-methyldopa (3-OMD) (figure 18). Administration of levodopa with a COMT inhibitor increases its elimination half-life (from about 90 minutes to about 3 hours) and increases its plasma area under the curve (AUC). COMT inhibitors were tested based on their potential to increase brain levodopa availability and enhance efficacy. Two COMT inhibitors have been approved as adjuncts to levodopa for the treatment of PD; tolcapone (Tasmar) and entacapone (Comtan, Comtess). Both COMT inhibitors reduce the formation of 3-OMD, which can potentially compete with levodopa for transport into the brain through the LNAA pathway. Tolcapone inhibits both peripheral and, to a lesser extent, central COMT, whereas entacapone acts only in the periphery.

COMT activity was inhibited by about 80% to 90% with tolcapone and by 50% to 75% with entacapone when both agents were administered in clinically relevant doses.[391,392] Pharmacokinetic studies demonstrate that both agents increase the plasma levodopa elimination half-life, with tolcapone being more potent and having a greater effect on levodopa pharmacokinetics and efficacy. Tolcapone nearly doubles the AUC, whereas entacapone increases it by 35%. Single doses do not cause a rise in either the maximal plasma concentration (C_{max}) or the time to reach maximal plasma concentration (T_{max}),[393,394] but chronic dosing is associated with accumulation

Figure 18 Peripheral and central metabolic pathways for levodopa.



BBB = blood-brain barrier; COMT = catechol-*O*-methyltransferase; MAO = monoamine oxidase; 3-OMD = 3-O-methyldopa; DOPAC = dihydroxyphenylacetic acid; 3-MT = 3-methoxytyramine.

over the course of the day. COMT inhibitors are effective when administered in conjunction with either regular or sustained-release Sinemet[395] and increase interdose, trough, and mean levodopa concentrations.[396] Thus, administration of levodopa plus a COMT inhibitor results in smoother plasma levodopa levels and more continuous brain availability compared with levodopa alone.[396] This can be illustrated with FD-PET studies, which demonstrate increased and more sustained striatal FD uptake when levodopa/carbidopa is administered with a COMT inhibitor.[397] Thus, administering levodopa with a COMT inhibitor has the potential to deliver levodopa to the brain in a more predictable and stable fashion, thus decreasing the fluctuations in levodopa concentrations seen when standard levodopa is administered intermittently.

The addition of a COMT inhibitor to levodopa has been shown to translate into clinical benefits for patients with PD. Double-blind, placebo-controlled trials have demonstrated that both tolcapone and entacapone increase "on" time, decrease "off" time, and improve motor scores for patients with PD who experience motor fluctuations.[398–401] Periods of poor motor function ("off" time) were reduced by 26% to 50%, whereas periods of good motor function ("on" time) were increased by 15% to 25%. Mean daily "on" time was increased by as much as 2.5 hours compared with placebo ($p < 0.001$) and the mean duration of the "on" response after each dose of levodopa was increased by 34 minutes. This benefit was associated with a 16% to 40% reduction in the mean daily dose of levodopa. Benefits have been shown to persist for 3 years or longer.[402] In general, superior clinical benefits have been achieved with tolcapone, reflecting the increased level of COMT inhibition.

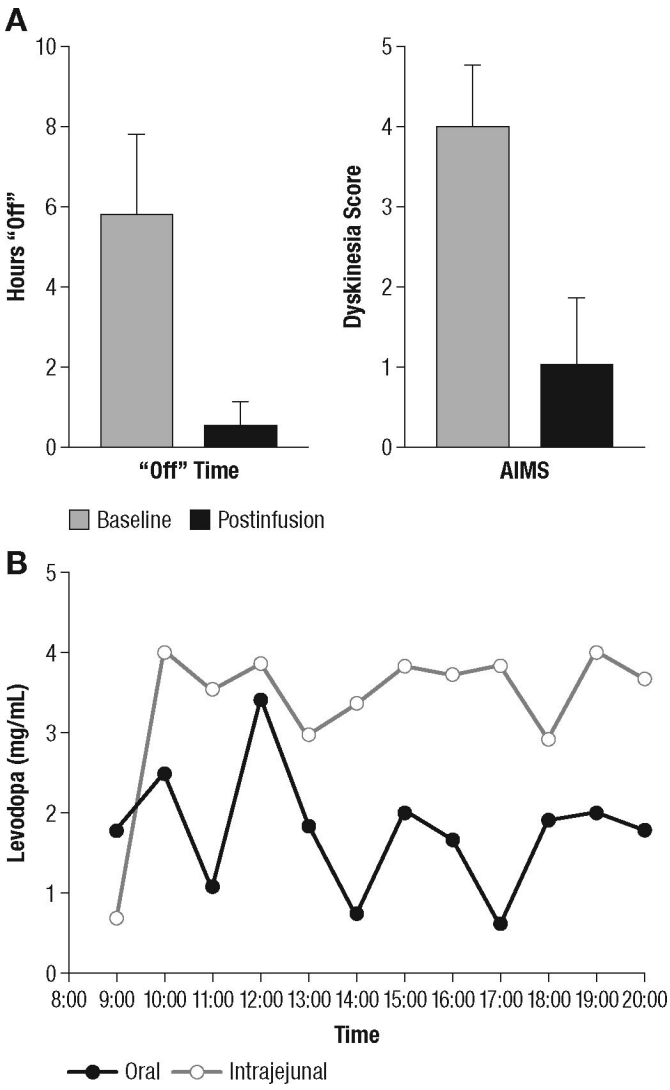
Benefits with COMT inhibitors have also been observed in stable patients PD who have not yet begun to experience motor fluctuations. Two double-blind, placebo-controlled studies in patients with PD with stable responses to levodopa demonstrated that patients randomized to receive tolcapone therapy had improved ADL and motor scores, and required lower levodopa doses, compared with placebo-treated patients.[403,404] Similar results were reported with entacapone in one study,[405] whereas in another study, the addition of entacapone to levodopa in stable patients with PD did not improve UPDRS motor scores but did provide significant improvement in several quality-of-life measures, including the PD Questionnaire-39 and investigator and subject clinical global assessments.[406]

Tolcapone is administered in doses of 100 or 200 mg TID, with the 200-mg dose providing greater efficacy. Entacapone is administered in a dose of 200 mg in combination with each dose of levodopa. Either of the agents can be initiated without titration, and side effects addressed if and when they occur. Neither tolcapone nor entacapone has antiparkinsonian effects when administered in the absence of levodopa.

A combination of carbidopa/levodopa plus 200 mg of entacapone has been made available in a single tablet (Stalevo) in formulations containing 50, 75, 100, 150, and 200 mg of levodopa. Because tablets of different levodopa strengths contain the same amount of entacapone, it is not recommended to take more than one tablet per dose. Stalevo has the advantage that the patient need to take only a single pill, and has been shown to be well tolerated in fluctuating patients with PD.[407] Studies comparing patients taking carbidopa/levodopa plus entacapone vs Stalevo have demonstrated comparable efficacy (to be expected), but a majority of patients preferred the convenience of taking Stalevo.[408,409] Conversion from sustained-release carbidopa/levodopa to Stalevo resulted in improved motor function, quality of life, and less sleepiness.[410]

A few studies have directly compared entacapone and tolcapone. An open-label study suggested that tolcapone was more efficacious than entacapone in long-term control of "off" time.[411] In a blinded study, substitution of entacapone did not fully compensate for withdrawal of tolcapone.[412] In a second double-blind study, patients were optimized on entacapone and then randomized to either remain on entacapone or switch to tolcapone.[413] In comparison with the original baseline, 29% of tolcapone-treated patients experienced an increase in "on" time of ≥3 hr/d, compared with 11% of

Figure 19 A comparison of levodopa administered by standard oral dosing and by continuous intraintestinal infusion.[416]



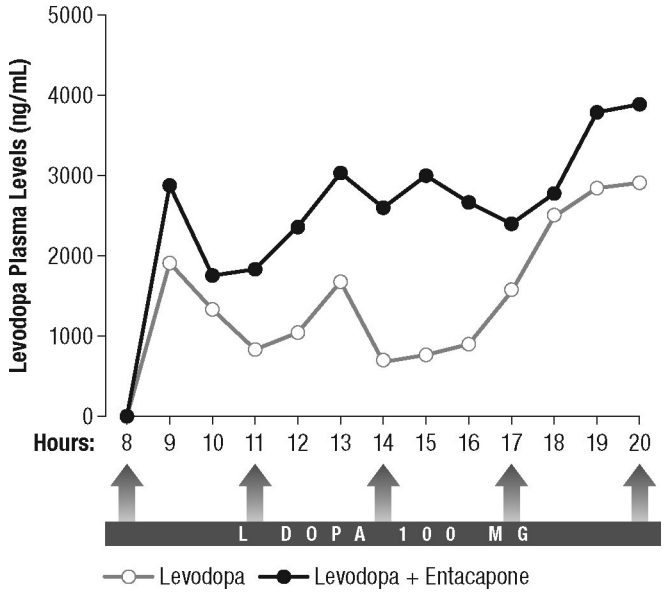
A) Mean number of "off" hours and dyskinesia scores at baseline when patients were treated with regular levodopa and after 6 months of treatment with a continuous levodopa infusion. Note that continuous delivery is associated with improvement in both "off" time and dyskinesia scores. B) Levodopa plasma pharmacokinetics when patients received levodopa administered orally or by continuous infusion. Note that infusion is associated with more continuous plasma levels and avoids low trough levels. AIMS = Abnormal Voluntary Movement Scale. Reproduced with permission from Stocchi et al.[416] Arch Neurol 62(6): 905–910. Copyright © 2005 American Medical Association. All rights reserved.

those maintained on entacapone ($p = 0.01$). Tolcapone-treated patients also had almost 1 hour more of "on" time than did patients in the entacapone treatment group ($p = 0.04$).

There has also been interest in the potential of COMT inhibitors to reduce the risk for motor complications associated with standard doses of levodopa.[414,415] This is based on the concept that intermittent doses of short-acting levodopa leads to pulsatile stimulation of dopamine receptors and motor complications (see section on motor complications earlier). COMT inhibitors extend the elimination half-life of levodopa (from 90 minutes to approximately 180 minutes) and thus, if administered frequently enough, might provide continuous levodopa to the brain.

A proof of concept study demonstrated that patients treated with a continuous infusion of levodopa had significant reductions in both "off" time and dyskinesias compared with those treated with intermittent oral doses of standard levodopa[416] (figure 19A). Pharmacokinetic analyses performed as part of this study showed that continuous infusion avoids the periodic low trough levels that are associated with intermittent oral doses of levodopa (figure 19B). The authors postulated that low plasma trough levels of levodopa translate into low striatal dopamine levels and result in discontinuous or intermittent (pulsatile) stimulation of striatal dopamine receptors. They further posited that continuous infusion causes fewer motor complications because infusion delivers levodopa to the brain in a more continuous and physiologic manner. They also hypothesized that an oral levodopa treatment strategy that mirrors the pharmacokinetic profile of a continuous infusion should provide comparable benefits. Attempts to reproduce this pattern with multiple dosing regimens of regular and controlled-release Sinemet (varying the dose and the timing) failed to avoid low trough levels. This may account for why Sinemet CR did not reduce the risk for motor complications compared with regular levodopa.[417,418] However, when levodopa was combined with a COMT inhibitor and administered at 3-hour intervals, the plasma pharmacokinetic profile strongly resembled that obtained with a levodopa infusion (figure 20).[233] Furthermore, studies in monkeys showed that administration of levodopa plus the COMT inhibitor entacapone provided enhanced benefits with reduced dyskinesias compared with treatment with levodopa alone.[419] This hypothesis has been tested in a clinical trial, Stalevo Reduction in Dyskinesia Evaluation (STRIDE-PD), which compared the time to onset and frequency of dyskinesia in levodopa-naïve PD patients who were randomized to initiate levodopa therapy with carbidopa/levodopa compared with carbidopa/levodopa/entacapone (Stalevo) administered four times per day (at 3.5-hour intervals). The study demonstrated that patients randomized to Stalevo had an increased frequency and a shorter time to dyskinesia than did those on standard levodopa, in contrast to the hypothesis (C.W. Olanow, personal observations, 2009). This disappointing result likely ensued because administering Stalevo at 3.5 hour intervals failed to achieve CDS, and because patients randomized to Stalevo had a higher levodopa load which has been shown to be associated with increased dyskinesia in both MPTP monkeys and PD patients.[232,262] While the study does not disprove the CDS theory, it does not support the early

Figure 20 **A comparison of the plasma levodopa pharmacokinetics when levodopa is administered at 3-hour intervals in a standard formulation or in combination with the COMT inhibitor entacapone.**



Note that administration of levodopa in combination with a COMT inhibitor provides a plasma pharmacokinetic profile that mirrors the pattern seen with an infusion (see figure 19B). Modified from Olanow CW et al.[233] with permission from Elsevier.

use of Stalevo, at least at 3.5 hour intervals, and provides further evidence for using relatively low doses of levodopa in order to minimize the risk of dyskinesia.

Side effects associated with COMT inhibitors are primarily dopaminergic (nausea, vomiting, hypotension, neuropsychiatric problems, and dyskinesia) and reflect increased levodopa availability to the CNS. These adverse reactions, especially dyskinesia, tend to occur within the first day or two after starting the COMT inhibitor, and can usually be controlled by reducing the dose of levodopa by approximately 15% to 30%. Patients should be advised to notify their physician if there is an increase in dyskinesia or other dopaminergic side effects. If patients already have dyskinesia when the COMT inhibitor is introduced, it can be anticipated that dyskinesia will intensify, and some physicians choose to preemptively lower the dose of levodopa. It is important to appreciate that the dopaminergic side effects should be treated by down-titrating the dose of levodopa, not the dose of the COMT inhibitor. A severe and explosive form of diarrhea occurs in about 5% to 10% of tolcapone-treated patients after a latency of several weeks to months, and usually necessitates discontinuing therapy. Both diarrhea and constipation have been described with entacapone, but these are typically milder and usually do not require discontinuation of therapy. The mechanism responsible for this diarrhea is still not fully understood. Interestingly, when patients who have had diarrhea are rechallenged, the diarrhea recurs almost immediately. Discoloration of urine resulting from the accumulation of a drug metabolite may occur with either of the COMT inhibitors. This is harmless, but may be a source of concern if the patient and caregiver are not informed.

A more important problem has been the potential of tolcapone to induce hepatic toxicity. Although liver toxicity was not detected in preclinical toxicology studies, liver enzyme elevations were observed in 1% to 3% of tolcapone-treated patients in clinical trials, although none experienced clinical evidence of liver dysfunction. As a result of these findings, periodic monitoring of liver function was required at the time of initial drug approval. During postmarketing surveillance, four cases of liver dysfunction with death in three individuals were observed in a total of 60,000 patients who had received the drug for a total of 40,000 patient-years.[420,421] These observations led to the drug being withdrawn from the market in Europe and Canada, and to the issuance of a black box warning in the United States. Patients in the United States receiving the medication were also required to sign an informed consent, to undergo monitoring of liver enzymes at 2-week intervals, and to discontinue the drug if liver enzymes were increased above the upper limits of normal on even one occasion.[422,423] This resulted in a marked decline in the use of the drug. However, a review of the four liver failure cases noted that none had undergone monitoring as required, and two had continued to take tolcapone even after the onset of clinical liver dysfunction. A panel of neurologists and hepatologists argued that tolcapone was safe to use if monitoring guidelines were followed, and that having to stop a drug if levels were above 1× normal on a single occasion was a higher standard than had been applied to any other drug.[421] Furthermore, a prospective study showed that, although minor elevation in liver enzymes was common after introduction of tolcapone, no clinical cases of liver toxicity were encountered.[424] On the basis of this new information, the drug has been reintroduced to the market in many countries and the FDA has removed the black box warning. The revised label now requires that physicians exclude patients with liver disease before initiating therapy with tolcapone, monitor liver function tests periodically (i.e., every 2 to 4 weeks) for the first 6 months of therapy and thereafter as deemed appropriate, and discontinue the drug if liver function tests exceed two times the upper limit of normal or if there are clinical features of hepatic dysfunction[425] (table 9). The precise cause of tolcapone-related liver dysfunction remains unknown. COMT inhibition could deprive liver cells of methylation, an important antioxidant

Table 9 Comparison of 1998 and 2006 FDA liver monitoring guidelines

	1998 guidelines	New 2006 guidelines
Patient selection	Tolcapone should ordinarily be used in patients with PD on levodopa/carbidopa who are not responding satisfactorily to, or are not appropriate candidates for, other adjunctive therapies	Unchanged
	Tolcapone should not be initiated if the patient exhibits clinical evidence of liver disease or 2 SGPT/ALT or SGOT/AST values > ULN	Unchanged
LFT monitoring requirements	Baseline	Baseline
	Every 2 wks for the first year	Every 2–4 wks for the first 6 mo
	Every 4 wks for the next 6 mo	After the first 6 mo, periodic monitoring is recommended at intervals deemed clinically relevant by the treating physician
	Every 8 wks thereafter	
Treatment with tolcapone should be discontinued if	SGPT/AST or SGOT/AST > 1× ULN	SGPT/ALT or SGOT/AST levels > 2× ULN
	Clinical signs and symptoms suggest the onset of hepatic failure	Clinical signs and symptoms suggest the onset of hepatic failure

ALT = alanine aminotransferase; AST = aspartate aminotransferase; PD = Parkinson disease; SGPT = serum glutamic-pyruvic transaminase; SGOT = serum glutamic-oxaloacetic transaminase; ULN = upper limit of normal; FDA = Food and Drug Administration; LFT = liver function test.
Reprinted with permission from Olanow and Watkins.[425]

defense mechanism in patients treated with an oxidizing agent such as levodopa.[426] Mutations in the UDP-glucuronosyltransferase 1A9 gene, which encodes for the enzyme that metabolizes tolcapone, have been reported in two patients with asymptomatic liver dysfunction.[427] These may have led to liver dysfunction by preventing the metabolism of tolcapone and increasing the level of COMT inhibition. Different degrees of COMT inhibition might also account for why liver dysfunction has been observed with tolcapone but not with entacapone. However, liver injury is not found in COMT-knockout mice,[428] so the role of COMT inhibition in the genesis of hepatic dysfunction remains uncertain. It has also been proposed that tolcapone is a mitochondrial toxin that causes uncoupling of oxidative phosphorylation.[429,430] Indeed, mitochondrial damage was observed on electron microscopy in one of the tolcapone-treated patients who died of liver failure.[431] Fortunately, liver dysfunction has not been a major problem in patients treated with entacapone.[432] Preclinical toxicology studies showed no evidence of liver damage, and liver enzymes were not elevated compared with placebo in clinical trials. Two cases of liver dysfunction have been attributed to entacapone during postmarketing surveillance, but the causal relationship of the liver damage to the drug has not been established and there was no mortality.[433] Liver monitoring is not required with entacapone in any country.

Another intriguing issue with COMT inhibitors is their potential to reduce or prevent the elevated plasma homocysteine levels induced by levodopa.[434] High homocysteine levels in the general population are associated with an increased risk of stroke and dementia, but the clinical significance of the effect of levodopa and COMT inhibitors on homocysteine is not known.

In summary, double-blind, controlled studies with COMT inhibitors demonstrate clinical benefits in patients with PD with motor fluctuations and, to a lesser extent, in those with stable responses to levodopa. In theory, combining levodopa with a COMT inhibitor from the time levodopa is first introduced may reduce the risk that the drug will induce motor complications.[435] This hypothesis was not confirmed in the STRIDE-PD study testing Stalevo administered at 3.5 hour intervals. It is possible that better results could have been achieved with q3hr administration of Stalevo which provides pharmacokinetic curves that more closely reflect a levodopa infusion, but such studies remain to be performed. The most common side effect is dyskinesia, reflecting the increase in central dopaminergic activity. It is usually only a problem in patients who already have dyskinesia, and can generally be readily controlled by a 15% to 30% reduction in levodopa dose. Physicians should be aware of this side effect as it tends to occur within 1 to 2 days of initiating a COMT inhibitor and may require an immediate dose adjustment. Tolcapone, while probably clinically more effective, should be reserved for those patients who do not respond adequately to entacapone, because of the risk

Table 10 COMT inhibitors: Advantages and disadvantages

Advantages
No titration
Decreased "off" time, increased "on" time, and enhanced motor responses in patients with levodopa motor fluctuations
Mild improvement, particularly in ADL and quality of life scores, in stable levodopa responders
Disadvantages
Dopaminergic side effects
Discoloration of urine
Tolcapone is associated with explosive diarrhea in 5–10% of cases; less so with entacapone
Tolcapone is associated with liver toxicity

COMT = catechol-*O*-methyltransferase; ADL = activities of daily living.
Adapted with permission from Olanow et al.[15]

for liver damage. The advantages and disadvantages of COMT inhibitors are listed in table 10.

MAO-B inhibitors. MAO-B inhibitors have been used as symptomatic therapy for PD for approximately 20 years, based on their capacity to block the MAO-B oxidation of dopamine and thereby increase dopamine levels in the synapse. Which isoform of MAO is primarily responsible for dopamine metabolism in man is still debated. MAO-B inhibition leads to increased striatal dopamine levels, but there are reasons to believe that MAO-A may also be important because dopamine is cleared primarily from the synapse by reuptake into the cell and intraneuronal MAO exists primarily in the MAO-A isoform. Although this class of drug is described as MAO-B inhibitors, in doses used in clinical practice, some degree of MAO-A inhibition also likely occurs and may contribute to symptomatic effects.

Selegiline. Selegiline was initially approved as an adjunct to levodopa in patients with motor fluctuations. However, selegiline is primarily used in early disease, based on its putative neuroprotective effects (see section on Neuroprotection) and its capacity to provide mild symptomatic benefits.[163]

Selegiline is administered in a dose of 5 mg twice daily and is generally well tolerated when administered as monotherapy. When combined with levodopa, it can enhance dopaminergic side effects and lead to increased dyskinesia and neuropsychiatric problems, particularly in the elderly. Some physicians use lower doses (e.g., 5 mg or less per day) to try to avoid these problems. Amphetamine metabolites of selegiline may induce insomnia, and for this reason it is recommended that the drug be prescribed to be taken before, and not after, noon. The PD Research Group of the United Kingdom reported increased mortality in patients with PD who initiated therapy with selegiline plus levodopa compared with levodopa alone.[436] However, this study had methodological flaws,[437] and increased mortality in selegiline-treated patients was not observed in a meta-analysis of other trials.[438] A follow-up study of the DATATOP cohort similarly showed that cumulative exposure to deprenyl was not associated with increased mortality.[439]

Rasagiline. More recently, rasagiline (Azilect) has been approved for use in patients with both early and advanced PD. Rasagiline is an irreversible inhibitor of MAO-B. It is more potent and more selective than selegiline, and does not generate amphetamine or methamphetamine metabolites. It has been better studied than selegiline both as monotherapy in early disease and as an adjunct to levodopa in advanced disease. The TEMPO study compared rasagiline (1 or 2 mg/d) with placebo in a 6-month, prospective, multicenter, randomized, double-blind, placebo-controlled study of 404 patients with previously untreated PD.[212] Both doses significantly improved the motor and total UPDRS scores compared with placebo-treated patients ($p < 0.0001$). The adjusted effect size for the total UPDRS score vs placebo was 4.20 units for the 1-mg dose and 3.56 units for 2-mg dose. As part of this trial, patients initially treated with placebo were switched to rasagiline 2 mg/d at the 6-month time-point, whereas patients originally receiving rasagiline were maintained on their active medication. Thus, in the second phase of the study all patients were receiving rasagiline. Patients originally randomized to receive rasagiline (early start) had a greater improvement in their total UPDRS scores at the final visit than patients who were originally randomized to receive placebo and only received rasagiline at the 6-month time-point (delayed-start).[213] In other words, patients who received rasagiline for only 6 months never "caught up" with patients who had received rasagiline for 12 months. This concept was more formally tested in the ADAGIO study where early vs delayed start rasagiline 1 or 2 mg/day were compared.[213a] The study showed significant benefits for rasagiline 1 mg/day but not for 2 mg/day,[213b] although a greater symptomatic effect may have masked a disease modifying effect benefit with the latter dosage. These observations raise the possibility that the drug might have a neuroprotective or disease modifying effect, although, as discussed in the section on neuroprotection, there are other possible explanations for this result. Whatever the explanation, this study suggests that early treatment with rasagiline 1 mg/day provides benefits that cannot be attained with later initiation of the drug, and argues for starting symptomatic treatment at an earlier time point than has conventionally been used[440] (see section on when to start treatment, page S45).

Two pivotal studies examined rasagiline in more advanced patients. The PRESTO study evaluated the

effect of rasagiline in patients with levodopa-treated PD with motor fluctuations.[441] Four hundred seventy-two patients who experienced at least 2.5 hours of "off" time per day were randomized to treatment with rasagiline 0.5 or 1.0 mg/d or placebo and were followed up for 26 weeks. "Off" time was reduced by approximately 1 hour relative to placebo in the 1 mg/day rasagiline group ($p < 0.0001$) and a half an hour in the 0.5 mg/day group ($p < 0.02$). Patients treated with rasagiline also showed significant improvement in ADL and motor subscores of the UPDRS as well as on the clinical global impression scale. The LARGO study was a prospective 18-week, multicenter, randomized, double-blind study of 687 patients with advanced PD, which compared rasagiline 1 mg/d with entacapone 200 mg (taken with each dose of levodopa) and placebo.[442] Both rasagiline and entacapone reduced "off" time by about 1.2 hours/day relative to placebo-treated patients. Both drugs also reduced the daily dose of levodopa and significantly improved UPDRS total scores. Both drugs had similar AE profiles and neither treatment resulted in a net increase in dyskinesias. It is of interest that rasagiline has been reported to improve freezing of gait in patients with advanced PD[443] as has also been reported with selegiline.[185]

Zydis selegiline. Zydis selegiline (Zelapar) preparation is a once-daily formulation of selegiline that is placed on the tongue. The drug can be absorbed in the traditional manner if swallowed, but absorption via the buccal mucosa avoids first-pass metabolism in the liver and gut, thereby providing higher serum and brain concentrations than are attained with traditional oral delivery.[444] As primary metabolism is reduced, levels of metabolites are decreased compared with oral selegiline. Thus, levels of amphetamines that may cause AEs are reduced, but so too are levels of the desmethyl metabolite, which accounts for the putative neuroprotective effects of the drug in the laboratory. In pharmacokinetic studies, 1.25 mg/d of zydis selegiline leads to a serum concentration AUC comparable with 10 mg of the oral preparation.[444] Zydis selegiline has been approved as an adjunct to levodopa for patients with advanced PD. In one study, patients with PD experiencing motor fluctuations with at least 3 hours of daily "off" time were randomized to 3 months of treatment with zydis selegiline or placebo.[445] Zydis selegiline was initiated at a dose of 1.25 mg/d and increased to 2.5 mg/d after 6 weeks. Compared with placebo, zydis selegiline was associated with a significant reduction in daily "off" time (2.2 vs 0.6 hours), with most of the increase in "on" time being dyskinesia free (1.8 of 2.2 hours). However, another study did not show significant benefit compared with placebo, although there was a robust placebo response that may have precluded seeing any benefit.[446] Selegiline ODT was safe and well tolerated in both studies.

MAO-B inhibitors are generally well tolerated. Amphetamines generated by the metabolism of selegiline may result in insomnia and other side effects. The major concern with MAO inhibition is the theoretical risk of developing an acute and potentially fatal hypertensive reaction known as the "cheese reaction." Tyramine in the diet is metabolized in the gut by MAO-A. Inhibition of the MAO-A enzyme can permit excess tyramine absorption that promotes catechol release from nerve terminals that could induce a severe hypertensive crisis. This is referred to as a cheese reaction because aged cheeses contain high levels of tyramine. This adverse effect is not seen with selective MAO-B inhibitors. However, drugs that are marketed as MAO-B inhibitors are not totally selective and have the potential to block the MAO-A isoform if administered in sufficiently high doses.[447] In doses used in clinical practice, this risk is extremely low and cheese reactions have not been reported. However, rasagiline has not completed all testing required by the FDA, and in the US patients on this medication must be advised to restrict consumption of foods rich in tyramine such as aged cheese, aged meats, and tap beers. It is likely that these tests will soon be completed and this restriction removed. MAO inhibition also has the potential to interfere with serotonin metabolism and to induce a "serotonin syndrome," and it has been recommended that MAO-B inhibitors not be used in patients taking SSRIs and tricyclic antidepressants (TCAs), although these reactions are rarely encountered[448] and we routinely use these combinations.

Safinamide. Safinamide is a new MAO-B inhibitor that is currently being studied as a treatment for early and advanced PD. In addition to its MAO-B inhibitor properties, it also inhibits dopamine uptake, and blocks sodium channels and glutamate release.[449] It was originally developed as an antiepileptic drug, but is now being studied primarily in PD. A randomized, placebo-controlled trial of safinamide in early- to mid-stage PD demonstrated modest antiparkinsonian effects, with benefits specifically noted in patients who were already receiving a dopamine agonist.[450] Enhanced benefits in patients taking a dopamine agonist may permit a greater delay in the need for levodopa and a further reduction in the risk of motor complications. Interestingly, safinamide treatment was also associated with improvement in executive functions. The drug was well tolerated and had an excellent AE profile. Phase 3 trials are currently under way in the United States and in Europe. The advantages and disadvantages of MAO-B inhibitors are reviewed in table 11.

Other antiparkinsonian drugs. *Anticholinergics.* Belladonna alkaloids containing anticholinergics have been used to treat PD since the mid-19th century.[451]

Table 11 MAO-B inhibitors: Advantages and disadvantages

Advantages
Antiparkinsonian effects as monotherapy (selegiline and rasagiline)
Reduced motor fluctuations and increased "on" time as adjuncts to levodopa
Levodopa-sparing effect
Neuroprotective in laboratory models
Once-daily dosing (rasagiline and Zydis selegiline)
Well tolerated and good adverse event profile
Early start provides benefits not achieved with delayed start (rasagiline)
Disadvantages
Modest antiparkinsonian effect
Neuroprotection not established
Amphetamine and methamphetamine metabolites may cause side effects (selegiline)
Theoretical risk of "cheese effect" and "serotonin syndrome"

MAO-B = monoamine oxidase-B.

The use of anticholinergics has dramatically declined in the era of levodopa and dopamine agonists, but these agents are still occasionally used.[452] Currently available anticholinergic drugs include trihexyphenidyl (Artane), benztropine (Cogentin), biperiden (Akineton), orphenadrine (Disipal), and procyclidine (Kemadrin). It has long been postulated that there is a balance between dopamine and acetylcholine neurotransmission in the basal ganglia; cholinergic drugs have been shown to exacerbate and anticholinergic drugs have been shown to improve parkinsonian symptoms.[453] Cholinergic interneurons in the striatum bear D1 and D5 dopamine receptors[454] and exert powerful effects on the excitability of MSNs and dopaminergic function.[455–457] The precise mechanism of action of anticholinergic drugs in PD is not known, and it is possible that enhanced benefits with a better safety profile could be obtained with antagonists of muscarinic cholinergic receptor subtypes.

Anticholinergic drugs are typically used in younger patients with PD (i.e., ≤60 years of age) in whom resting tremor is the dominant clinical feature and where cognitive function is preserved. Anticholinergic drugs are of little value in the treatment of other parkinsonian features such as rigidity, akinesia, gait dysfunction, or impaired postural reflexes.[458] In some patients, tremor may respond particularly well to anticholinergic agents, but levodopa and dopamine agonists are probably just as effective.[459]

Trihexyphenidyl is the most widely used of the anticholinergic drugs, but there is no evidence to suggest that any one drug in this class is superior to any other in terms of either therapeutic efficacy or side effects. Trihexyphenidyl is typically initiated at a dose of 0.5 to 1.0 mg BID and increased gradually to a dosage of approximately 2 mg TID, as tolerated. Benztropine is the second most commonly used anticholinergic and it is typically prescribed in doses of 0.5 mg to 2.0 mg BID. Peripherally acting anticholinergic agents such as propantheline (Banthine) or glycopyrrolate (Robinul) may be useful in treating sialorrhea.

Adverse effects of central acting anticholinergic drugs are common and often limit their use. The most important are memory impairment, confusion, and hallucinations. These are most likely to occur in older individuals, but even younger patients with PD without evident cognitive impairment can experience neuropsychiatric dysfunction during anticholinergic treatment. Even in patients who seem to be tolerating these drugs well, improvement in short-term and long-term memory has been demonstrated after their withdrawal.[460] Interestingly, treatment with anticholinergic drugs was reported to be associated with increased (2.5-fold) amyloid plaque and neurofibrillary tangle densities.[461] Other CNS side effects include sedation and dysphoria. Anticholinergic drugs have also been reported to cause dyskinesia.[256] These tend to be orobuccal in distribution and more closely resemble those seen in tardive dyskinesia than after treatment with levodopa. Peripheral side effects can include dry mouth, blurred vision, constipation, nausea, urinary retention, impaired sweating, and tachycardia. Particular caution should be exercised in the use of anticholinergic medications in the presence of prostatic hypertrophy or closed-angle glaucoma as they may be exacerbated. Milder side effects such as dry mouth and blurred vision may subside with continued treatment, and, although a nuisance for patients, do not usually limit therapy. Baseline cognitive evaluations, psychiatric history, and supine and standing blood pressure should be obtained in older patients before beginning anticholinergic therapy.

Because of the many side effects associated with the use of anticholinergic medications, many physicians prefer not to use this class of drug, particularly in the elderly. Anticholinergic drugs should be discontinued gradually to avoid withdrawal effects and acute exacerbation of parkinsonism, even in those patients in whom there seems to have been no clinical response.

In summary, anticholinergic agents are sometimes used in the treatment of younger patients with PD in whom resting tremor is the predominant symptom. Anticholinergic therapy in older patients, in patients without tremor, and in demented patients is not in-

Table 12	Anticholinergic agents: Advantages and disadvantages
Advantages	
Some antiparkinsonian efficacy (particularly with respect to tremor)	
Peripherally acting agents may be useful in treating sialorrhea	
Disadvantages	
Relatively ineffective for the more disabling features of PD	
Cognitive side effects	
Troublesome central and peripheral cholinergic side effects	
May be associated with withdrawal effects	

PD = Parkinson disease.
Reproduced with permission from Olanow et al.[15]

dicated. Because of the side effect profile and the limited efficacy associated with these drugs, many physicians are reluctant to use them at all. If they are used and it is decided to stop them, they should be gradually withdrawn. A summary of the advantages and disadvantages of anticholinergic drugs is listed in table 12.

Amantadine. Amantadine (Symmetrel) is an antiviral agent that was discovered by chance to have antiparkinsonian activity.[462] Its mechanism of action has not been established, but it has been considered to increase dopamine release, block dopamine reuptake, stimulate dopamine receptors and, possibly, to have anticholinergic effects. It has also been recognized that amantadine acts as an NMDA receptor antagonist.[463] Amantadine has been shown to improve akinesia, rigidity, and tremor in placebo-controlled trials when used as monotherapy or in combination with levodopa.[464-466] In one study, amantadine was found to be more effective than anticholinergic drugs with regard to akinesia and rigidity, but it seems to be less effective with respect to tremor.[467] Early studies suggested that benefit with amantadine is transient, but some patients enjoy more sustained benefits.

Amantadine is administered in dosages of 100 to 200 mg one to three times daily. Larger dosages increase the likelihood of adverse effects and seem to provide no additional benefit.[468] Amantadine is not metabolized and is excreted unchanged in the urine. Accordingly, patients with renal impairment should receive lower doses and be monitored carefully for adverse effects.

Side effects include confusion, hallucinations, insomnia, and nightmares. These are more common in older patients, but can be seen in patients of any age. Peripheral side effects include livedo reticularis and ankle edema, although these are rarely severe enough to limit treatment. Dry mouth and blurred vision can occur and are presumed related to its peripheral anticholinergic effects. Some patients experience dramatic worsening when amantadine is withdrawn, even when no evident clinical benefit has been detected, and may represent a withdrawal effect. For this reason, amantadine should be withdrawn gradually.

In the laboratory, NMDA receptor antagonists protect dopaminergic neurons from excitotoxic damage,[469] suggesting that amantadine might have neuroprotective effects in PD.[470] Indeed, a retrospective clinical study has suggested that patients with PD who received long-term amantadine treatment have increased survival.[471] Another study found that amantadine may delay the onset of dementia in patients with PD, and attenuate its severity.[472]

Chase and Oh[473] have proposed that amantadine might also have antidyskinetic effects because of its NMDA receptor antagonist property. They hypothesized that levodopa-induced pulsatile stimulation of dopamine receptors on MSNs induces abnormal phosphorylation of NMDA receptors leading to glutamate-mediated plastic changes and the development of motor complications.[474] In support of this concept, they have shown that NMDA receptor antagonists, and specifically amantadine, can improve levodopa-induced dyskinesia in MPTP monkeys[475,476] and in patients with PD.[477,478] Amantadine is the only currently available agent that is capable of blocking dyskinesia without interfering with the parkinsonian response and has proven to be of considerable benefit for some patients. The utilization of amantadine, however, may be limited by its propensity to cause cognitive impairment, particularly in patients with advanced PD, and benefits may be transient.

Although amantadine infusions are not generally available, an open-label study suggested that amantadine infusion might be useful for patients experiencing severe complications following a "levodopa holiday."[479] IV administration of amantadine was effective and safe in this setting. This approach, however, cannot be recommended without further study.

In summary, amantadine is used by some practitioners in the treatment of patients with early PD as a means of delaying the need for levodopa and possibly providing protective effects. In patients with advanced disease, it can be used to try and provide an antidyskinetic effect. Its use is limited by its potential to cause neuropsychiatric side effects. Further studies are necessary to better establish its role in the management of dyskinesia and on the natural history of PD. A summary of the advantages and disadvantages of amantadine is listed in table 13.

Pharmacologic approach to patients with early PD.

The issue of neuroprotection. In approaching the patient with newly diagnosed PD, the first therapeutic

Table 13	Amantadine: Advantages and disadvantages
Advantages	
Some antiparkinsonian efficacy	
Antidyskinetic effect in some patients	
Possible neuroprotective effects	
Disadvantages	
Antiparkinsonian benefits are limited	
Cognitive side effects	
Livedo reticularis and edema	
Tolerance may develop	
Potential for withdrawal effects	

Adapted with permission from Olanow et al.[15]

issue that should be considered is neuroprotection. If an agent were known to slow or halt PD progression, it would be introduced as soon as the diagnosis is made. Indeed, the development of a neuroprotective therapy for PD would add urgency to the effort aimed at defining a preclinical marker of the disease that might permit introduction of such a therapy before the emergence of overt clinical motor signs and symptoms (see section on Diagnosis). As discussed in the section on Neuroprotection, none of the agent has yet been established to be neuroprotective in PD. However, several drugs have demonstrated neuroprotective effects in laboratory models and, indeed, several have had positive results in controlled clinical trials.[86] These include selegiline, rasagiline, coenzyme Q10, and dopamine agonists pramipexole and ropinirole. Although it remains uncertain whether positive results in clinical trials with any of these agents are due to protection against degeneration of nigral neurons or due to a confounding symptomatic or pharmacologic effect, the possibility that they may be neuroprotective has not been excluded. For example, patients in the DATATOP trial who received selegiline were able to forestall the need for levodopa 9 to 12 months longer than those patients receiving placebo.[163] Although this observation was largely ascribed to the symptomatic effect of selegiline, a longer-term follow-up study of patients taking selegiline for 7 years found less motor impairment, motor fluctuations, "on-off" episodes, and freezing than in patients who were converted to placebo after 5 years of selegiline treatment.[480] Interpretation of these results must be made with caution, but a disease-modifying effect of selegiline beyond its symptomatic effects is certainly a viable possibility. Furthermore, more recent studies with the MAO-B inhibitor rasagiline have not only shown a symptomatic benefit in patients with early PD,[212] but have also demonstrated improved UPDRS motor scores in patients randomized to receive rasagiline for a full 12 months compared with those who were randomized to initiate treatment with placebo for 6 months and then take rasagiline for the next 6 months.[213] Further, the recent ADAGIO study using the novel delayed start design showed that early treatment with rasagiline 1 mg/day provides benefits that cannot be achieved with later introduction of the same drug, consistent with the drug having a disease-modifying effect. Although these studies do not necessarily prove that the drug is protective, this observation cannot be readily explained by a purely symptomatic effect. It is hoped that new animal models and new clinical trial designs will facilitate a determination of whether these, or other agents, are neuroprotective. For the present, physicians are left with the option of starting patients with PD on a putative neuroprotective agent because of its potential to provide a disease-modifying effect or withholding it because it has not been conclusively established to alter disease progression. This decision should be made in conjunction with the patient after a full discussion of the pros and cons and consideration of the drug's side effect profile. Putative neuroprotective agents are usually not used in patients with cognitive impairment or in those with more advanced disease in whom protection is a less critical issue. The determination that any intervention is neuroprotective and can slow the progression of the PD would represent a major turning point in the management of this disorder.

The issue of when to initiate symptomatic therapy. The next issue that must be addressed is that of symptomatic therapy. Here, two important issues must be considered: when to start therapy and what to start with.

The decision regarding when to initiate therapy for PD has long been debated. Some have advocated early treatment to provide patients with maximal functional benefit at the start of their illness[481]; others have argued for a delay in initiating treatment to minimize the risk of developing long-term motor complications and/or accelerating disease progression due to oxidative radicals derived from levodopa metabolism.[482-484] The misconception that levodopa treatment benefits are limited to a finite period of time has further caused many physicians to inappropriately delay the introduction of symptomatic therapy. With the development of pharmaceutical agents that are safe, well tolerated, and with the potential to influence disease outcomes, there has been a call to reconsider the potential value of early intervention.[440] This view is supported by the recent delayed start study suggesting that early treatment with rasagiline is associated with a better long-term outcome

than delayed treatment regardless of the mechanism of action (see discussion under Neuroprotection).[213] There are several possible explanations for the difference between these two groups. One is that rasagiline provides a neuroprotective effect. Another is that there is a cumulative symptomatic benefit that occurs over more than 6 months, although this is unlikely as measures of the rate of deterioration in UPDRS score between weeks 48 and 72 in the early and delayed start groups show no tendency to converge arguing against a delayed symptomatic effect. It is also possible that the early introduction of symptomatic therapy preserves basal ganglia compensatory mechanisms, which if lost cannot be restored. Such an explanation might account for the findings in studies in which patients with early PD randomized to receive levodopa have better UPDRS scores at each visit than those randomized to receive a dopamine agonist, even though patients in either group could receive supplemental levodopa at a later time point if it was deemed necessary.[333,340] The ELLDOPA study similarly showed that patients with early PD who received levodopa had benefits compared with placebo that persisted even after 2 weeks of drug washout.[232] Although there are several explanations for this persistent benefit (see discussion of ELLDOPA study on page S20), it could also be explained by early symptomatic therapy preventing or delaying decompensation. Although in the past it was common to delay treatment with levodopa until patients experienced functional disability, current thinking suggests initiating therapy at an earlier time point, possibly even as soon as the time of diagnosis.

Although these issues may seem straightforward, the decision to treat is often not easily reached, and assessing the impact of parkinsonian features on an individual patient may be difficult. If no symptoms were present, the patient would probably not have sought medical attention. Symptomatic therapies can provide benefits for patients even in the earliest stages of the illness. Employment is another consideration, as even minor symptoms can impair job performance and threaten employability.

The decision to withhold early treatment in the past was largely due to the potential of levodopa to induce motor complications. With the introduction of drugs that can provide symptomatic benefits with a low risk of motor complications and with the growing body of information suggesting that early treatment may lead to a better outcome, we believe it is reasonable to reconsider this position. Furthermore, there are at least theoretical reasons to consider that some therapies may have disease-modifying effects. Accordingly, it is our view that it is preferable in most cases to initiate therapy at the time of diagnosis or soon thereafter.

The issue of what symptomatic agent should be used to initiate therapy. Several factors influence the decision as to which drug to use to initiate therapy in PD, including the following:

- Level of disability of the patient
- Efficacy of the individual therapy
- Acute side-effect profile (nausea, vomiting, hypotension)
- Late side-effect profile (i.e., motor complications, ICDs, sleepiness)
- Convenience (i.e., number of doses, ease of administration)
- Patient-specific factors (e.g., age, employment status)

In the past, levodopa was traditionally used to initiate therapy for PD because it was the most effective symptomatic agent, and levodopa is still commonly used as initial therapy by some physicians. In the past decade, however, many movement disorder neurologists have elected to initiate symptomatic therapy with a dopamine agonist in appropriate patients (see below), and to supplement with levodopa when satisfactory control cannot be attained with dopamine agonist monotherapy. This treatment philosophy is based on the body of laboratory and clinical information indicating that dopamine agonists are associated with a reduced risk of inducing motor complications compared with levodopa. This observation has been confirmed in prospective, double-blind trials comparing levodopa with ropinirole, pramipexole, pergolide, and cabergoline,[310,311,333,334] suggesting that it is a class effect, possibly due to these agents having a relatively long plasma half-life, and/or a decreased propensity to induce dyskinesia compared with levodopa. Virtually all patients with PD, however, eventually require levodopa, and its introduction is associated with increased motor complications. Indeed, in both the ropinirole and pramipexole studies, the time to onset of dyskinesia after the introduction of levodopa was the same whether the drug was used as initial therapy or as an adjunct to a dopamine agonist.[345,346] These studies illustrate that dopamine agonists are associated with a low risk of motor complications but do not prevent dyskinesia once levodopa is introduced. They are, nonetheless, still frequently used as initial therapy because they delay the time until levodopa is required and permit use of lower doses of levodopa. In addition, there is some preclinical and clinical evidence suggesting that dopamine agonists might have a disease-modifying effect. Although this has not been established, it has not been excluded and is a

factor that should be considered in starting therapy. In prescribing a dopamine agonist, its side-effect profile—specifically, its potential to induce hallucinations, ICDs, and sedation—should be kept in mind.

MAO-B inhibitors such as selegiline and rasagiline provide another therapeutic option in early disease. MAO-B inhibitors have been shown to provide modest antiparkinsonian effects when used as monotherapy and also delay the need for levodopa. Direct comparisons with dopamine agonists have not been performed, but clinical experience suggests that benefits are not as marked with these agents as with a dopamine agonist. Conversely, they are well tolerated, require once- (rasagiline) or twice-daily dosing (selegiline), do not require titration, and have a very good side-effect profile. Furthermore, both rasagiline and selegiline have neuroprotective effects in the laboratory, and the TEMPO and the ADAGIO studies suggests that early treatment with rasagiline provides benefits that cannot be attained with later introduction of the same medication.[213] Although this does not establish neuroprotection and long-term studies are required to determine the effect of the drug on cumulative disability in the long run, it does indicate that earlier treatment with rasagiline may provide a better outcome, at least at the 18-month time point. For these reasons, many physicians now choose to initiate therapy in patients with early PD with an MAO-B inhibitor. Selegiline is available in a generic formulation, but comparable clinical trials have not yet been performed with this drug.

There may be advantages to initiating therapy in patients with early PD with both an MAO-B inhibitor and a dopamine agonist (not at the same time) to enhance clinical benefits and further delay the need for levodopa. However, there have been no studies as yet examining the effects of combining an MAO-B inhibitor with a dopamine agonist on the need for levodopa and the risk of inducing dyskinesia. However, subset analyses in studies testing rasagiline in advanced patients[441,442] and preliminary studies with a new MAO-B inhibitor safinamide,[450] suggest that adding an MAO-B inhibitor to a dopamine agonist improves UPDRS scores.

Physicians thus have choices in deciding on initial symptomatic therapy for a patient with PD. One approach is to initiate therapy with a dopamine agonist and/or an MAO-B inhibitor so as to reduce the risk of inducing motor complications, and to add levodopa when it is deemed necessary to maintain satisfactory clinical control. This strategy is the preferred approach of the authors for relatively young patients who do not have cognitive dysfunction. In cases with relatively mild disease severity, we would start with an MAO-B inhibitor because of the relative ease of administration and good side-effect profile. In cases with greater disability, we would begin with a dopamine agonist because of its greater efficacy.

An alternative approach is to begin with levodopa. Levodopa is the most effective antiparkinsonian agent and has a reduced risk of inducing side effects, such as leg swelling, sleepiness, hallucinations, and ICDs, compared with dopamine agonists, but its use does increase the risk of motor complications. The authors believe that levodopa is the preferred treatment for patients with PD with cognitive impairment, the elderly who have a reduced propensity to develop motor complications, and patients suspected of having an atypical parkinsonism who are undergoing a trial of dopaminergic therapy. The STRIDE-PD study showed no benefit of using Stalevo at 3.5 hour intervals instead of levodopa, but did not disprove the CDS theory. Indeed, it is theoretically possible that the development of a long-acting formulation of levodopa that provides more continuous availability of levodopa to the brain might provide all of the benefits of levodopa without motor complications, and obviate the need for polypharmacy in the treatment of the dopaminergic features of PD (see treatment of nondopaminergic features later). The authors emphasize that if it is elected to initiate therapy with a dopamine agonist and/or an MAO-B inhibitor, levodopa should not be withheld if and when the patient is not satisfactorily controlled. For reasons discussed, the authors do not routinely prescribe amantadine or anticholinergics in patients with early PD, although some movement disorder specialists might use these drugs if tremor is the predominant feature.

Factors that might influence the choice of initial therapy in PD include the following:

Age: We favor initiating therapy with levodopa plus a decarboxylase inhibitor in older individuals (>75 years of age) because of concerns about incipient cognitive dysfunction and because older patients are less likely to develop levodopa-related motor complications, possibly because of reduced brain plasticity. Anticholinergic drugs and amantadine are specifically discouraged in older patients because of the risk of aggravating underlying mental dysfunction.

Cognitive impairment: We would favor initiating treatment of PD symptoms with levodopa plus a decarboxylase inhibitor in patients with cognitive impairment regardless of age. The immediate-release formulation of levodopa/carbidopa is simpler to initiate and to adjust in this population of patients, is more effective than other agents, and is associated with fewer psychiatric problems than dopamine agonists. In general, it is best to eliminate polypharmacy in cognitively impaired patients (see discussion under cognitive impairment and dementia, page S70).

Disease severity: Many neurologists favor starting with levodopa plus a decarboxylase inhibitor in patients with PD who are untreated and present with severe disease. However, disease severity is a risk factor for the development of motor complications, and this should be considered in deciding whether to initiate therapy with levodopa or introduce a trial of a dopamine agonist, particularly in a younger patient. We would probably not start with an MAO-B inhibitor in this population because of their relatively limited efficacy.

Threatened loss of employment: Many neurologists would start with levodopa plus a decarboxylase inhibitor because they want a rapid response. However, some dopamine agonists can be titrated relatively quickly (e.g., pramipexole), and the titration schedule can be accelerated if it can be coadministered with domperidone to minimize side effects. As patients who are still working are frequently younger and are at greater risk for developing motor complications, it might be best to consider the long-term outcome before making a short-term therapeutic decision.

Cost: Despite the potential for obtaining future benefits, current healthcare realities might dictate initiating treatment with less expensive generic antiparkinsonian medication. Where there is no difference in the specific agent that is available, we do not disagree with this approach. However, in recommending a different treatment strategy, one should consider that there are also financial and personal costs associated with inadequate PD control and with the subsequent development of motor complications and the need for a surgical intervention. Pharmacoeconomic studies specifically addressing these issues are warranted.

In the final analysis, the determination of when to initiate therapy and what drug to choose is a judgment that must take into consideration all factors reviewed above, as well as the personal treatment philosophy of the physician and patient. Table 14 summarizes the potential advantages and disadvantages of the different therapeutic options.

Table 14 Therapeutic options for initial therapy of PD

	Levodopa	Dopamine agonists	MAO-B inhibitors
Efficacy	+++	++	+
Acute side effects	++	+	+++
Motor complications		++	+
Neuroprotection	+/−	+/−	+
Toxicity	+/−		
Convenience	+		+++

+ mild advantage; ++ moderate advantage; +++ marked advantage; +/− uncertain.
PD = Parkinson disease; MAO-B = monoamine oxidase-B.

Some specific questions related to the treatment of patients with early PD are as follows:

What is the role of anticholinergics and amantadine in early therapy? Most physicians use these drugs sparingly because of the risk of cognitive impairment, but they may have a role for young patients with PD with minor parkinsonian features (especially tremor) in delaying the need to introduce dopaminergic therapy.

Are there differences between the different dopamine agonists? Few comparison studies between dopamine agonists have been conducted. Ergot dopamine agonists carry a risk of cardiac valve dysfunction. Ropinirole and pramipexole seem to have superior efficacy to rotigotine, but this may simply reflect tolerance due to continuous patch delivery of the drug. Apomorphine has not been compared with other agonists, but it seems to be the most effective and the most like levodopa. However, it requires injection and is short lasting. Pramipexole has a faster titration schedule and leads to relatively rapid benefit. Ropinirole has a relatively slower titration schedule and may be associated with fewer acute side effects. No clear-cut advantages between the different dopamine agonists are currently appreciated. In individual cases, one agonist may be preferable to another, but in general it is probably best to use the agent with which the individual physician has the most experience. There are no data supporting the use of combined dopamine agonists, although this approach has been used by some physicians.

Is there any reason to push the dose of dopamine agonists to higher levels than are currently recommended to maximally delay the introduction of levodopa? This issue has not been satisfactorily studied to provide an adequate answer to this question. If it can be established that exposure to even a small amount of regular levodopa primes for the development of motor complications, an argument could be made for trying to delay the introduction of levodopa for as long as possible. In considering higher doses of dopamine agonists, it is important to consider that this may lead to psychosis, sedation with EDS, and ICDs. Currently, it is probably best to titrate the dopamine agonist to currently recommended doses and then supplement with levodopa rather than attempting to use doses higher than what are currently recommended. Indeed, the authors favor using relatively low doses of dopamine agonists in order to minimize the risk of side effects which for the most part appear to be dose-related.

How do you manage patients who have already been started on levodopa therapy but do not yet have motor complications? There are as yet no data on the best way to manage this population of patients. Labora-

tory studies in MPTP monkeys suggest that the risk of levodopa inducing motor complications is reduced if it is combined with a dopamine agonist and the dose lowered. Most experts today would supplement with a dopamine agonist rather than increasing the levodopa dose in a stable patient who was already receiving levodopa. Current evidence suggests that the risk of motor complications with levodopa is independent of the presence of a dopamine agonist, but concurrent agonists may permit the use of lower levodopa doses. There is also no information on whether it is beneficial to replace levodopa with a dopamine agonist, and we would not do this at the present time.

What is the role of Sinemet CR or Madopar HBS in the management of early PD? Two prospective, double-blind trials compared immediate- with sustained-release formulations of levodopa to determine if the longer half-life of the controlled-release formulation vs regular levodopa might lead to reduced motor complications. No difference in prevalence or time to onset of motor complications was detected between the two treatment groups.[417,418] There are, however, several factors that might account for why no benefit was observed with the longer-acting preparation in these studies. First, controlled-release levodopa preparations have variable absorption and do not avoid low trough levels. Second, the frequency of administration of controlled-release formulations of levodopa in these studies may have been too infrequent (BID) to avoid fluctuations in plasma levels, and different results might have been obtained with more frequent dosing. For the present, there is no compelling reason to use controlled-release formulations of levodopa in patients with early PD.

In summary, correct and early diagnosis and consideration of whether or not to introduce a putative neuroprotective agent are the first steps in managing early PD. Although symptomatic therapy was historically reserved for patients with functional disability, a growing body of evidence suggests that early treatment may be preferable and have short-term and long-term benefits. Increasing evidence argues in favor of initiating therapy with an agent that does not induce motor complications, such as an MAO-B inhibitor, a dopamine agonist, or a combination of the two, and then supplementing with levodopa when satisfactory clinical control can no longer be achieved. In this way, we believe that patients with PD can be treated so as to obtain maximal clinical benefit with a reduced risk of developing motor complications.[229] On the basis of the existing basic science and clinical data, we have modified our previous treatment approach for patients with early PD[2] and recommend the following approach for the treatment of appropriate patients (table 15).

Table 15 Approach for the patient with early PD

Ensure that the correct diagnosis has been made
Consider neuroprotective therapy as soon as the diagnosis is made
Initiate symptomatic therapy with an MAO-B inhibitor and/or a dopamine agonist for patients who are relatively young and cognitively intact
Consider starting symptomatic therapy at the time of diagnosis
Supplement with levodopa when MAO-B inhibition/dopamine agonist therapy can no longer provide satisfactory clinical control
Initiate with levodopa in an elderly or cognitively impaired patient

PD = Parkinson disease; MAO-B = monoamine oxidase-B; COMT = catechol-*O*-methyltransferase.

Pharmacologic management of advanced PD patients with motor complications. This section provides strategies for the management of the motor complications associated with chronic PD therapy.

Motor fluctuations. *No initial response.* Some patients with PD experience little or no beneficial response to levodopa or other dopaminergic therapies. An adequate trial of medication must be conducted before concluding that the patient is a nonresponder. Occasionally, patients with PD will require a daily levodopa dose of 1,000 to 1,500 mg before they show a response, and an attempt should be made to see if they can benefit from levodopa. It should also be appreciated that levodopa may take several days or weeks to become fully manifest, and patients should be maintained on a dose for at least 1 week to allow for the full effect to occur. Care must be taken before concluding that a patient is a nonresponder as it may be difficult to detect clinical improvement when features are mild, particularly if tremor is the dominant feature. If a patient does not respond to levodopa, the possibility that they have an atypical parkinsonism such as MSA or PSP should be considered. Neuroimaging, autonomic, ophthalmologic, cardiac, and electromyographic studies may be helpful in differentiating PD from an atypical parkinsonism other than PD. Patients suspected of having atypical parkinsonism should nonetheless have the levodopa dosage gradually increased until they either show a response or develop side effects, as some patients with atypical parkinsonism may demonstrate some benefit from levodopa, particularly in the early stages of the disorder. Once it is determined that levodopa provides no meaningful benefit or causes side effects, the dose should be decreased to the lowest level that is beneficial to the patient. In these circumstances, it is preferable to use the standard rather than the sustained-release formulation of levodopa or a dopamine agonist. If a patient does not respond to levodopa, it is highly unlikely that they will respond to any other dopaminergic agent.

Suboptimal clinical response. There are a variety of ways to enhance motor response in patients who experience suboptimal motor control with dopamine agonist or levodopa monotherapy. The simplest approach is to gradually raise the dose of the dopaminergic agent. In the case of dopamine agonists, there is a rationale for trying higher doses of the agonist to maximally delay the introduction of levodopa and prevent motor complications. However, high doses of dopamine agonists can be associated with neuropsychiatric side effects, sedation with EDS, and ICDs. If patients cannot be satisfactorily controlled on an agonist, then levodopa should be added. It is not wise to compromise patient care to further delay the introduction of levodopa. If the patient is receiving levodopa monotherapy, increased doses might be effective. Higher doses are associated with an increased risk of motor complications, but may be justified if required to provide a satisfactory clinical response. Conversely, patients and physicians should have realistic expectations and avoid using high doses to obtain only a minimal additional benefit (which may not be obtainable in any event) at the risk of side effects. The addition of a dopamine agonist may enhance benefit without increasing the risk of motor complications. COMT and/or MAO-B inhibitors may also be useful in managing patients with a suboptimal clinical response. As described above, COMT inhibitors block peripheral levodopa metabolism, whereas MAO-B inhibitors block central dopamine metabolism. Each of these approaches can increase brain dopamine availability and enhance motor benefits.

"End-of-dose" deterioration or the wearing-off phenomenon. End-of-dose deterioration or the wearing-off effect is operationally defined when the duration of benefit after a given dose of levodopa wanes after less than 4 hours (it should be appreciated that every dose of levodopa will "wear off" at some point). Early in treatment, the duration of benefit after a dose of levodopa can be long lasting, but over time it shortens and begins to approximate the half-life of the drug. As a result, patients experience deterioration in motor function toward the end of the dosing cycle, before the next dose has taken effect. Although less prominent, wearing-off has also been reported with dopamine agonists.[485] The particular treatment will depend on the severity of the wearing-off problem, whether it is complicated by dyskinesia, and on how dopaminergic therapy was initially started. Treatment options are similar to those for suboptimal motor response and include the following:

- Manipulate the dose of levodopa: increase the levodopa dose if the patient is not experiencing dyskinesia or increase the frequency of administration (possibly with lower individual doses) if the patient does have dyskinesia. Levodopa dose manipulation carries with it the risk of inducing or aggravating dyskinesia with higher doses and providing inadequate antiparkinsonian responses with more frequent lower doses. A controlled-release formulation of levodopa (Sinemet CR or Madopar HBS) can be useful for some patients with wearing-off, but absorption is unpredictable and can lead to troublesome diphasic dyskinesias. Long-acting formulations of levodopa are perhaps most valuable in addressing wearing-off effects that occur overnight.
- Add a dopamine agonist: if the patient is not already on a dopamine agonist, the introduction of a dopamine agonist can reduce "off" time by 1 to 2 hours in fluctuating patients with PD.[308,322,323] Once an adequate dose of the dopamine agonist has been achieved, the dose of levodopa can be gradually lowered to reduce the risk of dyskinesia. In general, it is preferable to use a low dose of levodopa plus a low dose of a dopamine agonist rather than to use high doses of levodopa alone. Occasionally, switching from one dopamine agonist to another is helpful, but there are no data supporting the concurrent use of multiple dopamine agonists. The more constant availability of patch rotigotine or extended-release ropinirole may be useful for treating parkinsonian features that emerge overnight.
- Add a COMT inhibitor: as an adjunct to levodopa, COMT inhibitors can significantly reduce "off" time and increase "on" time by about 1 to 1.5 hr/d in patients with wearing-off episodes.[398-401] COMT inhibitors are generally well tolerated, but may induce the new onset or worsening of dyskinesia in this population, and a 15% to 30% reduction in levodopa dose may be required. This is more likely to occur if the patient is already experiencing dyskinesia. Entacapone seems to be less effective than tolcapone, but should be the first COMT inhibitor used because of the risk of liver dysfunction with tolcapone. COMT inhibitors also alter the pharmacokinetics of levodopa, which theoretically may reduce the risk of further inducing motor complications.
- Add an MAO-B inhibitor: prospective, double-blind, controlled studies have demonstrated that rasagiline can reduce "off" time. The PRESTO and LARGO studies demonstrated that the addition of rasagiline to levodopa resulted in a reduction in daily "off" time of 1 to 1.2 hours compared with placebo.[441,442] This

was comparable with what was obtained with entacapone in this same study, but with fewer side effects. Zydis selegiline reduced "off" time by 1.6 hours compared with placebo in one study,[445] but was not superior to placebo in another.[446]

- Reduction or redistribution of dietary protein: LNAA breakdown products of dietary proteins can compete with levodopa for absorption and entry into the brain. In patients with advanced PD, striatal dopamine is increasingly dependent on peripheral levodopa availability. Under these conditions, even a minor reduction in levodopa absorption can lead to a dramatic reduction in striatal dopamine levels and an impaired antiparkinsonian response. To avoid this problem, some have recommended a protein redistribution diet in which all dietary proteins are consumed during the evening so that the patient can enjoy a better motor response during the day.[486] However, the benefits obtained with dietary manipulation are short term, the diet is unpleasant, and a dietician should be involved to assure that minimum daily protein requirements are met. A more practical approach is simply to administer levodopa on an empty stomach 1 hour before or 1 hour after each meal.
- Subcutaneous injections of apomorphine: such injections can be used as rescue therapy in patients experiencing severe "off" episodes.[379,380,383,384,487] The response to subcutaneous apomorphine is rapid but short lasting, with onset of benefit in approximately 3.5 to 12.5 minutes and duration of benefit lasting approximately 1 hour. The apomorphine-induced "on" state is comparable with the peak levodopa response, and while the motor response is relatively brief, it provides predictable "on" time for the patient in which he or she can complete a chore and during which the next dose of levodopa/carbidopa may take effect. The potential emetic side effect of apomorphine may necessitate concomitant use of an antiemetic such as domperidone, a peripheral dopamine antagonist that does not cross the blood-brain barrier and hence does not exacerbate parkinsonism. Domperidone is not available in the United States but can be obtained in most other countries. In the United States, drugs such as Tigan can be used as an alternative. Because of the inconvenience, subcutaneous apomorphine is generally reserved for patients who have severe "off" episodes and who have exhausted other treatment methods.
- Continuous dopaminergic infusion: many studies have demonstrated the capacity of continuous infusion of levodopa or dopamine agonists (lisuride or apomorphine) to reduce "off" time when administered continuously.[488-491] Most of these studies have been open-label and uncontrolled, but one prospective study showed that patients randomized to receive continuous subcutaneous infusion of lisuride had significantly fewer "off" periods than did those randomized to remain on standard oral levodopa therapy.[492] Interestingly, reduced "off" time in this study was also associated with significant reduction in dyskinesia. The basis of this effect is thought to relate to more continuous and more physiologic activation of striatal dopamine receptors (see discussion of infusions, page S64). Although these procedures may be cumbersome to administer, they have the potential to avoid the need for surgical interventions.
- Surgical interventions: patients who do not respond to the above measures and are experiencing disabling "off" episodes may be candidates for a surgical intervention (see section on surgical treatments, page S55).

Delayed-on and no-on response. In advanced disease, fluctuating patients may occasionally experience a marked delay in responding to a given dose of levodopa, known as delayed-on response, or fail to respond entirely, referred to as no-on response. These phenomena generally result from inadequate absorption and transport of levodopa into the brain in patients who are totally dependent on the peripheral availability of levodopa. This can be due to an inadequate levodopa dose, slowing of gastrointestinal transit time (levodopa is absorbed in the small intestine and not in the stomach), and competition for levodopa absorption by dietary amino acids. An increased dose of levodopa can provide more dopamine to the brain. However, these patients often have advanced disease and a narrow therapeutic window. Thus, a dose of levodopa sufficient to induce a motor response in this type of patient may also induce severe dyskinesia. Controlled-release formulations of levodopa are erratically absorbed and are particularly prone to be associated with delayed or no-on responses, and patients should be switched to a regular formulation of levodopa should this problem occur. COMT inhibitors may help by preventing the breakdown of levodopa in the gut and providing more predictable levodopa absorption. No-on or delayed-on episodes often occur after heavy-protein meals. Taking levodopa on an empty stomach or reducing the protein concentration in the meal may permit the same dose of levodopa to induce an "on" response. Finally, levodopa

is absorbed in the small bowel and not in the stomach. Many patients with PD experience slowing of gastrointestinal transit time, so that delivery of levodopa to the stomach is delayed and sufficient concentrations to provide an "on" response are not present at any one time. Agents that enhance bowel motility may be helpful in this situation, although one of the most effective of these agents, cisapride, was withdrawn from the market in the United States because of the potential for cardiac toxicity.

Methyl and ethyl ester formulations of levodopa are currently being investigated. They are prodrugs of levodopa that have greater gastric solubility, more rapid transition into the small intestine and are rapidly hydrolyzed to form levodopa. Their pharmacokinetic profile demonstrates rapid absorption and suggests that they might provide more predictable on responses in fluctuating patients with PD who experience delayed-on or no-on episodes.[493,494] A double-blind study of ethyl ester levodopa in patients with PD who had motor fluctuations showed no improvement in time to "on," response failures, or "off" time compared with standard levodopa.[495] The efficacy of a methyl ester levodopa/carbidopa preparation (CHF 1512) in fluctuating patients with PD is currently being studied.[224] A gel preparation of levodopa (Duodopa) is available in many countries in Europe and is under investigation in the United States. This preparation is used for continuous intraintestinal infusion of levodopa and may be able to reduce "off" time and dyskinesia.[489]

Unpredictable "off" episodes. Most levodopa-treated patients with PD with motor fluctuations experience predictable "off" periods that occur when the beneficial effect of a given dose of levodopa wears off (see earlier). Occasionally, patients may experience "off" episodes that seem to be unpredictable and occur suddenly and without warning. Patients may convert from an "on" to an "off" state in seconds or minutes. In these cases, the "off" periods seemingly have no relationship to the time of levodopa administration or to the plasma levodopa concentration. These complications tend to occur with advanced disease and patients are often profoundly akinetic during the "off" episode and markedly dyskinetic when "on." The basis of this phenomenon is not known. Many of the sudden "offs" are probably pharmacokinetically based and occur in patients with advanced PD and minimal capacity to store and buffer levodopa fluctuations. They are, thus, particularly vulnerable to even minimal fluctuations in peripheral levodopa availability. It may be that pharmacodynamic mechanisms play a role as well.

The treatment approach is similar to that described above for wearing-off episodes, but unpredictable "off" episodes are generally much more difficult to treat. It is important to take a good history, and if possible to observe the patient through a series of dosing cycles, so as to define the nature of the levodopa response and determine if the "off" episodes are actually occurring on a pharmacokinetic basis. Patients with unpredictable "offs" may have plasma levodopa levels that are relatively low and fluctuate around a threshold level. In these cases, higher doses of levodopa can be tried. As indicated above, controlled-release formulations of levodopa provide less predictable plasma levels, and a regular levodopa formulation should be substituted in these instances. In many cases, these unpredictable motor fluctuations cannot be satisfactorily controlled with any of the conventional medical strategies and it may be necessary to consider an infusion or a surgical intervention. This underscores the importance of early treatment strategies designed to minimize the likelihood that motor complications will develop.

Freezing (motor blocks). Freezing of motor behavior can occur with any movement, but it is most apparent and troublesome to patients with PD when it involves gait. This frequently occurs on initiating gait (start hesitation) or when passing through a tight space such as a doorway. Freezing can occur during "on" or "off" states and typically lasts seconds to minutes. The mechanism responsible for freezing is not known, but it has been postulated that it occurs in levodopa-treated patients with PD as a consequence of a diminished dynamic range in remaining SNc dopamine neurons.[227] Thus, maximal firing in remaining dopamine neurons may preclude upregulation in response to a stress situation leading to motor blocks or freezing.

Attention to the timing of freezing in the levodopa response cycle determines the treatment strategy. Freezing during the "off" state can often be treated by increased dose of dopaminergic medications (see Treatment of "Off" Periods). Freezing, in conjunction with other prominent signs of parkinsonism at the time of the peak levodopa effect, suggests an underdosed state that may respond to larger doses of levodopa/carbidopa or other dopaminergic strategies (see section Suboptimal Peak Response). Occasionally, patients improve with increased levodopa dosages, even if signs of parkinsonism seem to be optimally controlled. Hence, a brief trial of increased levodopa doses may be indicated. Patients with true "on" period freezing or those who experience freezing despite receiving maximal medical treatment are more difficult to manage. A reduction in the dosage of levodopa or dopamine agonists may be helpful for "on" period dyskinesia, but this does not tend to help freezing and may lead to worsening of parkinsonian features. In the majority of patients with freezing, the addition of levodopa or dopamine

agonists is not effective. Interestingly, a reduced risk of developing freezing has been reported with selegiline and rasagiline.[185,443] Gait freezing and motor blocks may be helped by nonpharmacologic techniques that involve the use of sensory cues or devices.[496] Some approaches that have been used to try and counter freezing episodes include the following:

- Stepping toward a target on the ground
- Stepping over a cane laid on the floor in front of the foot
- Taking the first step with a stiff leg, in a military manner
- Counting out a rhythm or singing and then trying to walk in concert with the rhythm

The general idea is to substitute a conscious motor program for a malfunctioning automatic motor program. After experimenting with different ploys, patients often find one particular strategy that is helpful. Anxiety can exacerbate the tendency for motor blocks/freezing, and treatment of the anxiety state may be useful (see the Behavioral Impairment section of Neuropsychiatric Problems).

Management of dyskinesias. *Peak-dose dyskinesia.* Peak-dose dyskinesias occur at the time of maximal levodopa benefit and peak plasma levodopa concentration, and frequently develop in patients who experience motor fluctuations. They are thought to be related to abnormal neuronal firing patterns in basal ganglia neurons that develop in response to pulsatile stimulation of the denervated dopamine receptor (see section on Motor Complications). In the earliest stages, dyskinesias are not usually troublesome to the patient, and may be managed by small reductions in levodopa dosage. However, in more advanced disease dose reductions often lead to inadequate control of parkinsonian features. If the patient is only on levodopa, the addition of a dopamine agonist coupled with a reduction in levodopa dose may reduce dyskinesia while maintaining or even improving motor function. Dopamine agonists may be particularly valuable with dystonic forms of dyskinesia. COMT and MAO-B inhibitors are typically not helpful as they tend to increase dyskinesia, but in mild cases they might permit a reduction in levodopa dose with a reduction in dyskinesia. It is best to avoid controlled release formulations of levodopa in dyskinetic patients as they are long acting and can be associated with prolonged bouts of dyskinesia.

With advancing disease, dyskinesias can become more severe and represent a major source of disability to the patient. In this situation, patients often have a narrow therapeutic window such that even a small reduction in the levodopa dose aimed at controlling dyskinesia can result in a dose that is insufficient to induce an "on" response, and a dose sufficient to produce an "on" response can cause dyskinesia. Consequently, patients can cycle between "on" responses that are complicated by disabling dyskinesia and "off" responses in which they experience disabling motor impairment. These types of patients can be difficult to control with medical therapies and are potentially candidates for a surgical procedure. NMDA receptor antagonists such as amantadine have been shown to reduce dyskinesias in MPTP-treated monkeys and patients with PD,[475–477] but doses sufficient to attain these effects (usually >300 mg/d) may be associated with cognitive side effects, and benefits may not endure. Atypical neuroleptics have been reported to reduce dyskinesia in some studies, but results are inconsistent and benefits can be associated with worsening of parkinsonian features.[497,498] Sarizotan is a D2 receptor antagonist and a 5HT1A agonist that has been shown to have antidyskinesia effects in MPTP monkeys.[499] An open-label clinical trial reported significant benefits with doses up to 10 mg/d, but these doses were associated with worsening of parkinsonism.[500] Double-blind, controlled studies using a low dose that did not induce worsening of parkinsonian features (1 mg BID) did not show significant antidyskinesia benefit,[501] and for now the drug is no longer studied. There has been considerable interest in the potential of A2A antagonists to provide antidyskinesia benefits based on studies in MPTP monkeys.[502] However, although double-blind clinical trials in patients with advanced PD showed improvement in "off" time, no benefits were observed with respect to dyskinesia.[503]

Levetiracetam (LEV; Keppra) is an antiepileptic drug that is chemically related to piracetam, and has been shown to have antidystonic and antimyoclonic effects in hamsters.[504] LEV also reduces dyskinesia in the MPTP-lesioned marmoset model of PD, when administered with either levodopa or a combination of levodopa and ropinirole.[505] The effect of LEV has been evaluated in small open-label studies in patients with PD.[506,507] Results have been mixed, with some patients showing benefits, but others having worsened parkinsonism and increased dyskinesia. In addition, the drug is not well tolerated because of somnolence and leads substantial number of patients to drop out.

Thus, despite an intensive search, no drug other than amantadine has demonstrated an antidyskinesia effect that is not associated with a worsening of parkinsonism. Patients with severe dyskinesia that cannot be adequately regulated with any of the treatment approaches described above may be candidates for infusion or surgical treatments (see sections on Infusion and Surgery later). It should be emphasized again that motor complications can be extremely difficult to control in some patients, and efforts should be made to prevent

their development in the first place (see section on management of patients with early PD, page S44).

Diphasic dyskinesia. Diphasic dyskinesia or the D-I-D syndrome is another form of levodopa-induced dyskinesia (see section on Dyskinesia). Here, adventitious dyskinetic movements occur at the beginning and at the end of the levodopa dose response cycle, but not during the drug's peak clinical effect. Diphasic dyskinesias tend to be comprised of stereotypic, rhythmic movements primarily involving the lower extremities, and are with frequently associated with painful dystonia and parkinsonism in other body regions. D-I-D dyskinesias are usually transient, lasting seconds to minutes, and tend to be most troublesome when the patient is turning "off." Diphasic dyskinesias can be disabling for some patients and difficult to diagnose as they are transient and may merge into peak-dose dyskinesia. The cause of D-I-D dyskinesias is not known, nor is the anatomic basis for why they primarily involve the lower extremities understood. It is noteworthy that they disappear with rising or falling dopamine levels, suggesting that they somehow relate to suboptimal striatal levodopa/dopamine concentrations.

Diphasic dyskinesias can be difficult to treat. In contrast to peak-dose dyskinesias, patients may respond to more frequent or higher doses of levodopa/carbidopa. This may provide a more continuous "on" state and prevent the patient from cycling through D-I-D phases. Bear in mind that while higher doses of levodopa may improve diphasic dyskinesias, they may worsen peak-dose dyskinesias. One treatment strategy is to overlap doses of levodopa/carbidopa at intervals that are just long enough to preclude the development of the diphasic dyskinesia at the end of each dosage cycle. Although administering levodopa/carbidopa doses at short intervals can successfully prevent the end-of-dose dyskinetic period for a while, this strategy tends to fail eventually. With advancing disease, patients can begin to note a decreasing threshold for D-I-D dyskinesias and an inability to suppress them despite larger and larger doses of levodopa/carbidopa. Patients can try to time their dosing cycle so that they are more predictable and arrange to be at home during the time when diphasic dyskinesias occur.

Patients with D-I-D dyskinesia should not receive controlled-release levodopa as this formulation is prone to be associated with prolonged periods of suboptimal plasma levodopa levels, thereby prolonging the D-I-D dyskinesia. COMT inhibitors may similarly worsen D-I-D dyskinesia because of their tendency to be associated with a more prolonged levodopa half-life (the opposite of what has been proposed as a treatment for peak-dose dyskinesias). If this occurs, higher doses of regular levodopa should be tried. The addition of a dopamine agonist is usually not helpful for D-I-D dyskinesia. Subcutaneous apomorphine may be useful in eliminating diphasic dyskinesias until the beneficial effect of the next levodopa dose is achieved. Patients who have disability from diphasic dyskinesia frequently do not achieve acceptable relief from medication adjustment maneuvers and may be candidates for surgery or infusion therapy.

It should be noted that falling dopaminergic levels associated with discontinuation of dopaminergic infusions can lead to painful dystonias that likely represent a form of diphasic dyskinesia (see later). Fetal nigral transplantation has also been reported to be associated with a persistent form of dyskinesia that resembles diphasic dyskinesias. It has been postulated that off-medication dyskinesia associated with fetal nigral transplantation may be a prolonged form of diphasic dyskinesia related to suboptimal levels of dopamine release.[508]

All dyskinesias can be unmasked or worsened by anxiety-provoking situations, and interventions directed at treating underlying neuropsychiatric issues may be helpful (see section on neuropsychiatric problems, page S70).

Dystonia. Dystonia may occur as a side effect of levodopa or as feature of untreated parkinsonism. It is important to take a careful history and to note the relationship between the onset of the dystonia and the timing of levodopa administration. Painful dystonic cramping of the toes and feet is a common complaint in untreated patients with PD, or before the initial morning dose of levodopa takes effect. Some patients may also experience painful or uncomfortable dystonia at the end of their levodopa response cycle as part of diphasic dyskinesia (see earlier). In these cases, increased doses of levodopa and other strategies designed to improve PD motor control may be useful. Additional options aimed at managing early morning dystonia include administration of a bedtime dose of sustained-release levodopa/carbidopa or a long-acting dopamine agonist. Patients may also try taking a dose of levodopa/carbidopa before they are scheduled to arise after sleep, but this requires the patient to remain in bed after awakening. The value of the rotigotine patch in this situation remains to be determined but it may be helpful, as this technology provides continuous 24-hour/day delivery of the agonist and is likely to be beneficial for early AM dystonia.

Dystonia may also be a manifestation of a levodopa-induced dyskinesia. In fact, dystonia may be the earliest manifestation of dyskinesia. Strategies designed to prevent the development of motor complications may also prevent the development of levodopa-induced dystonia.

Once peak-dose dystonia occurs, therapy is similar to that described for peak-dose dyskinesia. A reduction in the size of the individual doses of levodopa/carbidopa may reduce dystonia but may cause deterioration in PD signs and symptoms. Dopamine agonists are particularly helpful in controlling levodopa-induced dystonia and can be used as an adjunct to levodopa coupled with a reduction in levodopa dose if they are not already being used. If all other measures fail and dystonia is disabling, patients may be considered for a surgical procedure.

SURGICAL PROCEDURES AND OTHER INVASIVE APPROACHES FOR THE TREATMENT OF PARKINSON DISEASE The capacity of surgical therapies to provide benefit for patients with PD who can no longer be satisfactorily controlled with medical therapies due to motor complications has been a major advance in the modern treatment of PD.[509] Over the past century, a number of surgical treatments have been attempted in PD.[510] Historically, lesions of the corticospinal tracts were noted to improve parkinsonian features (especially tremor), but only at the expense of voluntary motor paresis, and were abandoned as a treatment for PD. In the 1940s, lesions of the ansa lenticularis and GPi were noted to provide benefit to patients with PD without paralysis, and pallidotomies began to be routinely performed.[511,512] However, AEs were a concern because of the proximity of the GPi to the internal capsule and the optic radiation. Furthermore, bilateral lesions were associated with risks of dysphagia, dysarthria, and cognitive impairment.[513] In the 1950s, Cooper[514] accidentally ligated the anterior choroidal artery with resultant infarction in the thalamus, and noted improvement in PD tremor. Because of improved results and reduced side effects, thalamotomy replaced pallidotomy as the preferred treatment for PD tremor. However, with the introduction of levodopa in the late 1960s, surgical procedures for PD were largely abandoned.

In the 1990s, there was a resurgence of interest in surgical procedures for the treatment of patients with advanced PD because of a) the limitations of levodopa therapy; b) advances in the ability to safely perform stereotactic neurosurgical procedures; c) advances in neuroimaging and microelectrode recording techniques that permit more accurate target localization; d) new insights into the organization of the basal ganglia that provide a rational basis for targeting specific brain regions[263-265]; e) evidence that pallidotomy benefits are most pronounced when lesions are made in the posteroventral (sensorimotor) portion of the GPi[515]; and f) the development of high frequency DBS, which does not necessitate making a destructive brain lesion. Surgical therapies that have been used or are being investigated in PD are listed in table 16.

Table 16 Surgical procedures for patients with PD

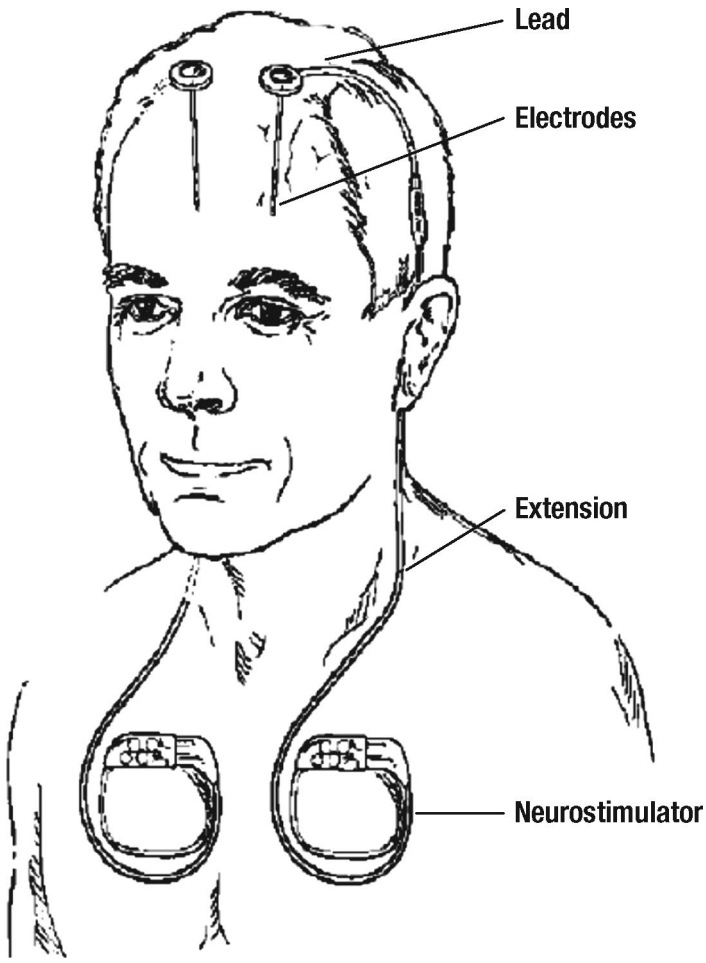
Ablative procedures
Thalamotomy
Pallidotomy
Subthalamotomy
Stimulation procedures
Thalamus (ventral intermediate nucleus)
Globus pallidus pars interna
Subthalamic nucleus
Pedunculopontine nucleus
Cell-based procedures
Fetal human nigral transplant
Retinal pigmented epithelial cell (Spheramine) transplant
Trophic factors
Gene therapy
Aromatic-AADC
Glutamic acid decarboxylase
Neurturin

PD = Parkinson disease; AADC = aromatic L -amino acid decarboxylase.
Adapted with permission from Olanow et al.[15]

Targets for surgical procedures and the underlying rationale for choosing them are as follows:

- Ventral intermediate (VIM) nucleus of the thalamus—this target has been chosen for ablative and stimulation procedures based on evidence that lesions in this target provide potent antitremor effect in PD.[516-518] Antidyskinesia effects have also been observed with lesions in the thalamus.[519] Because similar benefits can be obtained with other targets that are associated with more widespread antiparkinsonian effects, the thalamus is rarely selected as a target site today.
- GPi and STN—physiologic and metabolic studies indicate that neurons in both the STN and GPi are overactive in PD,[53,520,521] and that lesions of these structures provide antiparkinsonian benefits in animal models of PD.[522–524] Both ablation and high frequency stimulation of these targets have been shown to provide antiparkinsonian benefits as well as a profound reduction in dyskinesia (especially GPi) in patients with PD. The reduction in dyskinesia is contrary to the classic model, which suggests that impaired firing in the STN or GPi would induce rather than ameliorate dyskinesia (see section on motor complications). It is thought that lesions and high frequency stimulation of

Figure 21 Schematic representation of the deep brain stimulation system. Courtesy of Dr. M. Tagliati.



these targets act by eliminating abnormal neuronal firing patterns (not just frequency alone) and thereby prevent basal ganglia output neurons from sending "misinformation" to thalamic and cortical motor regions that ultimately result in dyskinesia.[265]

- Striatum (particularly the postcommissural putamen)—the striatum is the major target of the nigral dopaminergic neurons that degenerate in PD, and the major site of dopamine loss. Indeed, restoration of dopamine to the striatum, and not the SNc per se, is essential for improvement in the dopaminergic motor features of PD. It has, therefore, been selected as the primary target site for cell-based, trophic factor, and gene delivery strategies aimed at restoring dopaminergic function.[525,526]
- Pedunculopontine nucleus (PPN)—the PPN is a diffuse nucleus that extends throughout the upper brainstem. Stimulation and lesions in the PPN influence locomotion, and for this reason it has been referred to as the mesencephalic locomotor center.[527] Current medical and surgical therapies have had little affect on gait and balance dysfunction in PD, and they remain major sources of disability for many patients. Preliminary studies suggest that stimulation of the PPN may provide locomotor benefits for patients with PD (and possibly even those with PSP).[528] DBS of the PPN is being actively investigated.

Surgical therapies have historically used ablative procedures (e.g., chemical, radiofrequency, or thermal lesions) to make a destructive lesion in overactive or abnormally firing brain targets. However, ablative procedures are associated with the risk of inducing damage to neighboring structures with consequent neurologic dysfunction.[513] This is a particular problem with bilateral procedures, in which there are additional risks of cognitive, speech, and swallowing impairment. Lesions of the STN are also associated with the risk of a severe and potentially fatal hemiballismus.[529] As a result, physicians have been reluctant to perform bilateral surgical procedures or unilateral subthalamotomy in patients with PD.

The introduction of high-frequency DBS procedures in PD has resolved many of these issues. High-frequency stimulation of specific brain targets induces functional benefits that simulate the effects of a destructive lesion, but without the need for making a destructive brain lesion. DBS is performed by implanting an electrode with four contacts into a target site within the brain and connecting it to a pulse generator placed subcutaneously over the chest wall (figure 21). Stimulator settings can be adjusted periodically with respect to electrode configuration, voltage, frequency, and pulse width. Advantages of DBS include 1) it does not require making a destructive lesion in the brain; 2) it can be performed bilaterally with relative safety; 3) brain targets can be used that one might be loathe to lesion; 4) stimulation settings can be adjusted periodically to try and improve efficacy or decrease adversity; and 5) it does not preclude the use of future therapies that require preservation of the integrity of the basal ganglia.[530]

Side effects of DBS can be related to the surgical procedure, the device, or to the stimulation. The procedure requires a needle to be passed through the brain, carrying with it the risk of hemorrhage and damage to neighboring brain structures, although risks are less than are seen with ablative procedures, particularly when performed bilaterally.[513] Complications associated with the device can be related to infection or mechanical problems (e.g., lead fracture, movement of the electrode, skin erosion), and may require lead removal or reimplantation. Side effects related to stimulation are generally transient and may be controlled by adjusting the stimulation variables. However, multiple visits may be required to determine

the optimal stimulation settings. Furthermore, in some patients, stimulation benefits cannot be obtained without the presence of stimulation-related side effects (see later). Finally, the battery must be periodically replaced (usually within 1 to 3 years), which currently requires performing another surgical procedure under general anesthesia. Longer battery life can be obtained with lower voltage settings.

The different surgical procedures used in patients with PD are described below.

Ablative procedures. With the advent of DBS, ablative procedures have largely been abandoned in PD (for more detailed information on their rationale and historical significance see Algorithm 2001).[15] Ablative procedures are still occasionally used in individuals from remote areas who do not have access to DBS or to the neurologic expertise necessary for monitoring and adjusting stimulator settings.

Thalamotomy. This procedure was extensively performed as a treatment for PD tremor in the prelevodopa era and provided long-lasting tremor reduction in more than 90% of patients.[517,518,531-534] Thalamotomy is less effective for rigidity and does not improve other parkinsonian features such as bradykinesia and gait dysfunction. Some reports indicate that thalamotomy can provide an antidyskinetic effect[519]; this seems to be associated with lesions placed slightly anterior and ventral to the VIM nucleus. The basis for thalamotomy providing an antitremor effect is not known, but may be due to destruction of autonomously firing tremor-synchronous neurons or circuits. The VIM nucleus receives input from the GPi and the cerebellum and in turn projects to the motor cortex. As a result of its central connections within motor circuitry, the VIM could become entrained by oscillations originating in other sites and promote abnormal oscillations throughout the motor system. Thus, lesions in the VIM could reduce tremor by curtailing this entrainment, even though this may not be the site of origin of abnormally firing neurons. *The observation that thalamotomy is so effective in ameliorating tremor but has little effect on other parkinsonian features suggests that the brain regions that underlie the different motor features of PD may be anatomically disparate.*

Pallidotomy. A resurgence of interest in pallidotomy occurred in the 1990s based on evidence that GPi neurons are overactive in PD[263,264,520,521]; that maximal benefits are attained when lesions are placed in the posteroventral portion of the nucleus, which contains the sensorimotor area[23]; and the finding that pallidotomy induces a consistent and dramatic amelioration of contralateral dyskinesia.[21,269] In a prospective single-blind study, patients who were randomized to receive unilateral pallidotomy had significant benefits in dyskinesia and UPDRS scores during the "off" stage compared with patients randomized to receive best medical treatment.[535] In a randomized trial comparing pallidotomy to medical therapy, patients in the surgical group had improvement in motor score and dyskinesia, with two thirds having complete resolution of dyskinesia on the contralateral side.[536] Interestingly, there was also a 36% reduction in ipsilateral dyskinesia. No changes were seen in the medical group. Benefits after pallidotomy have been shown to persist for 5 years.[537] Some debate remains with respect to the need for microelectrode guidance, with some arguing it is essential to find the optimal site for the lesion,[538] whereas others argue that the extra needle passes required increase the risk of hemorrhage and that similar results can be obtained without it.[539] There is little information on the efficacy of bilateral pallidotomy, as the procedure is rarely performed because of risk of side effects mentioned earlier.

Subthalamotomy. Subthalamotomy has been performed in a few patients with PD and shown to provide substantial benefit.[540-542] Dyskinesia may be seen transiently after surgery, but typically disappears concomitant with a reduction in antiparkinsonian medication. Long-term studies of bilateral subthalamotomy have shown persistent benefits lasting 3 to 6 years, with results comparable with those obtained with DBS.[543] Patients typically do not experience serious side effects; however, in one series, 3 of 12 cases who underwent unilateral subthalamotomy developed hemiballismus.[544] Further investigation of this procedure needs to be performed to determine its safety and efficacy. Very few centers perform this procedure at present, however, because DBS can provide comparable results and virtually eliminate the risk of hemiballismus. The advantages and disadvantages of ablative lesions are outlined in table 17.

Table 17 Ablative lesions: Advantages and disadvantages

Advantages
Marked and sustained improvement in tremor (especially thalamotomy)
Mild to moderate improvement in rigidity and bradykinesia (pallidotomy and subthalamotomy)
Consistent and dramatic improvement in contralateral dyskinesia (pallidotomy)
Widely available
Disadvantages
Necessitates making a brain lesion with risk of damage to neighboring structures (e.g., internal capsule and visual pathways for pallidotomy)
Bilateral lesions associated with additional risks (cognitive impairment, dysphagia, dysarthria)
Lesion may preclude use of more effective therapy in the future

Deep brain stimulation. ***DBS of the VIM.*** DBS was first used in the VIM nucleus of the thalamus in patients who had previously undergone a contralateral thalamotomy, to avoid performing bilateral ablative procedures.[545] On the basis of excellent results that were obtained, DBS–VIM was then used as a primary therapy for tremor in patients with PD, and demonstrated the amelioration of contralateral tremor in about 80% of patients, comparable with what had been observed with thalamotomy.[546-548] Benefits of DBS–VIM have been confirmed in double-blind crossover evaluations,[549] and shown to be long lasting with tremor amelioration persisting for more than 7 years.[550] Even after this prolonged period of time, the tremor returns within seconds when stimulation is stopped suggesting that DBS does not permanently influence the underlying cellular/physiologic mechanisms responsible for tremor. Benefits have not been observed with respect to rigidity, bradykinesia, or gait dysfunction, similar to what was found with thalamotomy.

A double-blind study randomized 45 patients with drug-resistant tremor to receive thalamotomy or thalamic DBS.[551] Tremor was either completely or almost completely suppressed in more than 70% of patients in both treatment groups. However, functional improvement reflecting both clinical benefit and side effects was significantly better in patients receiving thalamic stimulation.

This procedure is currently rarely used because DBS of the STN or GPi can provide comparable antitremor results with superior effects on other parkinsonian features.

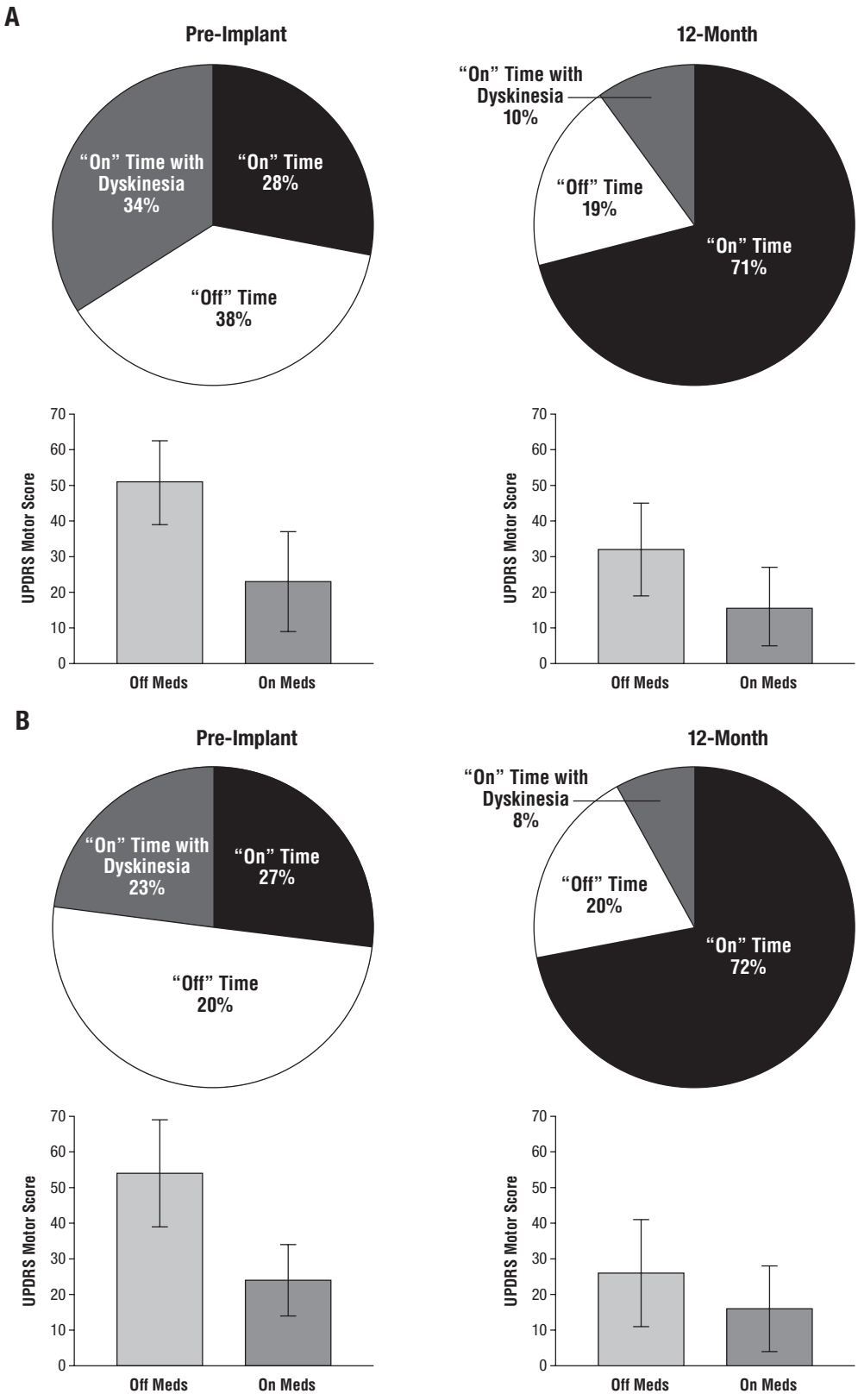
DBS of the GPi. Stimulation of the GPi was attempted based on the greater success of pallidotomy in ameliorating parkinsonian features and dyskinesia compared with thalamotomy. In general, the benefits of DBS-GPi mimic the effects of pallidotomy. Several small open-label studies reported improvement in motor scores, "on-off" fluctuations, and dyskinesias after both unilateral and bilateral pallidal stimulation.[552-556] Bilateral pallidal stimulation was consistently associated with a marked reduction in contralateral dyskinesia and a 30% to 50% improvement in "off" period motor scores.[557,558] A prospective multicenter trial of the effects of DBS in patients with advanced PD included 38 patients who underwent bilateral DBS–GPi.[559] After 6 months, pallidal stimulation improved UPDRS motor scores during the "off" medication state by up to 59% and increased "on" time without dyskinesia by about 35% compared with baseline ($p < 0.001$). Improvement was noted in each of the cardinal features of the disease. Home diary assessments of motor function demonstrated increased "on" time without dyskinesia during the waking day from 28% to 64% ($p < 0.001$), whereas "off" time was reduced from 37% to 24% ($p = 0.01$). Global estimates of severe disability improved at 6 months from 76% at baseline to 11% for the physician rating and 82% at baseline to 14% for the patient rating. These benefits were confirmed in a double-blind crossover evaluation performed 3 months after the procedure. UPDRS motor scores were improved by 37% when patients were randomized to stimulator "on" vs stimulator "off" ($p < 0.001$). The effect of GPi stimulation on UPDRS motor scores and percent of "on" time without dyskinesia are shown in figure 22A.

Benefits of GPi stimulation were confirmed in a meta-analysis of patient outcomes in 136 patients who participated in 14 studies.[560] Although there was significant variability among centers, perhaps reflecting electrode placement and stimulation methodology, the mean UPDRS motor score in the "off" medication state was improved by 40% at 6 months after the procedure. Long-term studies have shown persistent antidyskinesia benefits, but with some deterioration in UPDRS scores.[556,561] This may reflect the development of nondopaminergic features which would not be expected to respond to stimulation of the GPi.

DBS of the STN. The STN is a rational target for stimulation in PD because: 1) it plays a central role in striato-pallidal-thalamic-cortical loops that are thought to mediate motor, cognitive, and emotional functions[562]; 2) it provides excitatory innervation to both segments of the GP, the SNr, the PPN and the SNc[563,564]; 3) STN neuronal firing frequency is overactive in the parkinsonian state[565] and could thereby contribute to the development of parkinsonian features according to the classic model; and 4) lesions of the STN improve motor function in the MPTP-lesioned monkey.[522,523] Furthermore, it has been hypothesized that lesions of the STN might block STN-mediated excitotoxic damage to target neurons and therefore provide a neuroprotective effect.[389] Indeed, STN lesions have been reported to protect SNc neurons in rodents from 6-OHDA–induced toxicity.[566] For these reasons, and because it represents a discrete target with characteristic features on both microelectrode recording and MRI, many consider the STN to be the preferred brain target for treating PD. However, because lesions of the STN can cause hyperkinesias and hemiballismus, physicians have been reluctant to lesion this target. With the introduction of DBS, the possibility of targeting the STN in PD has become feasible.

Benabid et al. were the first to report on the beneficial effects of DBS-STN. They noted a 60% improvement in UPDRS motor and ADL scores in 24 patients after 1 year, with benefits in all cardinal PD

Figure 22 Results of the home diary and UPDRS motor score in "on" and "off" states at baseline and at 12 months after stimulation of (A) the internal globus pallidus and (B) the subthalamic nucleus.



Note that stimulation of either target results in significant improvements in "on" time without dyskinesia and in UPDRS motor score during the "off" stage. Adapted with permission from The Deep-Brain Stimulation for Parkinson's Disease Study Group. Deep-brain stimulation of the subthalamic nucleus or the pars interna of the globus pallidus in Parkinson's disease. N Engl J Med 2001;345:956–963. Copyright © 2001 Massachusetts Medical Society. All rights reserved.

features.[567,568] Dyskinesia severity and duration were decreased by more than 50%, in conjunction with a similar reduction in levodopa dose. Several studies subsequently confirmed the safety and efficacy of DBS–STN in the treatment of advanced PD.[558,569] In these studies, stimulation of the STN improved UPDRS motor scores in the "off" state by an average of 50%. This was associated with a consistent reduction in dyskinesia and levodopa dose.

A prospective, multicenter, study of DBS–STN was performed in 96 patients with advanced PD.[559] At 6 months, stimulation in the "off" state was associated with a mean improvement of approximately 50% in UPDRS ADL and motor scores. The benefits of stimulation were confirmed in a double-blind crossover component of the study, which demonstrated a 40% to 50% improvement in UPDRS motor scores. Importantly, home diary measures of motor state during the waking day demonstrated that mean daily "off" time without dyskinesia increased from 27% at baseline to 74% at 6 months, and that on time with dyskinesia fell from 27% to 7% (figure 22B).

Long-term studies demonstrate sustained benefits with respect to motor function, dyskinesia, and quality of life. A prospective study of 49 consecutive patients treated with DBS–STN noted that off-medication motor scores were still 54% better than baseline at 5 years, and dyskinesias remained improved with respect to both severity and duration.[570] Worsening was noted with respect to akinesia, speech, postural stability, and freezing of gait, which probably reflect progression of nondopaminergic features of the disease which are not affected by DBS. In another long-term study, sustained motor and dyskinesia benefits were reported in 37 patients with PD who were followed for 5 years after DBS-STN surgery.[571] These patients experienced some cognitive decline probably unrelated to the surgical procedure. Finally, a comprehensive meta-analysis of 34 DBS–STN studies published between 1993 and 2004 with results from 921 patients noted consistent motor improvements with stimulation, and sustained improvement in dyskinesia in 69.1% of patients.[569] Other studies have similarly documented persistent motor benefits 4 to 5 years after DBS despite some progression of the underlying disease.[572-574]

To further assess the value of DBS–STN, 156 patients with advanced PD were randomized to receive DBS–STN or best medical treatment.[575] Patients treated with STN stimulation had significant improvements in motor function, quality of life, and dyskinesia scores compared with those treated medically. A comparison of preassigned pairs showed that 55 of the 78 pairs who were randomized to receive DBS had improved motor scores compared with those receiving best medical treatment. Similarly, 50 of the 78 pairs who received DBS had greater improvement on the PD Questionnaire-39 quality of life summary index. However, serious adverse effects were more common in the surgery group (1 patient died of a perioperative hemorrhage) and it is noteworthy that medically treated patients did just as well or better in approximately one third of cases. These observations underscore the importance of patient selection, surgical technique, and considering the risks and benefits for each individual patient before recommending DBS.[576] A large-scale, multicenter, VA Cooperative Study is currently under way in which subjects were randomized to immediate DBS surgery vs best medical therapy for 6 months. Patients who were randomized to DBS were also randomized to receive stimulation of either the STN or the GPi. In the first phase of the study, patients undergoing DBS (regardless of target) were substantially improved in all motor domains compared with patients receiving best medical therapy).[576a] Phase 2 of the study, in which GPi will be compared with STN DBS after 2 years of treatment, has not yet been reported.

Other issues regarding DBS. To obtain maximal benefit from DBS, it is important to be sure that the electrode is placed in the desired location and that stimulation settings are optimized. Toward this end, it is important to appreciate that stimulation of different sites within the same target can induce different responses. For example, stimulation of the ventral GPi improves parkinsonian motor features, whereas stimulation of the dorsal pallidum can worsen them.[577,578] Furthermore, stimulation of the same STN electrode at one voltage can ameliorate dyskinesia, whereas stimulation at a different voltage can induce both dyskinesia and dystonia.[579] These kinds of observations argue for careful mapping of the sensorimotor region of the selected brain target and for the use of microelectrode recordings to ensure that the optimal target site has been chosen.

The precise mechanism of action of DBS remains to be defined. Current hypotheses include depolarization blockade, local release of inhibitory neurotransmitters, jamming of abnormal neuronal firing patterns, and backfiring with activation of inhibitory neurons. Dyskinesia reduction with DBS–STN has been attributed, at least in part, to the reduction in levodopa dosage that stimulation of the STN can permit. This would not, however, account for the antidyskinesia benefit observed with stimulation of the GPi where levodopa dose is typically not reduced. In addition, we have observed individual patients where dyskinesia has gradually disappeared after DBS–STN without any change in dopaminer-

gic medication. It has been proposed that attenuation of dyskinesia with both of these procedures, as well as with pallidotomy, may be due to a stimulation-induced obliteration or jamming of an abnormal neuronal firing pattern in basal ganglia output neurons that is conveying misinformation from the basal ganglia to cortical motor regions.[270] Through whatever mechanism, DBS induces clinical benefits that mirror those obtained with destructive lesions.

The expanding application of DBS to PD therapeutics has fueled research into finding other potential brain targets. Some investigators have felt that targeting pallidofugal fibers in the region of the zona incerta, dorsal, and dorsomedial to the STN, may be preferable to the STN itself. Placement of stimulation electrodes in the caudal portion of the zona incerta was reported to produce contralateral motor improvement superior to what could be obtained with STN stimulation.[580] However, it may be difficult to know with certainty where the electrode is placed in a given patient, and, further, to know which areas are specifically affected by the stimulation.

Other investigators have evaluated the PPN as a target for DBS because of its potential effects on locomotion. Preliminary studies suggest that stimulation of the PPN can improve gait, and that this benefit could not be obtained by stimulation of concurrently implanted electrodes in the STN.[528] The PPN is a brainstem nucleus that extends between the pons and mesencephalon and is divided into compacta and diffusa segments. It has extensive connections with the STN, GPi, and SNc and is thought to play a major role in motor function, particularly locomotion. In fact, it is referred to as the mesencephalic locomotor nucleus because stimulation of this area in cats can lead to alterations in locomotion. If the benefits of DBS–PPN can be confirmed, it would be a major advance, as gait and postural instability are typically not meaningfully improved with available medical or surgical therapies, and represent a major source of disability for patients with advanced PD.

Investigations examining the effects of stimulation of cortical motor and supplementary motor areas are being conducted, but results to date are not encouraging.[581] There is also an interest in the potential of DBS to target brain areas associated with compulsive behaviors and depression that might be of value for patients with PD.[582] These observations underscore the early stage of development of DBS and the clinical research yet to be done to refine how DBS might be applicable to the treatment of specific PD symptoms.

Adverse events associated with DBS. AEs associated with DBS can be divided into those related to the procedure, the device, and stimulation. Intracerebral hemorrhage, infarction, and infection with persistent neurologic deficits are the most serious perioperative AEs, occurring in approximately 1% to 5% of patients.[559,569] Device-related mechanical and infectious complications are more common than was previously appreciated, and occasionally necessitate an additional operation to reposition or replace the lead. One study in patients followed up for 17 to 54 months after DBS found that 2.5% of patients had infections requiring system removal; 3.7% had infections requiring implantable pulse generator removal; 12.5% had misplaced leads; and 26.2% had hardware complications, including lead migration, lead fracture, erosion and fracture of the extension wire, and implantable pulse generator malfunction.[583] Stimulation may be associated with muscle twitch or paresthesias in the contralateral hand or face. In most instances, these effects are transient and can be eliminated or minimized by stimulator adjustment. Occasionally, patients may experience persistent stimulation-related adverse effects, including oculomotor dysfunction, dysarthria, mood disturbances, and ICDs, that cannot be satisfactorily controlled with stimulation adjustment. Stimulation of the GPi or STN can induce transient dyskinesias, but neither persistent dyskinesias nor hemiballismus are problematic in DBS-treated patients. When patients experience stimulation-related AEs, a choice has to be made between better PD symptom control and elimination of stimulation-related side effects.

The short-term and long-term effects of DBS surgery on cognitive and neurobehavioral functions must also be considered. To date, mixed results have been observed on neuropsychological studies of cognitive function after DBS. Some studies have found decrements in verbal fluency and working memory,[584] whereas others have found no significant impairment in patients who did not have preoperative cognitive impairment.[585] In the multicenter VA-NIH study, lower scores in verbal fluency, working memory, and processing speed were observed at 6 months in patients with DBS compared with a medically treated control group. Conversely, another study found mild increases in apathy but no significant cognitive decline in patients followed up for 3 years after STN–DBS.[586] However, psychoses, hypomania, and even attempted suicide were noted in several patients. A meta-analysis of cognitive outcomes after DBS found small declines in executive function, verbal learning, and verbal memory.[587] Whether, and to what extent, cognitive and behavioral deficits relate to passing multiple needles through frontal cortex, microlesions in brain targets, or chronic stimulation, and whether one target is more likely to be

associated with specific motor or neurobehavioral sequelae remains to be determined.

DBS–STN has also been associated with mood disorders. Cases with suicidal ideations or uproarious laughter have been described, which begin with the onset of stimulation and disappear when stimulation is stopped.[588,589] DBS–STN has also been reported to be associated with personality alterations, exacerbation of previous psychiatric disorders,[590] problems with psychosocial adjustment,[591] and suicide rates in the range of 0.5% to 2.9%.[592] These cases make it evident that the basal ganglia, and the STN in particular, are involved in regulation of mood in addition to motor function.

Of particular interest is the relationship between stimulation of the STN and ICDs. Recent studies in patients with PD and computational models demonstrate that stimulation of the STN interferes with the ability to slow down, or inhibit, impulsive behaviors when faced with decision conflict, and suggest that stimulation of the STN might lead to an ICD.[593,594] There are reports of improvement in ICDs after DBS–STN,[595] but this might reflect a reduction in dopaminergic medication. In contrast, there are several reports of ICDs that seem to be induced by DBS of the STN.[596-598] We recently evaluated consecutive patients with DBS–STN with the Minnesota Impulsive Disorders Interview and the Barrett Impulsivity Scale, and found an increased risk of ICDs and higher Minnesota Impulsive Disorders Interview scores in patients with DBS–STN, compared with age-matched medically treated patients with PD and healthy controls.[599]

Overall, DBS provides dramatic benefits, particularly for patients with motor complications and the procedures are relatively well tolerated. It is clear, however, that the procedure is associated with potentially serious AEs and the risks and benefits of the procedure and alternate options must be carefully considered for each individual patient.

What is the best surgical procedure? Who is a candidate for surgery? DBS has emerged as the most widely used surgical procedure for the treatment of PD, but it should be appreciated that it does not provide antiparkinsonian benefits that are superior to what can be achieved with levodopa, and it is primarily used to control motor complications. Although the STN is currently the preferred surgical target in most centers, there is no conclusive data indicating that comparable results cannot be obtained with stimulation of the GPi. Indeed, the larger size of the GPi may permit more accurate localization of the electrode within the sensorimotor target area to achieve optimized benefits with minimal side effects. Stimulation of the VIM target is rarely used today, even in tremor-dominant cases, because stimulation of the STN and GPi can also improve tremor, and can benefit rigidity, bradykinesia, and dyskinesia should they develop at a later time point.

A prospective, multicenter, randomized, double-blind crossover study of DBS of the STN and GPi showed significant benefit with stimulation of both targets.[559] Results with stimulation of the STN were superior, but patients were not randomized and the two targets were not directly compared. In a small randomized, blinded study comparing bilateral stimulation of the STN and GPi, DBS–STN provided greater antiparkinson benefits, but stimulation of the GPi yielded a better effect on dyskinesia.[600] A meta-analysis compared patient outcomes in 31 DBS–STN and 14 DBS–GPi studies.[560] Motor function improved by 54% in the STN group and by 40% in GPi patients, with a 40% improvement in activities of daily living in both groups. Medications were reduced in DBS–STN but not in patients with DBS GPi. There were insufficient data to assess the response of each target to specific symptoms (i.e., dyskinesias) and adequate data to determine differences in safety or adverse effects.

A recent review of AEs in 69 patients who underwent stimulation of STN or GPi noted that AEs were primarily comprised of neuropsychiatric problems and impairment in speech, gait, and balance. Most AEs were mild, and were more commonly encountered with DBS–STN (53%) than with GPi (35%).[601] A large-scale study is currently being conducted by the VA and the NIH in the United States comparing DBS–STN with GPi.

It is also important, as discussed earlier, to appreciate that different effects can be obtained with different stimulation settings, or stimulation of different sites, within the same target. Without controlling for this type of variable and ensuring that benefits are optimized, it is difficult to compare the results of different studies which stimulated different targets. For example, stimulation of the ventral contact in the GPi usually provides the best antidyskinesia effect but may worsen parkinsonian features, whereas stimulation of the most dorsal contact is usually most effective in treating akinesia but can induce dyskinesia.[577,578] In addition, dyskinesias may either be caused or reversed by different patterns of stimulation using the same electrode in the same target site.[579] It is thus evident that the stimulation settings chosen can make a big difference in patient response, making it even more difficult to compare different targets. Failure to establish the optimal stimulation settings may explain, in part, some of the variability that has been reported in the literature.

DBS has demonstrated benefits in patients with PD with motor complications that cannot be ade-

quately controlled by medical therapy. There is no evidence to indicate that any of the surgical procedures can provide benefits superior to those achievable with levodopa, but they do have the potential to alleviate the motor complications that prevent patients from experiencing the full benefit of the medication. Patients with disabling tremor are also candidates for a DBS procedure. Patients with parkinsonian features who do not respond to levodopa are not good candidates for DBS (at least of the GPi and STN). When to perform surgery has not been definitively established, and some argue for interventions at an earlier time point in the disease. However, one must be cognizant of the risk of inducing complications in a relatively intact individual, and the potential of an intracranial surgical procedure to make a functioning patient worse. Indeed, patients with improved UPDRS scores after surgery may not experience an improved quality of life because of side effects. Relative contraindications to surgery include advanced age, comorbidities, cognitive impairment, and speech dysfunction. Thus, the optimal candidate for a surgical procedure is a patient who has a good response to levodopa, but experiences disability because of motor fluctuations and dyskinesia that cannot be satisfactorily controlled. Those parkinsonian features which respond to levodopa such as tremor, bradykinesia, and rigidity are the ones most improved by surgical procedures. It is less clear if surgery also benefits features such as gait dysfunction, freezing, and postural instability which do not respond well to levodopa. Preliminary studies with stimulation of the PPN offer some promise for patients with gait dysfunction. Long-term studies indicate that benefits of DBS persist, but DBS does not prevent the evolution of disabling nondopaminergic features such as falling, freezing, and dementia, just as with levodopa. The VA-NIH long-term study should shed light on the comparative effects of DBS on the GPi and STN, and provide further information on the long-term effects of DBS on motor function, quality of life, cognition, and other measures of PD disability, which will be useful in helping clinicians select the most appropriate patient and target for DBS. If surgical intervention is shown to restore functions that levodopa cannot treat or to provide neuroprotective benefits, this would further support their earlier use.

In the final analysis, the determination of which surgical procedure to use for an individual patient is a matter of judgment. DBS now has an established role in PD therapeutics, but clinicians must be aware of both its potential to improve PD symptoms and its practical limitations. Although some patients may report a dramatic response to surgery, others may be hampered by adverse effects, progressive motor decline, and neurobehavioral problems. This underscores the importance of selecting patients carefully for DBS and understanding that there are, as yet, unanswered questions regarding the long-term consequences of surgery. The next chapter in the surgical management of PD will determine the effects of DBS stimulation on different regions within the same target (e.g., STN and GPi) and with different brain targets (e.g., PPN, supplementary motor area). It is also important to appreciate that DBS, as with other current surgical therapies, primarily acts to improve motor complications and does not provide antiparkinsonian benefits greater than those achievable with levodopa. This reinforces the importance of using strategies in the early stages of the disease that reduce the risk of developing motor complications. If medical therapies could be developed that provide benefits without inducing motor complications, the need for currently available surgeries would be dramatically reduced. Furthermore, disability in patients with advanced PD seems to be primarily related to the development of nondopaminergic features, such as gait dysfunction and dementia, which are not affected by current DBS approaches. Clinicians must recognize that although DBS can provide extraordinary benefits for some patients with PD, it is an invasive procedure in which the risks of short-term and long-term adverse effects must be weighed against the potential for substantial motoric benefit in carefully selected patients. The advantages and disadvantages of DBS procedures are listed in table 18.

Principles that we apply in trying to determine who is a candidate for surgery and which surgical procedure to perform on an individual patient are as follows (Adapted from Olanow et al.[602]):

a. Ensure correct diagnosis. Many patients with PD referred for surgery are doing poorly because they have atypical parkinsonism. There is no evidence that any of the currently available surgical procedures are of value for patients with atypical parkinsonism.

b. Establish preserved cognitive function preoperatively to ensure that patients can give informed consent and to minimize the risk of inducing worsening of cognitive impairment, particularly with bilateral procedures. In this regard, it is important to appreciate that cognitive impairment in patients with PD tends to affect primarily executive functions, which are not well captured on the Mini-Mental State Examination (MMSE), and formal neuropsychological testing is recommended.

c. We believe that there is not sufficient evidence to choose between DBS–STN and DBS–GPi at this time, and both seem capable of providing antiparkinson and antidyskinesia benefits. Surgeons should choose the target with which they

Table 18 DBS procedures: Advantages and disadvantages

Advantages
Does not necessitate making a destructive brain lesion
Bilateral procedures can be performed with relative safety
Potential to stimulate brain targets one might be hesitant to lesion (e.g., bilateral targets, STN, supplementary motor area)
Stimulation settings can be adjusted at any time to maximize benefit and minimize adverse effects
Stimulation of STN and GPi benefit all cardinal features of PD
Does not preclude future therapies that depend on the integrity of the basal ganglia
Disadvantages
Necessitates needle passage(s) through the brain with risk of side effects
Adverse events associated with the implant system and with stimulation
Neurobehavioral side effects
Need to periodically replace battery
No additional benefit for nondopaminergic features compared with levodopa
High cost

DBS = deep brain stimulation; STN = subthalamic nucleus; GPi = internal globus pallidus.
Adapted with permission from Olanow and Koller.[14]

are most familiar until more information becomes available.

d. DBS–VIM can provide excellent antitremor effects, but DBS–STN or DBS–GPi provide comparable antitremor effects and offer the advantage of controlling other parkinsonian features if they are already present or if they should develop at a later time. DBS–VIM is rarely performed for patients with PD at the present time.

Our view of the relative merits of the different surgical approaches and targets is listed in table 19.

Infusion therapies. Infusion therapies offer a nonsurgical means of potentially reversing established motor complications. The treatment is based on the principle that continuous infusion of a dopaminergic agent provides more constant and physiologic activation of striatal dopamine receptors than is accomplished with intermittent administration of the same drug, and thereby reduces the risk of motor complications. Indeed, in all instances where it has been tested, continuous administration of a short-acting dopaminergic agent is associated with a reduced frequency of motor complications compared with intermittent administration of the same agent.[298,299,416] Continuous infusion of either levodopa or a dopamine agonist (apomorphine and lisuride) has been tested in patients with advanced PD and consistently

Table 19 Relative merits of different surgical procedures for PD

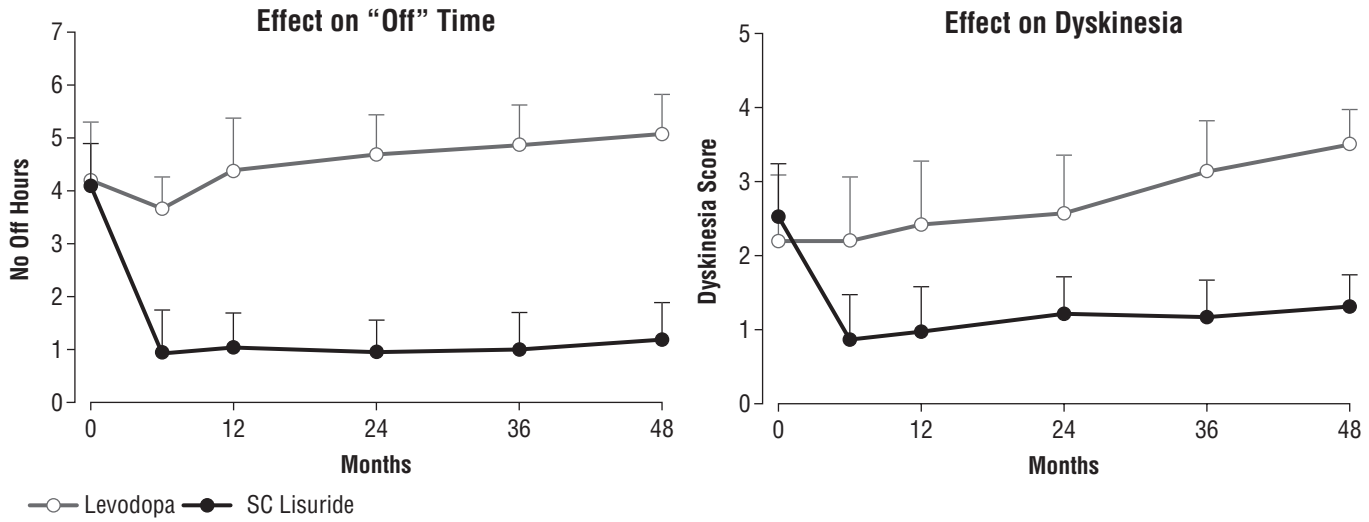
	Tremor	Rigidity/ bradykinesia	Dyskinesia	Adverse events*
Thalamotomy	+++	+/−	+/−	3
Pallidotomy	++	++	+++	3
DBS-thalamus	+++	+/−	+/−	2
DBS-GPi	++	+++	+++	2
DBS-STN	+++	+++	+++	2

*For bilateral procedures: 1 = minimal risk; 2 = more pronounced risk; 3 = greatest risk.
+ mild benefit; ++ moderate benefit; +++ marked benefit; +/− uncertain.
PD = Parkinson disease.
Reprinted with permission from Olanow and Brin.[602]

been reported to reduce the frequency of motor complications.[488-491] In one prospective study, patients randomized to receive a continuous subcutaneous infusion of lisuride had significant reductions in both "off" time and dyskinesia compared with patients receiving standard oral dopaminergic medications (figure 23).[492] Benefits persisted throughout the 4-year duration of follow-up. Similar results have been observed with continuous infusion of apomorphine. Dopamine agonists (perhaps with the exception of apomorphine), however, do not provide benefit comparable with levodopa, and it would theoretically be preferable to offer continuous infusion of levodopa. However, levodopa must be maintained at a low pH to maintain stability, and accordingly must be delivered in large volumes, making continuous subcutaneous or intravenous infusion somewhat problematic. Methyl levodopa can be administered in a much smaller volume and can be delivered subcutaneous by an insulin mini-pump or by continuous intraintestinal infusion. One study examined the effect of continuous intraintestinal infusion of methyl levodopa in patients with advanced PD who had severe motor complications. When they were switched from standard oral formulations of levodopa to continuous infusion of levodopa, they had a marked reduction in both "off" time and dyskinesia.[416] The Duodopa system uses a gel to reduce the volume that must be administered, and is now being developed for commercial use. Initial studies demonstrated substantial improvement in both "off" time and dyskinesia,[225,603] and these benefits have endured in many patients during 4 to 7 years of follow-up.[604] Double-blind studies to test Duodopa infusion in patients with advanced PD in prospective, double-blind trials are now being organized.

Dopaminergic infusions are generally well tolerated, but infusion systems used in the past have been somewhat large and cumbersome and are not suitable

Figure 23 "Off" time and dyskinesias scores in patients randomized to receive treatment with standard oral formulations of levodopa vs continuous subcutaneous infusion of lisuride.



Note that continuous delivery is associated with a significant reduction in both "off" hours and dyskinesia scores, and that benefits persist for the 4 years of follow-up.[492] SC = subcutaneous. Reproduced from Stocchi F, Ruggieri S, Vacca L, Olanow CW. Prospective randomized trial of lisuride infusion versus oral levodopa in PD patients. Brain 2002;125:2058–2066, by permission of Oxford University Press.

for patients with early disease. Smaller programmable pumps can be used with dopamine agonists such as lisuride and apomorphine and with levodopa methyl ester, which can be administered in a reduced volume. Most investigators prefer to administer infusions during the waking day and stop them overnight to reduce the risks of tolerance and psychiatric problems that have been reported with 24-hour round-the-clock infusion. Apomorphine infusions are associated with skin lesions, and levodopa intraintestinal infusions require the surgical placement of a catheter, which is prone to obstruct and may periodically require replacement. There are also risks associated with percutaneous endoscopic gastrostomy placement, such as peritonitis.

Dopaminergic infusions provide benefits that are on the same order of magnitude as surgical therapies such as DBS and avoid the need for an intracranial operation. Although infusions have their own limitations, informal series indicate that patients generally prefer an infusion to an intracranial procedure. Infusion therapies are currently available in some countries (e.g., Italy, England), and are being tested in the United States. Attempts to obtain continuous delivery with a levodopa patch and with novel oral levodopa formulations are currently being investigated.[231]

Transcranial magnetic stimulation. Functional imaging studies have shown that the supplementary motor area and prefrontal cortex are underactive in PD,[605-607] presumably due to dopamine depletion, pallidal overactivity, and excess inhibition of thalamocortical motor connections. Hypoactivation of these regions could play a role in the movement disorder that occurs in PD, particularly bradykinesia. This has been the scientific rationale for considering cortical stimulation as a potential therapeutic modality. Repetitive transcranial magnetic stimulation (rTMS) has generated interest because it is noninvasive, well tolerated, and may alter cortical excitability in functionally connected areas.[608] In a sham-treatment controlled study, UPDRS scores were reported to be significantly improved after 2 months of weekly rTMS.[609] However, in another study, where 85 patients were randomly assigned to rTMS of the motor cortex, occipital cortex, or sham stimulation there were no significant differences in motor outcomes in the three groups.[610] High-frequency rTMS has been reported to improve motor function in patients with PD when applied to the motor cortex,[611,612] but to worsen PD features when applied to the supplementary motor cortex.[613] In contrast, rTMS of the supplementary motor cortex has been reported to lessen dyskinesias when administered at low frequency.[614] Stimulating regions such as the dorsolateral prefrontal cortex has also been reported to induce antidepressant effects but not motor improvement.[615]

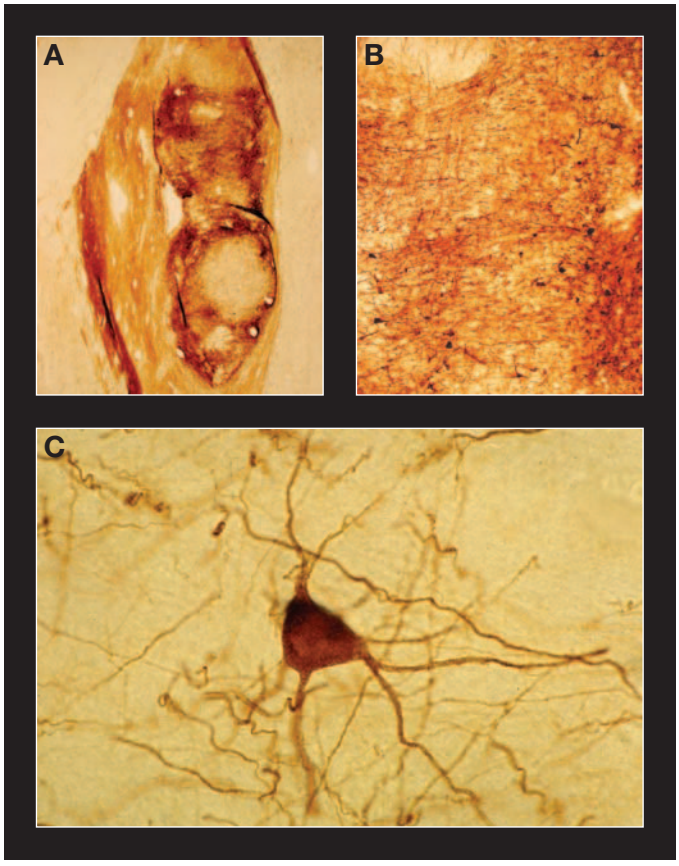
Conflicting results in controlled and uncontrolled studies suggest that, at best, motor benefits associated with rTMS are likely to be modest. It is clear that if rTMS is to become a more widespread therapy for PD, several questions remain to be answered. Specifically, what are the effects (both clinical and physiologic) of different stimulation parameters in different brain regions? What is the mechanism of action of rTMS, and can variability in cortical excitability be more accurately mapped and controlled so that ap-

propriate stimulation parameters can be chosen for a specific patient? Finally, patients with PD are notoriously susceptible to the placebo effects of new therapeutic interventions; therefore, positive results in double-blind, controlled trials incorporating sham rTMS must be used before this procedure can be considered to be effective in PD.

Experimental Surgical Approaches. ***Cell-based therapies.*** Cell-based therapies have been studied based on the notion that transplantation of dopaminergic cells could replace dopamine neurons, which degenerate in PD, and restore dopaminergic function in a more physiologic manner than can be achieved with oral therapies.[616] Fetal nigral transplantation has been the best studied of these approaches to date. Numerous laboratory studies have demonstrated that embryonic dopaminergic neurons implanted into the denervated striatum can survive, extend axons, provide organotypic innervations of the striatum, produce dopamine, and provide behavioral benefits in the 6-OHDA rodent and MPTP-monkey.[525] These studies have served as the basis for initiating clinical trials in patients with PD. Many transplant variables can influence whether or not implanted cells survive and the likelihood that clinical benefits will ensue. These include donor age, number of donors, method of storage, type of tissue transplantation, site of implantation, distribution of tissue, the use of immunosuppressants, and patient entry criteria.[525] To date, there is no universal agreement on the optimal transplant protocol. Open-label clinical trials using a variety of different transplant regimens produced variable clinical results. Some reported long-term clinical benefits with improvement in motor function during "off" time, increased "on" time without dyskinesias, and significant increases in striatal FD uptake on PET.[617–620] Furthermore, postmortem studies performed 18 months after the transplant procedure showed robust survival of implanted neurons with extensive dopaminergic innervation of the target region (figure 24).[621,622] Normal staining in transplanted regions was observed for tyrosine hydroxylase (TH) and DAT; TH mRNA expression was also normal and there were normal appearing synaptic connections between host and graft. These findings demonstrate the potential of transplanted fetal nigral cells to reinnervate a denervated region in PD.

This initial enthusiasm has, however, been dampened by the failure of two NIH-sponsored prospective, double-blind, sham-controlled trials to demonstrate significant benefits of transplantation over placebo despite increased striatal FD uptake on PET and robust cell survival at postmortem.[508,623] The first was a 1-year study in which 40 patients with advanced PD were randomized to receive bilateral implantation of cultured mesencephalic tissue from four human embryos in the putamen (2 donors per side) without immunosuppression, or sham surgery.[623] The primary end point was the change from baseline in quality of life. The second was a 2-year study in which 36 patients with PD were randomized to receive bilateral transplantation with solid grafts derived from one or four donors per side implanted exclusively into the postcommissural putamen and treated with cyclosporine for 6 months, or sham surgery.[508] The primary end point was the change from baseline in UPDRS motor score during the practically defined "off" state. In both trials, the sham placebo group received a partial burr hole. Although neither study met its primary end point, post-hoc analyses demonstrated that patients younger than 60 years were significantly improved by transplantation in one study,[623] whereas transplanted patients with milder disease at baseline had significant improvement compared with the placebo group in the other.[508] In this latter study, deteriora-

Figure 24 **Tyrosine hydroxylase (TH) stain of fetal mesencephalic tissue implanted into a patient with PD.**



A) Low power demonstrating a healthy-appearing graft implanted into the striatum. B) Low power demonstrating TH-positive fibers extending from the grafted neurons into the host striatum. C) High-power TH stain of a normal-appearing implanted dopaminergic neuron. Courtesy of Dr. Jeffrey Kordower.

tion in UPDRS scores coincided with withdrawal of cyclosporine, and postmortem studies demonstrated prominent CD45 immunostaining for activated microglia.[624] These observations suggest that immune rejection may have occurred, which possibly explains the negative results. On the basis of a review of these two studies, it has been proposed that enhanced benefits might be attained if the transplant protocol were modified to include patients with milder disease and with pure dopaminergic lesions, and if long-term cyclosporine were used to diminish the risk of immune rejection.[625]

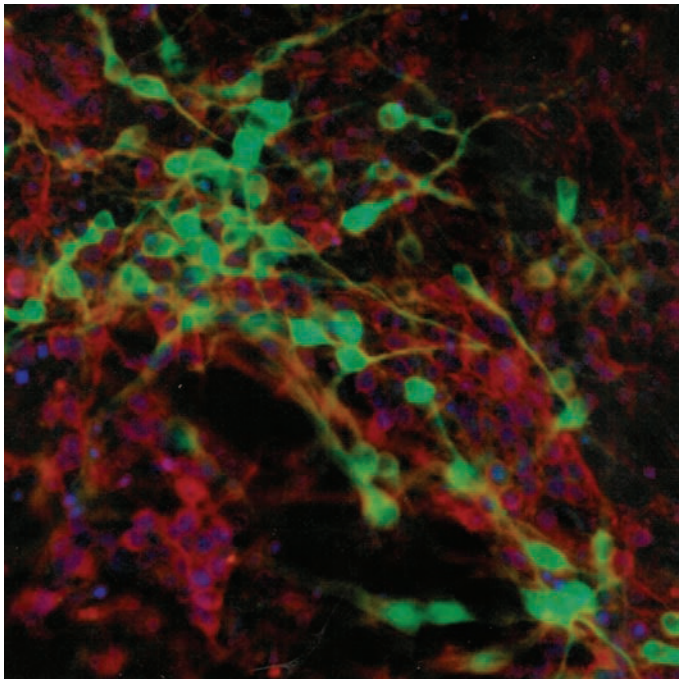
An unexpected finding in these studies was the development of a previously undescribed form of dyskinesia, referred to as off-medication dyskinesias.[508,623,623a] In contrast to classic on-medication or peak-dose dyskinesias, graft-induced dyskinesias are seen even after lowering or stopping the levodopa dose. In some instances, these dyskinesias were disabling and required surgical intervention with DBS. In one study, they were characterized clinically as being stereotypic, repetitive movements that predominantly affected the lower extremities and were accompanied by parkinsonian features in other body regions.[508,623a] They, thus, resembled a prolonged form of diphasic dyskinesias. In the other study, the head and neck were more prominently affected and the movements had more of a dystonic quality.[626] The mechanism responsible for off-medication dyskinesias is not known. One group postulated that they are related to transplant deposits forming "hot spots" that lead to pulsatile stimulation.[627] It has also been postulated that they might represent a prolonged form of diphasic dyskinesia due to incomplete dopaminergic innervations of the striatum.[508,623a] The latter concept has important implications, because it would imply that transplantation of more cells might both reduce the risk of off-medication dyskinesia and increase the likelihood of achieving a better antiparkinsonian response. This issue is a major impediment to continued research in the transplant field.[628] The potential value of cell-based therapy has been further complicated by recent reports indicating that 11–14 years after transplantation, fetal dopamine neurons contained Lewy body-like aggregates that were α-synuclein and ubiquitin positive, and had reduced staining for DAT.[629,629a,629b] These findings suggest that the implanted cells were affected by an ongoing PD process, which may have limited their utility.

There has been an extensive search for alternate sources of dopaminergic cells that could be used for transplantation in PD. Xenografts, using embryonic porcine dopaminergic cells offer the potential of providing large numbers of fetal nigral porcine cells on demand. Preliminary open-label studies of this technique in patients with PD reported modest benefits and limited cell survival.[630] However, a double-blind trial that has yet to be published demonstrated no benefit.

Retinal pigmented epithelial cells have been studied as a potential source of cells for transplantation in PD based on their capacity to manufacture and release levodopa and possibly trophic factors.[631,632] When attached to gelatin microcarriers (Spheramine), retinal pigmented epithelials have been shown to have prolonged survival in rodent models and with minimal immunogenicity.[633] Spheramine transplantation has been reported to provide motor benefits and enhanced striatal FD uptake on PET in MPTP primates.[634] In an open-label study in six patients with PD, unilateral transplantation of Spheramine provided improvement in UPDRS "off" scores that has persisted for more than 2 years in some patients.[635] However, a 12-month prospective, double-blind, sham-controlled study that has not yet been reported showed no benefit of retinal pigmented epithelial cells in comparison with a sham procedure (C.W. Olanow, personal observation, 2009). It was noted that both groups had a marked placebo response. Off-medication dyskinesia has not been observed in any patient to date.

Stem cells have attracted particular interest as a means of generating optimized dopamine neurons for transplantation in PD.[636] Most research has been conducted with embryonic stem (ES) cells that are derived from the blastocyst, and can then be plated, expanded, and later induced to differentiate into dopamine cells by the addition of a variety of trophic factors and cytokines (figure 25).[637] Several groups have demonstrated the capacity to generate dopamine cells from mouse, rat, monkey, and human ES cells that are suitable for transplantation, and motor benefits have been detected after implantation into 6-OHDA-lesioned rodents and MPTP-lesioned monkeys.[638,639] Although there are some reports of long-term survival and motor benefits,[640] for the most part benefits have been modest and cell survival limited. Autologous stem cells can be generated from umbilical cord or bone marrow matrix, and more recently reprogrammed skin cells.[641,642] These approaches have the advantage of avoiding immunologic and ethical issues associated with the use of embryonic cells. However, it has proven even more difficult to produce robust numbers of dopamine cells with these techniques, and survival after implantation is even less than with ES cells. Endogenous stem cells and neural precursor cells reside within the subventricular and olfactory regions of the adult brain, but have not yet been shown to be able to replace degenerating SNc neurons in meaningful numbers.[643]

Figure 25 Dopaminergic nerve cells (green) derived from embryonic stem cells.



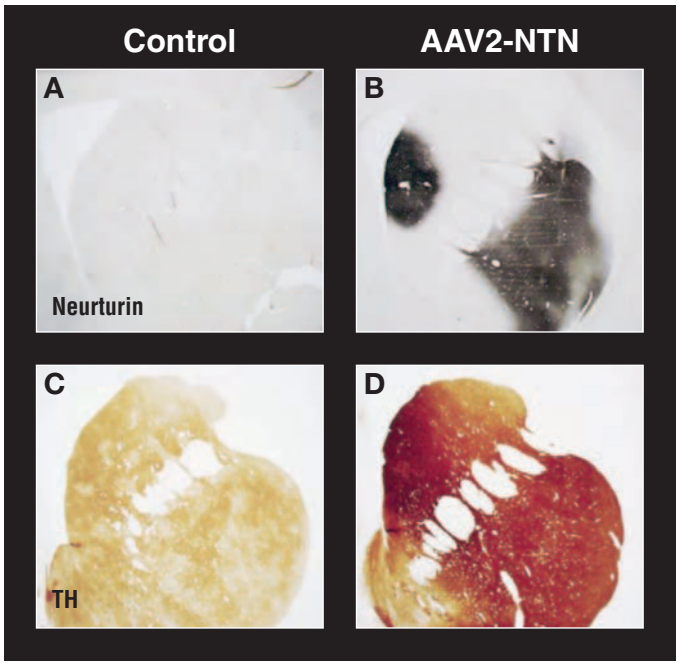
Courtesy of Dr. V. Nair.

Although stem cell research is promising, there are many obstacles still to be overcome. The optimal type of stem cell and transplant protocol remain to be defined, cell survival after transplantation is limited, and efficacy in animal models has not yet been established to exceed or even equal that obtainable with fetal nigral transplantation (which so far has failed in clinical trials).[644] Safety issues must be fully addressed preclinically before clinical trials can be initiated, particularly with respect to the risk of tumor formation and off-medication dyskinesia. Physicians and patients should be wary of unscrupulous groups in countries such as China, who are offering stem cell transplants to desperate patients with PD without proper preclinical studies or scientific expertise. Finally, it should be appreciated that current investigations into the use of stem cells for PD envision primarily a dopamine replacement strategy it is by no means clear how this will address the nondopaminergic features of the disease.

Gene therapies. Gene delivery approaches are also being actively investigated as a possible treatment for PD. In this technology, viruses are used as vectors to introduce the DNA of a desired protein into the genome of cells within a specific brain target. Furthermore, promoters can ensure that the virus vector infects specific brain cells (e.g., TH promoter targets dopamine cells). This sequence can thus potentially result in continuous production of the desired therapeutic protein in the desired target region of the brain.[526,645] Most human studies have used the adeno-associated virus serotype 2 (AAV-2) as the vector, as AAV-2 does not induce an immune response and permits long-term expression of the transgene. Three different gene therapy approaches are currently being tested in PD. The first delivers AADC to the striatum to promote the continuous conversion of levodopa to dopamine. This approach has been shown to provide benefits in MPTP monkeys,[646] and is currently being studied in patients with PD. A second approach used glutamic acid decarboxylase delivered to the STN to promote the formation of GABA, with the intention of inhibiting overactive neuronal firing in this nucleus. An open-label, 12-month trial in 12 patients with PD demonstrated significant improvement in UPDRS scores with no serious adverse effects.[647] A third approach involves gene delivery of the trophic factor neurturin to the striatum.[527] Trophic factors have attracted considerable attention as possible therapies for PD based on their capacity to protect in vitro and in vivo dopamine neurons from a variety of toxins. Glial-derived neurotrophic factor (GDNF) specifically has been shown to protect SNc dopamine neurons in MPTP monkeys even when administered weeks after the toxin.[648] Although an open-label clinical trial reported that direct infusion of GDNF into the striatum provided significant benefits,[649] these results were not confirmed in a double-blind, placebo-controlled trial.[650] This may relate to point source delivery of the trophic factor with inadequate diffusion of the protein throughout the target region.[651] Gene therapy offers the potential to provide more diffuse distribution of the therapeutic protein through the brain target. In MPTP monkeys, gene delivery of GDNF was diffusely distributed throughout the striatum, and provided motor benefits, restoration of striatal TH staining, and protection of SNc dopamine neurons.[652]

Neurturin is a trophic factor in the GDNF family[636] that has been demonstrated to protect and enhance dopaminergic function neurons in both aged and MPTP-lesioned monkeys (figure 26).[653-655] In these studies, AAV-2-neurturin had an excellent safety profile and was not associated with any toxicity or immune reactivity. In a phase 1, open-label study, AAV-2 was used to deliver neurturin to the striatum of 12 patients with advanced PD. Significant improvement was observed in UPDRS scores during practically defined "off" and "on" time without dyskinesia (figure 27).[656] On the basis of these pilot results, a double-blind, placebo-controlled study of AAV-2-neurturin was performed. While not yet reported, the study showed no benefit of AAV-2-neurturin in comparison with placebo with respect to the

Figure 26 Gene delivery of neurturin to the striatum of aged monkeys.



A) Neurturin staining in the striatum of the normal aged monkey. B) Neurturin staining following adeno-associated virus serotype 2 (AAV-2) gene delivery. Note the diffuse distribution of the protein. C) TH staining of the striatum in the normal aged monkey. D) TH staining in aged monkeys after gene delivery of neurturin. Note the marked increase in TH staining after administration of the trophic factor. AAV2-NTN = adeno-associated virus serotype 2-neurturin; TH = tyrosine hydroxylase. Courtesy of Dr. J. Kordower.

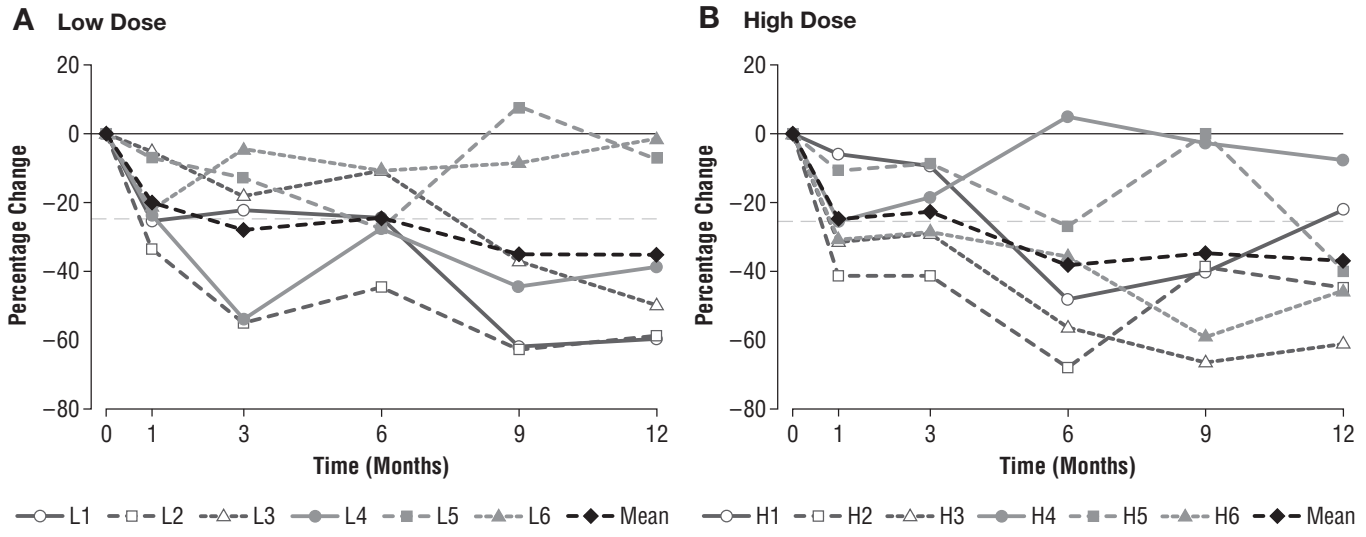
primary or secondary endpoints (CW Olanow, personal communication, 2009). No clinically significant or unanticipated AEs have been encountered in any of the gene therapy studies performed to date.

Safety is a major concern with gene therapy, as there is the potential of unanticipated side effects such as off-medication dyskinesia and tumor formation. A possible safeguard in gene therapy is the use of a regulator protein. Here, a gene can be inserted into the viral vector that can turn on or turn off production of the gene product.[657] For example, tetracycline or steroids could be used as regulators to turn off production of the therapeutic protein in case of toxicity. Although this is an appealing concept, there is no assurance that a regulator will be able to reverse toxicity that has already occurred, and there is concern that the regulator protein might itself induce an immune reaction. To date, no clinical trial has used a regulator, but work continues in this field.

While cell-based and gene therapies are exciting concepts and have the potential to provide benefits in PD patients, it is important to appreciate that benefits in open-label trials have not yet been confirmed in a single double blind study. In addition, we still do not know the basis of graft related dyskinesias or how to prevent them. Further, it is also important to consider that even if cell-based or gene therapies prove to be safe and effective, they target only the dopaminergic system and, as discussed earlier, nondopaminergic features are an important source of disability for many patients with PD. Thus, the need for a neuroprotective therapy remains paramount.

In examining experimental surgical therapies for PD, we have advocated for the use of double-blind, placebo-controlled trials.[658,659] There has been a reluctance by some to use placebo controls for surgical studies, but we do not find any of the reasons put

Figure 27 Percent improvement in UPDRS motor score following AAV-2 delivery of neurturin.



The black line with diamonds represents the mean values. Note that gene delivery of neurturin is associated with significant improvement in this open-label study. Reproduced from Marks et al.[656] with permission from Elsevier.

forth to be compelling. Double-blind, placebo-controlled studies are the gold standard for evaluating a new drug, and we do not see any reason why there should be a lower standard for the evaluation of a surgical intervention, particularly as surgical treatments are often more expensive and more risky. We have already seen that positive results in open-label trials of fetal nigral transplantation, fetal porcine nigral transplantation, spheramine, AAV2-neurturin and trophic factors were not confirmed in double-blind studies. Had it not been for rigorous, double-blind, placebo-controlled trials, these procedures might now be widely used despite clear risks and unproven efficacy. A survey of movement disorder specialists found that more than 95% favored the use of placebo-controlled studies when testing surgical therapies of PD to be sure that any benefits observed are not due to placebo effect or physician bias.[660]

MANAGEMENT OF NONDOPAMINERGIC AND NONMOTOR FEATURES OF PD The nonmotor, nondopaminergic features of PD are common, not fully appreciated, present in all stages of the disease, and potentially a major source of disability (table 20). This section will consider these features and possible therapeutic approaches.

Neuropsychiatric problems. Although PD has long been considered primarily a motor disorder, mental symptoms such as dementia, delirium, anxiety, and depression occur at one time or another in most patients, and can potentially be more disabling than motoric dysfunction. Indeed, dementia, hallucinations, and delirium are the leading causes of nursing home placement among patients with PD.[661] In addition, anxiety, panic, obsessive-compulsive disorder, apathy, ICDs, emotional lability, and personality changes are all increasingly recognized as sources of disability for many patients with PD. Some neuropsychiatric problems such as hallucinations, memory loss, confusion, and dementia may be part of the disease process itself, but they may also be aggravated by medications and comorbidities. Anxiety and depression might also be an inherent part of the disease process, but could also occur in response to having a chronic progressive neurodegenerative illness and in this context might be improved by antiparkinsonian medications. Thus, in devising a rational approach to the treatment of the neuropsychiatric problems that occur in PD, a decision must be made as to whether to add or reduce psychoactive medications, and whether to add to or reduce the dosage of antiparkinsonian agents.

Cognitive impairment and dementia. Cognitive impairment is commonly associated with PD. In its severe form, it may be global and meet DSM-IV criteria for dementia. Prevalence studies of dementia in PD vary depending on the age, disease duration, and population surveyed. Most studies cite a dementia frequency in the range of 30% to 60%,[662] and it is likely that this is an underestimate of the true frequency.[663] For example, in an 8-year prospective study, the cumulative prevalence rate of dementia in PD was 78% and patients with PD were found to be

Table 20 Nonmotor and nondopaminergic features of PD

Neuropsychiatric symptoms
Cognitive impairment and dementia
Apathy, anxiety, panic attacks
Anhedonia, depression
Delirium
Hallucinations, illusions, delusions
ICDs
Gait dysfunction, freezing, and postural instability
Sleep disorders
REM behavior disorder
Excessive daytime somnolence
Vivid dreaming
Insomnia
Restless legs syndrome and periodic limb movements of sleep
Autonomic symptoms
Orthostatic hypotension
Urinary disturbances like urgency, frequency
Nocturia
Sexual dysfunction
Hypersexuality (likely to be drug induced)
Paroxysmal sweating
Seborrhea
Dry eyes (xerostomia)
Gastrointestinal symptoms (often related to dysautonomia)
Drooling of saliva
Ageusia
Dysphagia
Constipation
Fecal incontinence
Sensory symptoms
Pain
Olfactory disturbance
Visual discrimination deficits
Miscellaneous
Fatigue
Diplopia
Blurred vision
Weight loss
Weight gain (often drug related)

PD = Parkinson disease; ICD = impulse control disorder.

at increased risk for developing dementia compared with age-matched healthy controls.[664] In another study, after 15 years of follow-up only 15% of patients with PD remained free of cognitive impairment and 50% had dementia severe enough to meet DSM-IV criteria.[9] PD dementia (PD-D) may also be associated with other neuropsychiatric problems. For example, in a study of 537 patients with PD-D, 89% had at least one and 77% had two or more neuropsychiatric symptoms. The most common were depression (58%), apathy (54%), anxiety (49%), and hallucinations (44%).[665] Nearly 60% of care givers reported at least one neuropsychiatric symptom to be present and to be the source of at least moderate distress. Patients with PD with psychosis and agitation symptom clusters had the lowest MMSE scores, the highest UPDRS scores, and caused the highest caregiver distress scores.[665] It is obvious that dementia is an important problem in PD, and there is a crucial need for better strategies for preventing and managing cognitive decline.

Risk factors for dementia in PD include early impairment in executive functions, age, and severity of PD motor features.[666] Patients with PD who develop dementia tend to be older, to have developed PD at an older age, to have a longer duration of disease, and to have a greater likelihood of antecedent hallucinations, than patients with nondemented PD.[667,668] The age effect is illustrated by a study in which the prevalence of dementia increased from 12.4% in the 50- to 59-year-old age group to 68.7% in those older than 80 years.[669]

It has been proposed that patients with PD have a subcortical dementia with preferential involvement of thought processing, decision making, attention, construction, visuospatial performance, memory, and verbal fluency with relative sparing of language and social behavior. Executive dysfunction (i.e., planning, sequencing, innovation) is the hallmark of PD-D and tends to be more prominent than in AD; memory impairment is also an early feature, but is not as prominent as in DLB or AD.[670] Memory problems in PD are related primarily to retrieval (and are responsive to cuing), rather than to encoding and storage, as seen in AD. Language tends to be relatively preserved in patients with PD, although it can be affected and dysnomia is common. In contrast to AD, dementia in PD is frequently accompanied by visual hallucinations (discussed later). MRI studies demonstrate whole brain atrophy with regional changes in the occipital lobes compared with patients with DLB or AD, but there is considerable overlap. Genetic studies are conflicting, and generally do not help to diagnose or differentiate PD-D from other types of dementia. DLB is usually diagnosed based on the early appearance of dementia and the later emergence of PD features. Operationally, many use the 1-year rule, where PD-D is diagnosed if dementing features develop more than 1 year after the onset of PD features, whereas DLB is diagnosed if dementia is an earlier feature in the disease process.[671] This has been hotly debated, however, and many argue that they are extremes of a single disease spectrum.

Formal neuropsychiatric evaluations may be required to recognize and define cognitive impairment in an individual patient with PD, particularly in the early stages of the disease. The MMSE is a simple means of assessing cognitive impairment. It provides a rapid measure of spatial and temporal orientation, attention span, language function, and constructional praxis.[672] An MMSE score of 24 or lower is suggestive, but not diagnostic, of dementia. The MMSE is not, however, particularly sensitive for the type of cognitive decline that occurs in early PD, and an intact MMSE score in a patient with PD does not exclude a selective impairment in executive functions. Specific tests of language function, visuospatial relations, speed of information processing, and executive function may be needed to detect selective and early cognitive impairment in a patient with PD. This may not be readily apparent to the patient, and questioning the family or formal neuropsychological testing may be necessary to identify the problem. It is particularly important to identify cognitive impairment in patients if they are being considered for a surgical intervention.

With formal neuropsychological testing, many patients demonstrate cognitive impairment even in the early stages of PD. Deficits in executive function and memory were noted in 24% of a consecutive series of newly diagnosed and untreated patients with PD.[673] A more rapid rate of cognitive decline is associated with age, presence of hallucinations, and severe motor impairment (particularly with axial involvement and impairment in gait, posture, and speech).[674] Cognitive impairment or hallucinations seen in patients with early PD are risk factors for the subsequent development of dementia.[668,675]

Because dementia represents a major cause of disability in patients with advanced PD, and is much more common than previously appreciated, attention has focused on better characterizing PD-D. A task force was established by the Movement Disorder Society and charged with defining and developing clinical diagnostic criteria for PD-D and how to operationalize them.[676,677] One of the primary missions of this task force was to try to better define the relationship between PD-D and DLB. Because these disorders share many clinical and pathologic features, the time course of cognitive decline and presenting symptoms are the key differentiating factors. For operational purposes, and to coincide with the views of

Table 21 Features of dementia associated with PD

I. Core features
Diagnosis of idiopathic PD according to United Kingdom-Brain Bank criteria
Dementia syndrome with insidious onset and slow progression, developing within the context of established PD and diagnosed by history, clinical, and neuropsychological examination, defined as:
Impairment in more than one cognitive domain
Representing a decline from premorbid level
Deficits severe enough to interfere with daily life (social, occupational or personal care), beyond those ascribable to motor impairment
II. Supportive features
Profile of cognitive alterations:
Attention: prominent impairment with fluctuations
Executive functions: prominent impairment
Visuospatial perception and construction: prominent impairment
Memory: impaired free recall, may improve with cueing
Language: core functions largely preserved, word finding difficulties
Behavioral symptoms
Apathy
Hallucinations (non–drug-induced or early on treatment initiation)
Delusions (non–drug-induced or early on treatment initiation)
Changes in personality and mood, including depressive features
Excessive daytime sleepiness
III. Features that do not exclude PD-D, but make the diagnosis uncertain
Coexistence of any other pathology that may by itself cause cognitive impairment, but judged not to be the cause of dementia (e.g., mild vascular disease on imaging)
Time interval between the development of motor and cognitive symptoms not known
IV. Features not compatible with PD-D, suggesting other neurologic, psychiatric, or systemic disease as the cause of dementia
Cognitive and behavioral deficits appearing solely in the context of other conditions that, by themselves, can cause cognitive impairment
Acute confusion due to systemic diseases or drug intoxication
Major depression, other primary psychiatric diseases
Probable vascular dementia according to NINDS-AIREN criteria

PD = Parkinson disease; PD-D = PD dementia.
Reprinted from Emre et al.[676]

Table 22 Criteria for the diagnosis of probable and possible PD-D

Probable PD-D
Core features: both must be present
Supportive features: typical impairment in at least two of the four core cognitive domains (attention, executive functions, visuospatial functions and memory) and at least one behavioral symptom present
None of the category III and IV criteria present
Possible PD-D
Core features: both must be present
Supportive features: atypical profile of cognitive impairment in one or more domains, such as prominent or receptive-type aphasia, or pure limbic type amnesia, behavioral symptoms may or may not be present
One or more of the category III criteria may be present, none of the category IV criteria present

PD-D = PD dementia.
Reprinted from Emre et al.[676]

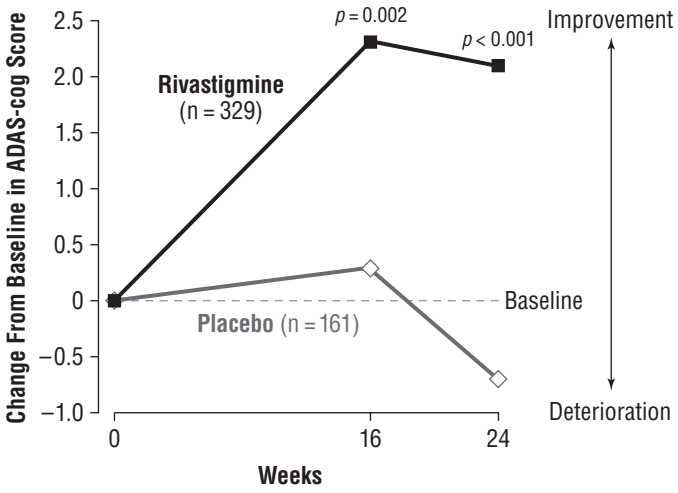
the DLB consortium,[671] the task force recommended that a diagnosis of PD-D be made in patients with established PD who develop dementia more than 1 year after the onset of PD motor features, whereas the diagnosis of DLB should be made in patients who develop dementia before or within 1 year after developing motor symptoms. Why patients with PD who develop dementia 11 months after the onset of motor features are considered to have DLB whereas those who develop cognitive impairment 13 months after symptom onset should be considered to have PD-D is not clear. It is certainly possible that these two conditions are part of a spectrum of neurodegeneration in which dementia comes first in DLB and PD comes first in PD-D.[678]

Clinicopathologic studies indicate that cognitive impairment in patients with PD can be associated with neurodegeneration and Lewy body formation in dopaminergic neurons in the SNc (especially the medial nigra), noradrenergic neurons in the locus coeruleus, cholinergic neurons in the nucleus basalis of Meynert, and diffusely throughout the cerebral cortex. Studies using α-synuclein immunohistochemistry suggest that Lewy body pathology in the cerebral cortex and limbic regions is the primary pathologic correlate of dementia in PD.[679] AD pathology is also encountered in patients with PD, who have six times the expected prevalence compared with an aged-matched control population.[680,681] Along these lines, patients diagnosed with AD are more likely than controls to develop parkinsonian motor features during life and to have PD pathology at postmortem.[682,683] Neuroimaging and autopsy studies demonstrate that there are also cholinergic deficits in patients with PD-D, and that these are more profound and occur at an earlier stage of the disease than found in patients with AD.[684,685]

The clinical features and criteria for diagnosing possible and probable PD-D, as defined by the Movement Disorder Task Force, are listed in tables 21 and 22.

The management of dementia in PD is a pressing problem because cognitive impairment is a common and important source of disability. As PD-D is associ-

Figure 28 AD Assessment Scale-cognition (ADAS-cog) scores in patients with PD dementia randomized to receive rivastigmine or placebo.[686]



Note that rivastigmine is associated with significant benefits compared with placebo. Reprinted with permission from Emre M, Aarsland D, Albanese A, et al. Rivastigmine for dementia associated with Parkinson's disease. N Engl J Med 2004;351:2509–2518. Copyright © 2004 Massachusetts Medical Society. All rights reserved.

ated with a cholinergic deficit, trials of the cholinesterase inhibitors donepezil (Aricept) and rivastigmine (Exelon) have been carried out in patients with PD-D. A large-scale, double-blind, placebo-controlled study demonstrated a modest, but significant, benefit in patients randomized to treatment with rivastigmine compared with controls (figure 28).[686] This benefit was interpreted as being meaningful in 20% of treated subjects. No adverse effect of the drug on parkinsonian features was detected. Follow-up studies suggest that benefits of rivastigmine are sustained.[687]

Donepezil was also found to be effective for the treatment of PD-D in a randomized, double-blind crossover study, and also did not worsen parkinsonism.[688] These studies are particularly important, because the primary end points chosen were those typically used in AD (AD Assessment Subscale-cognitive subscale [ADAS-cog], MMSE) and are not particularly sensitive to the executive dysfunctions that characterize PD-D. It is thus possible that benefits might be more profound than is apparent from these studies. In addition, it is possible that cholinesterase inhibitors may prove valuable for treating patients with PD with early cognitive impairment. Although mild cognitive impairment (MCI) in geriatric controls does not predictably lead to dementia and trials of cholinesterase inhibitors have not been shown to be of value, the situation may be different in PD, where the patient is known to have a neurodegenerative disorder that may cause dementia, and where cholinergic changes occur earlier in the course of the illness and are more profound than those seen in AD.

Memantine has not been approved as a treatment for PD, but is used by some physicians based on their experience with the drug in patients with AD. Metabolic disorders, dehydration, sedative and anxiolytic medications, and antiparkinsonian medications can all aggravate cognitive function in a patient with PD and should be actively addressed and treated. Anticholinergic agents and amantadine tend to worsen confusion and promote psychotic features in cognitively impaired patients. Depression is also common in PD.[689] It may complicate accurate diagnosis and impair cognitive function, and should be aggressively treated if appropriate.[690]

Management of the cognitive impairment associated with dementia involves the following steps:

1. Correct underlying problems, such as infection, dehydration, electrolyte imbalance, or other metabolic abnormalities.
2. Review drug history and eliminate unnecessary nonparkinsonian medications. In particular, sedative and anxiolytic medications should be withdrawn, if possible.
3. Gradually decrease or discontinue antiparkinsonian medications in the following order depending on response: anticholinergic agents, amantadine, MAO-B and COMT inhibitors, and dopamine agonists.
4. Consider introducing a cholinesterase inhibitor.
5. If, despite the above, the patient continues to experience confusion and/or hallucinations, gradually lower the dose of levodopa. Ultimately, a judgment may have to be made in choosing between cognitive benefits obtained by reducing the dose of levodopa and any worsening of parkinsonian features.
6. Ensure that adequate home care is provided and that the needs of the caregiver are considered.
7. If demented patients cannot be satisfactorily controlled with these actions, nursing home placement may have to be considered.

The management of patients with selective or MCI is similar to that for dementia. Proper treatment of these patients is particularly important as they may still be able to function independently if managed correctly. Particular attention should be paid to avoiding drugs that can adversely affect mental function and treatment of concomitant medical problems. Anticholinergic drugs, amantadine, and sedative medications may induce or worsen selective cognitive impairment and should be gradually withdrawn, if possible. Parkinsonian features in patients with cognitive impairment should be treated with regular formulations of levodopa in the lowest dose that provides acceptable

motor benefit and, ideally, does not worsen cognitive performance. Cholinesterase inhibitors may be valuable in this population (see earlier), and further studies of these agents are warranted.

Hallucinations and delirium. Hallucinations occur commonly in PD with prevalence estimates ranging between 15% and 40%, and higher frequencies in patients with PD-D.[691,692] In a study of 289 consecutive outpatients with PD, 18% had hallucinations, 7% had hallucinations plus "confusion," and 4% had hallucinations plus delusions.[693] The incidence of psychotic symptoms increases with age and with the degree of cognitive impairment.[694] The major risk factors for psychotic symptoms in PD include antiparkinsonian medications, cognitive impairment, severity of PD, visual impairment, and comorbid depression and anxiety.[695] The apolipoprotein ε4 allele seems to predispose patients with PD to psychosis,[696] although it is not clear that it is a risk factor for dementia in PD.

Hallucinations in PD are typically visual, although they can rarely be somesthetic or auditory. They usually comprise formed, stereotyped, nonthreatening images of a person or an animal such as a friend, a family member, or a pet. Patients often retain insight into their hallucinations and are frequently not bothered by them, although these symptoms may be troubling to family members. In more advanced cases, hallucinations can become more frightening and may be associated with paranoid delusions that often revolve around spousal infidelity and persecution. In these cases, insight is often lost and usually there is cognitive impairment.

Some patients with PD also experience delirium. Delirium may be insidious in onset, mild and nonprogressive in some patients, whereas in others it develops acutely over hours and worsens rapidly, particularly when there is an underlying medical problem or a rapid change in medication.[697] At first, patients may be restless and distractible, beginning a second task before they have completed the first. Behavior may be obsessional, fearful, or inappropriate. Patients may have vivid dreams or nightmares and experience disruption of sleep with reversal of sleep cycle such that they sleep during the day and stay awake during the night. In more advanced cases, patients can experience agitation, delusions, paranoid ideations, and frank psychosis. Patients who experience hallucinations are at increased risk for frank dementia and for nursing home placement. The presence of hallucinations may limit the ability of the physician to increase dopaminergic therapy to more satisfactorily control parkinsonian motor dysfunction.

The management of hallucinations and delirium in the patient with PD is similar to the management of cognitive dysfunction and should be approached in a stepwise fashion using the following steps:

1. Eliminate other causes, including infection, dehydration, electrolyte imbalance, or a structural lesion of the brain (e.g., subdural hematoma).
2. Discontinue nonparkinsonian, psychotropic medications whenever possible. Many drugs frequently used in patients with PD have anticholinergic properties and can induce psychosis. These include TCAs and bladder antispasmodics (e.g., oxybutynin).
3. Eliminate antiparkinsonian drugs with the most potential for inducing psychosis and delirium and the least antiparkinsonian activity in the following order: anticholinergics, amantadine, MAO-B inhibitors, dopamine agonists, and finally, levodopa/carbidopa. Antiparkinsonian medications should be reduced to the point of improving hallucinations and/or delirium without drastically worsening parkinsonism, if possible. Reduction or discontinuation of bedtime medication may alleviate nighttime hallucinations. It is best to reduce antiparkinsonian medications gradually, as sudden withdrawal of dopaminergic agents can lead to a neuroleptic malignant syndrome.[698]
4. Use the regular formulation of levodopa in the lowest dose that provides satisfactory control of parkinsonian motor features. The levodopa dose should be reduced only if hallucinations persist after eliminating all other antiparkinsonism agents. In some patients, it may be necessary to make a choice between lowering the dose of levodopa to improve mental function and maintaining the dose to manage motor dysfunction and accepting neuropsychiatric complications.

When the above adjustments fail to eliminate or sufficiently alleviate hallucinations and/or cannot be accomplished without inducing a meaningful deterioration in PD features, neuroleptic therapy should be considered. Haloperidol, perphenazine, or chlorpromazine are effective antipsychotics, but are not recommended for patients with PD because of their capacity to block striatal dopamine D2 receptors and exacerbate parkinsonian features. The "atypical" neuroleptics are the preferred agents to use, and can often effectively treat hallucinations and psychosis induced by dopaminergic medications.[699] They are called "atypical" because among other factors they preferentially block limbic and cortical dopamine receptors, but are relatively devoid of D1 and D2 receptor-blocking properties. Therefore, in principle, they can ameliorate or eliminate dopamine medication-induced psychotic features without worsen-

ing parkinsonism or inducing tardive dyskinesia. Control of hallucinations may further benefit patients with PD by permitting them to be able to tolerate higher doses of levodopa and to thereby obtain further improvement in parkinsonian status. All neuroleptic drugs are sedating, but fortunately it is possible to attain satisfactory results with doses that are much lower than those typically used in schizophrenia.[700] It is important to appreciate that neuroleptics are not effective for the treatment of confusion or dementia. Indeed, if patients have moderate to severe dementia they may demonstrate a paradoxical worsening of psychosis and confusion with neuroleptic treatment.

The best studied of the atypical neuroleptics is clozapine (Clozaril).[701,702] Both open-label and double-blind, placebo-controlled trials have demonstrated that clozapine can reduce hallucinations in patients with PD without worsening parkinsonian motor features. There are also reports of antidyskinesia effects with clozapine,[497] but benefits may be related to worsening parkinsonism. Clozapine should be started with a very low dose (6.25 to 12.5 mg) at bedtime, with gradual escalation every 3 to 5 days, until hallucinosis/psychosis is controlled and the normal sleep–wake cycle has been restored. The dose of clozapine required to treat dopamine-induced hallucinations in PD is much lower than that used to treat schizophrenia (ranges from 200 to 600 mg/day). In PD, clozapine is typically started with a dose of 6.25 to 12.5 mg at bedtime (1/4 to 1/2 of the 25-mg tablet) and gradually increased to 25 to 75 mg/d, depending on response. It is rare to need more than 50 to 100 mg of clozapine to control hallucinations or psychosis in patients with PD, but higher doses may be required if hallucinations are unrelated to antiparkinsonian medications or are related to a preexistent psychotic disorder. Clozapine may induce drowsiness, particularly in cognitively impaired patients. If this occurs, the majority of the daily dose can be given at night. Clozapine can also cause orthostatic hypotension, and the first dose should be given with the patient in a supine position, preferably at night when the patient is in bed. At higher doses, patients may experience seizures and severe sialorrhea. The most serious complication of clozapine is agranulocytosis that was originally thought to occur in approximately 1% to 2% of patients and is not dose related. For this reason, US regulatory agencies mandated that clozapine-treated patients must have weekly white blood cell counts for the first 6 months of therapy and biweekly counts thereafter. Postmarketing surveillance studies now suggest that the risk is much lower than was initially suspected, and monitoring regulations have been eased.

Newer selective antipsychotic agents that do not induce hematologic side effects, such as Quetiapine (Seroquel), have been evaluated as an alternate to clozapine. In one study, 20 of 24 patients treated with quetiapine at a mean dose of approximately 45 mg/d experienced marked improvement in psychosis without worsening of parkinsonism.[703] However, recent double-blind, placebo-controlled trials have failed to demonstrate a significant benefit in alleviating psychosis,[704,705] whereas another study showed a benefit but it was not as pronounced as that with clozapine.[706] A meta-analysis of studies testing the effect of atypical neuroleptics on PD psychosis concluded that only clozapine could be recommended based on the results of randomized, controlled clinical trials.[707] However, we routinely choose quetiapine as the initial therapy for psychosis in PD because it seems anecdotally to be effective in some patients and avoids the risk of agranulocytosis and the need for blood monitoring required with clozapine. Quetiapine should be initiated at a dose of 12.5 mg (1/2 of a 25-mg pill) at bedtime, and titrated at 3- to 5-day intervals until the desired effect is achieved or side effects emerge. If ineffective, we would then use clozapine.

Several other atypical neuroleptic agents have been tested to treat psychosis in PD. Olanzapine and risperidone (Risperdal) may be effective in some patients with dopaminergic-induced psychosis, but they are prone to exacerbate parkinsonism and are not nearly as effective as clozapine.[708,709] Another atypical neuroleptic, aripiprazole, was also found to be associated with worsening of parkinsonism in an open-label pilot study.[710] Ondansetron and granisetron are serotonin 5-HT3 receptor antagonists that have been used primarily to treat vomiting associated with cancer chemotherapy. A preliminary open-label trial reported that ondansetron could provide antipsychotic benefits to hallucinating PD patients.[711] Ondansetron is well tolerated and does not cause drowsiness or orthostatic hypotension. In addition, it can be given parentally, and thus may be useful in the management of postoperative delirium in patients with PD. However, this agent is extremely costly, and additional supportive clinical experience is needed before it can be recommended. Cholinesterase inhibitors and antidepressants may have antipsychotic benefits in some patients with PD and can be considered in individual patients.[712-714]

Treating psychosis in PD is usually a balance between reducing neurobehavioral symptoms and exacerbating parkinsonism. If medical therapy is required because a secondary cause of psychosis cannot be identified and dopaminergic medications cannot be reduced, quetiapine is a reasonable initial therapeutic choice. However, clozapine is the most effective antipsychotic in PD and, despite the inconvenience of regular blood monitoring, the threshold for its use

should be low. Antidepressants should be used for comorbid depression and cholinesterase inhibitors may benefit psychotic patients with PD with comorbid dementia. It should be emphasized that for many patients with hallucinations, treatment regimens such as described here can dramatically influence their quality of life because such therapy permits use of higher doses of antiparkinsonian medications in attempts to enhance control of parkinsonism.

Behavioral impairment and mood disturbance. Mood disturbances in PD can take the form of depression, anxiety, panic attacks, or agitation.

Depression. Depression is pervasive in PD and affects approximately 40% of patients at least once during the course of their disease.[715-717] As in other conditions, depression in PD is characterized by feelings of guilt, helplessness, remorse, and sadness. The depression in PD is independent of age, disease duration, disease severity, or cognitive impairment. Depression in PD is associated with increased disability, increased caregiver burden, and a declining quality of life. Although depression can be overdiagnosed because the physical appearance of a nondepressed patient with PD can mimic that of depression (hypomimia, hypophonia, psychomotor retardation, and stooped posture), depression is more often underrecognized and undertreated.[718] Depression may be underdiagnosed because symptoms such as loss of energy, loss of appetite, loss of libido, and insomnia may be mistakenly attributed to PD. In one study, 34% of patients evaluated in a PD Center met criteria for depression but in most of these patients, depression remained unrecognized and untreated.[719] Even in those who were treated, almost half remained depressed and were not receiving adequate doses of antidepressant medications nor had they been tried on more than one antidepressant. A structured interview with the patient and spouse, the use of a depression rating scale, and a psychiatric consultation may be helpful in arriving at a correct diagnosis and treatment plan. Depression may be mistaken for dementia (pseudo-dementia) and as such represents a potentially treatable cause of dementia. It may also occur concurrently with dementia, or be a forerunner of a developing dementia.[715,716]

It is uncertain whether depression in PD is endogenous, exogenous, or both.[720] Exogenous depression is liable to occur in a patient with a chronic, progressive neurodegenerative disease. This is particularly relevant in young onset patients who must bear the burden of a disrupted career and the associated changes in lifestyle often required in patients with evolving PD. Conversely, endogenous depression might occur as a result of the monoamine deficiency that characterizes PD. Patients with PD are more likely to be depressed than patients with other chronic disabling diseases,[721] and depression may predate the onset of motor symptoms.[722] In addition, both dopaminergic and noradrenergic innervation are reduced in several brain regions of depressed compared with nondepressed patients with PD.[723] These observations argue for depression being, at least in part, an integral part of the disease process.

Both exogenous and endogenous forms of depression in PD may be improved by antiparkinsonian treatment. In some patients, mood changes occur in relation to motor fluctuations, with the patient feeling more depressed during the "off" state. In this case, management of depression consists of strategies designed to reduce motor fluctuations (see motor complications section, page S49). In general, treatment of PD should be the first step before considering more specific antidepressant therapy, unless the patient experiences a profound depression. Patients with PD who experience sustained depression despite adequate antiparkinsonian therapy may require psychotherapy and antidepressants.

SSRIs are the most widely used antidepressants in PD. They are effective antidepressants and avoid the anticholinergic side effects such as confusion and sedation that are frequently associated with the use of TCAs in this population. Fluoxetine (Prozac), sertraline (Zoloft), paroxetine (Paxil), and fluvoxamine (Luvox) are the major treatment options, and they are generally preferred in the treatment of the patient with PD. However, there remains inconclusive data on their beneficial effects in controlled clinical trials. In fact, there have been only isolated controlled clinical trials testing SSRIs for the treatment of depression in PD.[724] SSRIs, in general, and fluoxetine, in particular, can be activating. This may be desirable in patients who are apathetic or withdrawn, but undesirable in agitated patients. Fluoxetine has an extended elimination half-life and an active metabolite that may cause persistent side effects even after drug withdrawal. The doses of SSRIs used to treat depression in patients with PD are the same as for other causes of depression in the general population: fluoxetine or paroxetine (20 to 40 mg/d) and sertraline (50 to 150 mg/d). There have been isolated case reports of extrapyramidal symptoms (akathisia, dystonia, worsening of parkinsonism, and tardive dyskinesia) with SSRIs.[725,726] These have mostly been reported with fluoxetine and are rare occurrences that generally do not restrict the use of these drugs in patients with PD. Jitteriness and increased tremor may also be seen with SSRIs in some patients with PD. Concern has been raised about administering SSRIs in conjunction with MAO-B inhibitors for fear of inducing a serotonin syndrome or a hypertensive crisis,[727] but if this is a real concern it must be extremely rare. In a survey of Parkin-

son Study Group investigators, a possible serotonin-like syndrome was noted in only 11 of 4,568 patients (0.24%) receiving both selegiline and an SSRI, and in only 2 (0.04%) was the syndrome considered to be serious. Selegiline itself has recently been approved in a patch delivery formulation as a primary treatment for major depression,[728] but it has not been specifically studied in PD.

The tricyclic and tetracyclic antidepressants may also be effective in the management of depression. However, they are associated with anticholinergic effects (which can cause cognitive dysfunction) and orthostatic hypotension, both of which may limit their usefulness in patients with PD. They also have sedative properties that can be detrimental to apathetic patients, although they may be advantageous for those with anxiety or insomnia. Clinically, the propensity to induce sedation among TCAs can be ranked as follows: mirtazapine (most sedative), doxepin, imipramine, desipramine, trazodone, and nortriptyline (less sedative). Nortriptyline, desipramine, and trazodone have less anticholinergic activity than the others and are cleared more rapidly. For these reasons, they are the preferred agents in this class of drugs for treating depression in PD. For purposes of facilitating sleep, nighttime doses of nortriptyline 20 to 40 mg, desipramine 25 to 50 mg, and mirtazapine 7.5 to 30 mg can be useful.

There have been very few controlled trials comparing the different classes of antidepressant agents in PD. In one single-blind clinical trial, amitriptyline and sertraline were shown to have comparable antidepressant effects, although only sertraline was associated with enhanced quality of life.[729]

Antiparkinsonian medications may themselves have antidepressant properties. Studies suggest that the dopamine agonist, pramipexole, is an effective antidepressant agent in both patients with PD and non-PD. In a prospective, double-blind trial performed in patients with major depression, pramipexole in doses of 1 mg and 5 mg/d yielded benefits comparable with those obtained with fluoxetine.[337] Statistically significant improvement was observed with pramipexole for all outcome measures used (Hamilton Depression Scale, Montgomery Asberg Depression Rating Scale, and Clinician's Global Impression Scale); benefits were greatest with the 5 mg/day dose. In a pilot study, ropinirole was also found to provide antidepressant effects in patients with treatment-resistant depression.[730] Very few studies have examined the effect of antiparkinsonian drugs on depression in patients with PD. In one study in nonfluctuating patients with PD, pramipexole produced similar improvements in depression rating scales, and had a greater number of patient responders, compared with sertraline.[338] Two placebo-controlled NIH-sponsored trials of antidepressant treatments in PD are currently under way.

For the present, in patients with PD with mild depression and motoric dysfunction, it is recommended that consideration be given to the introduction of a dopamine agonist to treat both problems with a single medication. Whether antidepressant effects are a feature of all dopaminergic medications is not known, although levodopa has not been shown to have consistent effects on mood. Interestingly, transdermal selegiline, which delivers very high plasma levels of selegiline, is effective in ameliorating major depression in the general population[731] and might be particularly valuable in patients with PD, but has not yet been studied in this population. In a meta-analysis of depression trials in PD, the effect sizes of antidepressants were not different from placebo.[732] Electroconvulsive therapy has been used to manage severe depression in PD that cannot be controlled with more traditional approaches. Benefits in both depression and parkinsonian motor features have been observed,[733,734] although the latter are typically transient and disappear in weeks to months, and this procedure is not widely used.

In summary, depression is a common and potentially serious problem for patients with PD, and physicians must be alert for its presence, treat it with adequate doses of antidepressant medications, switch to alternate drugs if adequate results are not obtained, and have a low threshold for referring the patient for further psychiatric evaluation and treatment if necessary. Additional studies are required to better define the effect and magnitude of the different antidepressant medications in the PD population.

Anxiety. It has been estimated that 40% of patients with PD manifest overt anxiety, either alone or in association with depression.[735,736] Symptoms may involve a generalized anxiety disorder, panic attacks, and obsessive-compulsive disorder. As with depression, anxiety may occur as a reaction to having PD or in relation to the loss of brainstem dopaminergic, noradrenergic and/or serotonergic neurons. Panic attacks are characterized by a variety of psychic, autonomic, and somatic symptoms, including fear of dying, fear of going insane, breathlessness, diaphoresis, chest pain, choking, and dizziness. A panic attack may occasionally simulate a myocardial infarction. Panic and anxiety may be prominent manifestations of "off" episodes and are often more disabling than the motor symptoms, particularly at the onset of "off" periods.[737] In such cases, adjusting anti-PD medications to minimize "off" periods is desirable and may adequately control anxiety (see section on management of motor fluctuations). If this approach is not sufficient, or if the anxiety persists throughout the dosing interval, then a trial of anxiolytic drugs

such as benzodiazepines is warranted. The short-acting benzodiazepines, alprazolam and lorazepam, are preferred. A typical dose of alprazolam is 0.5 to 1.0 mg TID and of lorazepam is 0.5 to 2.0 mg TID. Cognitively impaired patients may not tolerate these agents and the minimum effective dosage should be used.

For patients experiencing anxiety or panic attacks who do not benefit from benzodiazepines, an SSRI or a TCA with minimal anticholinergic activity and moderate sedative activity, such as nortriptyline, desipramine, or imipramine, can be tried. In patients with cognitive impairment, these drugs can increase confusion and occasionally precipitate delirium and must be used with caution. Anxiety and panic attacks that do not respond to anxiolytics may be part of an agitated depression and require more aggressive treatment of the depression. The SSRIs are a rational choice for patients with PD with both anxiety and depression. The anticholinergic and orthostatic hypotensive properties of the TCAs negate in part their usefulness for treating anxiety in patients with PD.

Agitation. Agitation is characterized by restlessness, irritability, apprehension, and dysphoria, and may be part of the spectrum of delirium or represent an independent anxiety syndrome. Patients who become agitated during "off" periods are probably experiencing extreme anxiety rather than delirium. Their management includes better treatment of the motor fluctuations, if possible. Patients who become agitated spontaneously (i.e., without provocation) or when "on" may be delirious.[735] Anxiolytics are the mainstay of treatment for primary agitation. The short-acting benzodiazepines, alprazolam, lorazepam, and even diazepam, can be helpful. Although buspirone may also be effective, it has dopamine-blocking properties that mitigate against its use in patients with PD.

For patients with drug-related agitation, nonparkinsonian drugs should be discontinued first, if possible. Next, antiparkinsonian drugs should be discontinued in order of their anxiogenic potential; anticholinergics, MAO-B inhibitors, amantadine, and dopamine agonists. If none of the above drugs are being used, or if they have already been discontinued, the dose of levodopa should be reduced to reach a balance between lessened agitation and control of parkinsonian motor features.

Apathy. Apathy is characterized by a diminution in goal-directed behavior and is a common feature of PD, representing part of a dysexecutive syndrome. Apathetic patients may seem withdrawn and disinterested, but are not necessarily depressed or anxious. Apathy is particularly disturbing to a patient's spouse, caregiver, or family members, and is best thought of as a disturbance in cognition rather than of mood.[737-739] Furthermore, the occurrence of apathy in PD is independent of PD-related bradykinesia. There are a number of rating scales to assess apathy in PD,[740] although there have been no controlled clinical trials evaluating treatments for apathy in PD. Stimulants such as methylphenidate or modafinil may be effective in some patients. Furthermore, pharmacologic strategies aimed at increasing central dopaminergic or noradrenergic function (reuptake inhibitors, TCAs, dopaminergic agents) might enhance the frontal and striatal pathways thought to be responsible for goal-directed behavior.

Emotional lability. Emotional lability occurs in many neurologic diseases and is a prominent feature of PSP, ALS, and MS. Patients with PD can also experience episodes of laughing or crying which are appropriate but disproportionate to the anticipated emotional reaction. These episodes can be distressing to the patient and family and are usually attributed to underlying depression. Because these symptoms are thought to result from disinhibition of bulbar nuclei, the term "pseudobulbar affect" has been applied. However, it has recently been proposed that the terminology be changed to "involuntary emotional expression disorder".[741] There have been no controlled clinical trials of drugs to treat involuntary emotional expression disorder in PD, although both SSRIs and TCAs have been effective in managing this problem in other conditions. Other possible treatment options include dopamine agonists, or the combination of dextromethorphan and quinidine.[742]

Impulse dyscontrol and dopamine dysregulation disorders. ICDs in patients with PD have begun to attract considerable attention because of their potential link to dopaminergic therapies and stimulation of the STN. The most common ICDs in PD are pathologic gambling, hypersexuality, and compulsive shopping and eating. These have been reported in association with the use of high-dose dopamine agonist therapy, with most agonists now having been implicated.[743-745] In addition, chronic levodopa treatment has been associated with punding, which is a series of repetitive and purposeless behaviors, such as collecting or assembling and disassembling objects for no apparent reason.[230] Dopamine dysregulation consists of an addictive-like need to take increasing doses of levodopa, even if they are not providing noticable benefit. In many ways this relates to other addictive behaviors and may relate to dopaminergic effects on the VTA-accumbens dopamine system rather than the nigro-striatal system.

ICDs are underrecognized because their onset is insidious and because patients may not appreciate that a slowly emerging destructive behavior pattern

may be related to their PD. Patients may also be reluctant to report potentially embarrassing behaviors to their physician or caregiver, family members may be unaware of the association between ICDs and PD, and physicians may not think to ask specifically about them. Risk factors for ICDs include current use of dopamine agonists, particularly in high doses, young age of PD onset, and a premorbid or family history of ICDs or depression.[746] ICDs were first identified in association with pramipexole, but have now been described with ropinirole and pergolide. Interestingly, they occur much less frequently with levodopa, although punding is primarily associated with chronic levodopa treatment.

Studies are currently under way to better assess the true frequency of ICDs in the PD population and their relationship to different dopaminergic medications. In one recent study, 4% of a random sample of patients with PD met criteria for an ICD, and 7% had an ICD at some point during the course of their PD.[378] Further studies are needed to determine whether ICDs are, in fact, more common in patients with PD (untreated and treated) than in the general population, and what role dopamine agonists play in their expression. In performing such studies, it will be important to include a contemporaneous control population so as to factor in the upsurge in casinos, Internet gambling, and lotteries, which have made gambling more readily accessible than it has been in the past. Indeed, since 1970 the availability of gambling in the United States has increased 10-fold.[747] Between 1975 and 2001, legal wagering increased from $3 billion to $64 billion and gambling expenditures more than doubled as a percentage of personal income.[748] Furthermore, problem and pathologic gambling in the general population is known to be associated with lifetime depression, as well as with mental and physical impairment, including limitations in motor activity.[749] Future studies will have to control for each of these variables and not simply rely on outdated historical controls. For example, the recent survey commissioned by the California state legislature indicated that the prevalence of problem and pathologic gambling among adults in the state was 3.7%, and this risk was significantly increased in individuals who were disabled or unemployed.[749] These numbers are substantially higher than what had previously been appreciated.

There seems to be a relationship between dopamine agonist use and the expression of compulsive behaviors, particularly gambling, as some individuals begin to express the ICD shortly after starting treatment with the agonist (or after an increase in dose), and lose the urge when the drug is discontinued. The precise mechanism whereby dopamine agonists might induce these ICDs is not known. It remains to be determined if dopamine agonists are directly responsible for inducing an ICD through a particular pattern of receptor stimulation, or if there is an underlying personality disorder that becomes clinically manifest with restoration of striatal dopaminergic tone.

Dopamine is known to play an important role in reward, and SNc dopamine neurons fire in anticipation of reward.[282] Furthermore, fMRI measures of metabolic activity in gamblers have shown activation of dopaminergic pathways that extend between the ventral striatum and prefrontal regions.[750] Patients with PD may therefore be particularly vulnerable to ICDs, as the dopamine system is relatively depleted in the untreated state and dopaminergic agents may not restore dopamine in a normal manner. Abnormal D3 receptor activation has been implicated because several of the dopamine agonists preferentially activate this receptor subtype and because these receptors tend to be localized in the ventral striatum. Because of the severity of the consequences of pathologic gambling and other ICDs, physicians should be aware of their potential to emerge in patients with PD, and patients should be advised of these risks when starting dopamine agonist therapy.

DBS of the STN has been reported to ameliorate ICDs,[595] but this may be due to a concomitant reduction in the dose of the dopamine agonist. There have also been reports of patients developing ICDs in association with DBS.[751] Indeed, a recent study found that patients with STN stimulation had a greater risk of developing ICDs and higher scores on tests of impulsivity than did patients with PD on drug treatment or healthy controls.[599] These latter observations are particularly interesting in view of recent studies showing that stimulation of the STN inhibits the capacity of some individuals to stop making wrong selections,[593,594] and seems to influence impulsivity in the opposite direction of dopaminergic agents.

It is important that physicians be aware of the potential for patients with PD to develop these types of problems. Treatment of each patient should be individualized based on the magnitude of the ICD problem and the need for dopaminergic drugs to control PD features.[752] Treatment at present is best achieved by lowering the dose or removing the dopamine agonist, if possible. Other approaches could include trials of various psychoactive agents and psychosocial interventions and referring patients for appropriate counseling services.

Autonomic dysfunction. A host of clinical manifestations in PD occur as a result of autonomic dysfunction that may affect cardiovascular, gastrointestinal, urogenital, and sexual functions.[753] In fact, severe constipation and urinary incontinence were promi-

nent features described by Parkinson[1] in his 1817 monograph. The estimated prevalence of autonomic dysfunction in PD ranges between 14% and 80%.[754] A recent study of 123 patients with PD and 96 age-matched controls using a newly validated nonmotor questionnaire for PD (NMSQuest) reported that autonomic symptoms were significantly more common in all stages of the disease than in controls.[343] Another study evaluated autonomic symptoms in patients with PD using the SCOPA-AUT, and found that autonomic symptoms were more common in patients with PD than controls and increased in association with increasing age, disease severity, and medication use.[755,756] Furthermore, many of these patients did not report features of dysautonomia even though they were taking medications for urinary problems and constipation, suggesting some degree of underreporting. Autonomic dysfunction, including constipation, nocturia, and orthostatic hypotension, can be disabling for some patients with PD and have a significant effect on their quality of life.[754]

Autonomic dysfunction in PD is attributed to pathologic involvement of central and peripheral autonomic neurons. The ventrolateral medulla, nucleus tractus solitarius, periaqueductal gray matter in the midbrain, descending sympathetic and parasympathetic pathways, and peripheral autonomic neurons and ganglia have all been reported to have Lewy bodies and to be involved in the PD neurodegenerative process.[757,758] Indeed, degeneration of the dorsal motor nucleus, and of cholinergic, monoaminergic, and serotoninergic brainstem nuclei, found in PD, could also contribute to the development of dysautonomia. Dysautonomia may further be caused or aggravated by dopaminergic therapy. Degeneration of autonomic neurons could be an early feature of PD that predates the development of dopaminergic pathology.[5,740] Indeed, α-synuclein aggregates have been described in peripheral autonomic neurons of normal individuals who did not have clinical features of PD,[759] and autonomic problems such as constipation have been reported to significantly increase the risk that an individual will develop PD.[79] Autonomic involvement may thus represent an early premotor phase of PD. Indeed, constipation was found to correlate with the presence of incidental Lewy bodies in the SNc of patients, studied postmortem, who had no parkinsonian features during life,[760] supporting this hypothesis.

For many patients, dysautonomia is mild and overshadowed by more prominent features of motor dysfunction. However, a significant minority of patients with PD experience very severe and disabling autonomic impairment. These symptoms tend to be most prominent in the advanced stages of the disease, but occasional patients will present with a primary autonomic failure syndrome and have PD pathology at postmortem.[761] Autonomic disturbances in PD can manifest as constipation, urinary problems with incontinence, impotence, orthostatic hypotension, impaired thermoregulation, and dysphagia.

Constipation. Gastrointestinal symptoms are common in PD, especially constipation.[762] In one survey, 58% of patients with PD reported constipation.[763] The importance of constipation in PD was noted by Parkinson who commented that the bowels "which had been all along torpid, now, in most cases, demand stimulating medicines of very considerable power."[1] Two distinct processes are responsible for normal defecation. First, muscles within the intestinal wall contract sequentially to move stool through the intestine. Second, there is coordinated contraction of the muscles of the rectum, pelvic floor, abdominal wall and diaphragm, combined with relaxation of the muscles of the anal sphincter. Collectively they permit defecation. Colonic muscle activity is regulated by intrinsic enteric neurons together with extrinsic parasympathetic afferent and efferent fibers that mediate excitatory and inhibitory innervation of the colon.[764-766]

Involvement of these neurons as part of the PD process is evidenced by the presence of Lewy bodies within degenerating neurons in the myenteric plexus of the colon.[767]

The primary clinical correlate of constipation is slowed stool transit time, which relates to impaired colonic muscle contraction. Patients with PD have impaired gastric emptying and delayed colon transit times relative to age-matched controls.[762] Impaired defecation may also relate to a primary defect in innervation of local musculature. Patients with PD may be unable to straighten the anorectal angle on straining, thereby accentuating its flap valve action and obstructing the passage of stool. It has been suggested that this paradoxical contraction of the pelvic musculature is dystonic in nature and correlates with the progression of PD. In support of this argument, apomorphine can alleviate this defecatory problem in some patients with PD.[768] Other disorders that can be associated with constipation in patients with PD include megacolon (Ogilvie syndrome) and sigmoid volvulus.

The management of constipation in PD consists of dietary changes, exercise, and pharmacotherapy. Dietary modification is primarily aimed at increasing the bulk and softening the stool. This should be the first treatment strategy and is efficacious in most patients. Patients should be encouraged to drink six to eight glasses of water each day and to increase the fiber content of their diet. Low-fiber foods such as

baked goods should be eaten infrequently and bananas should be avoided altogether. At least two meals per day should include high-fiber raw vegetables. Oat bran can be used to add fiber and bulk, and to stimulate the gastrocolic reflex while at the same time reducing protein consumption. Increasing physical activity can be helpful in managing constipation. Within the boundaries of an individual patient's physical capability, exercise should be as vigorous as possible. Walking or swimming is a good exercise choice for patients with PD (see later).

If stools remain hard despite the measures outlined above, stool softeners (e.g., docusate) given with meals or lactulose in doses of 10 to 20 g/day may benefit some patients. Patients should be educated about the delayed onset of effect of stool softeners and encouraged to continue with fluids, increased bulk, high-fiber diet, exercise, and antiparkinsonian interventions. Discontinuing medications such as anticholinergic agents may increase bowel motility, but this should be done gradually to reduce the risk of exacerbating motoric dysfunction. Miralex is now available over the counter and can be helpful.

Milk of magnesia and other laxatives or enemas should be reserved until it is evident that patients have not responded to more conservative interventions, although they can be used once weekly as part of an overall bowel regimen. Apomorphine, if available, may be useful as a rescue agent for relief of severe constipation. Agents that promote bowel motility such as cisapride have been shown to provide benefit to some patients with otherwise-resistant PD,[769] but this drug has been withdrawn from the market in the United States because of reports of QT interval changes on the EKG and the risk of cardiac problems. Mosapride, a 5-HT_4 agonist/partial 5-HT_3 antagonist that lacks potassium channel antagonist properties, has been reported to improve gastrointestinal motility and improve constipation in patients with PD-associated constipation.[770] Tegaserod, a 5-HT4 agonist, which was approved for irritable bowel syndrome in women, was reported to improve constipation in patients with PD in two small, open-label studies, but the drug has also been withdrawn from the market.[771,772]

Urinary problems. Nocturia is the earliest and most common urinary problem in patients with PD. It is usually followed by symptoms of urgency and frequency as well as difficulty in micturition.[773] These problems may be due to detrusor hyperreflexia and delayed or incomplete relaxation of the pelvic floor. In patients with supine hypertension, nocturia may also result from pressure natriuresis (see the orthostatic hypotension section, page S82). Urinary problems correlate with the duration and severity of PD.[774,775] In some patients, a sense of incomplete emptying may occur during "off" periods and represent one of the nonmotor fluctuations associated with levodopa treatment. It is interesting that L-dopa administration itself has variable effects on bladder function. In drug naïve patients urodynamic findings may worsen after levodopa treatment, but after chronic administration there is usually improvement in bladder dysfunction.[776]

Detrusor hypoactivity or urethral sphincter dysfunction are less common causes of urinary dysfunction, but may occur in patients with PD with autonomic failure. If daytime frequency or urgency precedes nocturia, mechanical outlet obstruction should be excluded. Any change or deterioration in voiding pattern in a patient with PD (even in the absence of dysuria) should raise the possibility of a urinary tract infection.

Patients with PD with refractory or persistent urinary dysfunction should have a urologic evaluation. This might include recording of bladder and sphincter pressure, sphincter electromyography, and fluoroscopy. Urinary tract infection should be treated immediately. If nocturnal frequency is a problem, this may be helped by curtailing fluid intake after the evening meal. In cases in which this is not effective, peripherally acting anticholinergics such as oxybutynin (5 to 10 mg at bedtime or 3 times daily), propantheline (7.5 to 15 mg at bedtime or 3 times daily), or tolterodine tartrate (Detrol) (1 to 2 mg twice daily based on individual response and tolerability) can be used as initial pharmacologic treatment. A long-acting formulation of tolterodine (Detrol LA) is available and the recommended dose is 4 mg/d. If these are ineffective, hyoscyamine administered in doses of 0.15 to 0.30 mg at bedtime or on a four times per day schedule can be tried.

Anticholinergic agents reduce detrusor contractions and may be useful in the treatment of detrusor hyperactivity, but may worsen voiding problems and even produce urinary retention in patients who have detrusor hypoactivity or outlet obstruction. Anticholinergic drugs should be administered with caution to patients with clinically significant gastrointestinal obstructive disorders because of the risk of inducing gastric retention. These drugs may also worsen cognitive problems and result in hallucinations (see anticholinergics, page S42). α-Adrenergic blockers decrease tone in the bladder neck and may be helpful for patients with a hypoactive detrusor. However, these agents are not recommended in patients with PD as they may also cause or worsen preexisting orthostatic hypotension. Alternatively, the use of an α-adrenergic agonist such as midodrine (Proamatine) to treat orthostatic hypotension may worsen

bladder emptying by increasing sphincter tone.[777] Diazepam, baclofen, or dantrolene may be useful in relaxing striated muscle in patients with hyperreflexic external sphincters. Intermittent catheterization may be necessary if the patient has overdistension of the bladder wall.

Sexual problems. Sexual dysfunction is a common problem in patients with PD. It may represent the initial manifestation of autonomic dysfunction and even precede the development of motor features.[763] Sexual dysfunction may be caused by a combination of factors, including the disease process, PD medications, and psychological issues. Testosterone deficiency may also play a role.[778] In one study, 17 of 21 male patients with PD had substantial impairment in sexual arousal, behavior, drive, and orgasm, whereas in those with longer duration of the disease sexual fantasy was increased.[779] The most common sexual problem is achieving or maintaining an erection. Most attention has been focused on men, but there is evidence to suggest that PD is also associated with sexual dysfunction in women. In one study, women reported difficulties with arousal, reaching orgasm, low sexual desire, and achieving sexual satisfaction.[780]

A high prevalence of sexual dysfunction, particularly hypersexuality, has been reported with dopaminergic therapies, and especially dopamine agonists.[781] Sexual dysfunction has also been observed after bilateral STN stimulation.[782] Interestingly, normal aging in all mammalian species is associated with reduced levels of dopamine and increasing sexual dysfunction, whereas dopamine agonists enhance sexual function in both rodents and humans.[783,784]

The management of male sexual dysfunction in patients with PD involves identifying and correcting any underlying treatable causes, and introducing pharmacologic therapy aimed at improving erectile function. Previously untreated or undertreated patients with PD may find that antiparkinsonian treatment helps sexual function, possibly by alleviating bradykinesia or by restoring dopaminergic tone. Some patients on high doses of antiparkinsonian therapy become hypersexual, even in the face of inability to perform, and dose reduction may be beneficial in this situation. Many drugs can cause male sexual dysfunction, and a thorough medication history to uncover causative or contributory agents should be conducted. Propranolol and other β-adrenergic blockers, which are occasionally used to treat postural tremor or hypertension in patients with PD, can cause impotence and should be discontinued if possible. Other drugs that can induce impotence include α-adrenergic blockers, guanethidine, thiazide diuretics, anxiolytics, digoxin, cimetidine, and some antidepressants. Medical evaluation of the impotent patient should also be performed, but is rarely fruitful. Endocrine dysfunction should be assessed by obtaining serum levels of prolactin, testosterone, luteinizing hormone and thyroid function, and appropriate referral and treatment made as necessary. Depression is a common cause of impotence, and some antidepressants (e.g., SSRIs and TCAs) may themselves cause anorgasmia. Anxiety can also be associated with sexual dysfunction and patients may benefit from low-dose anxiolytics.

If treatment of medical and/or psychological causes of impotence is ineffective, several therapeutic options may be considered. Orally active inhibitors of the type 5 cGMP-specific phosphodiesterase (the predominant isoenzyme in the human corpus cavernosum), such as Sildenafil (Viagra), vardenafil (Levitra), and tadalafil (Cialis), can be effective as treatments for impotence.[785] Sildenafil has also been shown to be effective in patients with PD.[786] Intracavernous injections or transurethral suppositories of alprostadil, a synthetic prostaglandin E_1, can provide short-term vasodilator effects by relaxing smooth vascular muscle. This increases arterial inflow and decreases venous[787] outflow by relaxing the corporal smooth muscles that occlude draining venules thereby inducing penile erection.[887] More invasive approaches, such as implants, are available but are not readily accepted or probably appropriate for most patients with PD.

Preliminary studies have found low levels of testosterone in men with PD, and open-label replacement has been reported to provide benefits for some nonmotor features.[778] However, a double-blind trial using injectable testosterone in elderly PD men showed no significant difference from placebo in either motor or nonmotor scales.[788] Until more definitive studies are reported, practitioners should be cautious about treating PD men with erectile dysfunction with testosterone, even if they have borderline testosterone deficiency.

Orthostatic hypotension. Orthostatic hypotension is common in all stages of PD with a prevalence that varies from 30% to 58%.[789] In most cases, clinically significant orthostasis occurs in the advanced stages of the disease, and can be aggravated by dopaminergic therapies. The presence of prominent symptomatic orthostasis in the early stages of the disease suggests autonomic failure as seen in MSA, but rarely this is also seen in PD. Indeed, one study found that orthostatic hypotension could occur early in the course of the disease, and to even precede the onset of motor symptoms in some cases.[789]

Orthostatic hypotension in PD may be due to central or peripheral autonomic dysfunction. This is suggested by the finding of neurodegeneration and Lewy bodies in neurons involved in autonomic func-

tion in both the CNS (e.g., the hypothalamus and brainstem autonomic nuclei)[757,758] and peripheral nervous system (e.g., sympathetic ganglia, myenteric and cardiac plexi).[790,791] Cardiac sympathetic denervation can also be found in PD using MIBG scanning to assess dopamine innervations of the heart, and may be useful in differentiating PD from MSA. In PD, there is evidence of postganglionic sympathetic denervation in almost all patients, whereas in MSA, the MIBG scan is consistently normal despite the presence of orthostatic hypotension, which is generally more pronounced than in PD and is most likely of central origin.[792-794] Cardiac involvement in PD is also reflected by findings of Lewy body pathology in the cardiac plexus.[795]

Maintenance of blood pressure in the standing position is a function of peripheral vascular resistance (i.e., vasoconstriction) and intravascular volume. Orthostatic hypotension in patients with PD frequently develops as a result of impaired vasoconstriction due to decreased sympathetic outflow. In many patients, intravascular volume is also reduced because of excessive renal sodium loss and/or anemia with decreased red blood cell mass. Excessive sodium loss may occur as a result of reduced renin release, diminished renal sodium reabsorption, and pressure natriuresis due to supine hypertension. Patients with PD with autonomic failure frequently have elevated supine blood pressure and may be incorrectly diagnosed with hypertension. Antihypertensives can worsen orthostatic hypotension and are contraindicated in these patients. Anemia and decreased red blood cell mass in patients with PD may result from reduced renal secretion of erythropoietin.[796] Patients with PD with autonomic failure are extremely sensitive to small changes in blood volume, so that even a mild reduction in plasma or red blood cell mass can markedly worsen orthostatic hypotension. Thus, orthostatic hypotension in patients with PD can result from both impaired vasoconstriction and reduced intravascular volume.

There are a number of effective strategies that can help to avoid or treat orthostatic hypotension in PD. A complete medication history should be obtained to identify and eliminate (if possible) agents that can cause or contribute to orthostatic hypotension such as antihypertensive agents or diuretics. Levodopa, dopamine agonists and MAO-B inhibitors may all cause or exacerbate orthostatic hypotension, especially during the first weeks of treatment.[797] Indeed, it has been proposed that orthostatic hypotension induced by selegiline might lead to increased mortality,[798] but increased mortality with selegiline has not been confirmed in other studies[437,438] and all dopaminergic agents have the potential to aggravate hypotension.[797] Gradual dosage increases when initiating therapy or dose reductions in established patients can minimize the risk of orthostatic hypotension.

Sodium intake should be increased in patients with PD with symptomatic orthostatic hypotension. Practical methods for increasing sodium intake are the liberal use of table salt or administration of sodium tablets. Patients should also be instructed not to lie prone at night or even during the day. Lying flat results in accelerated sodium loss from pressure-natriuresis and reduced renin release leading to loss of intravascular volume. This can lead to nocturnal hypertension with overnight volume depletion and worsening of orthostatic hypotension during the day. Elevating the top of the bed by 30 to 40 degrees by placing books under the legs may be helpful in preventing this phenomenon.[799] The beneficial effect of nocturnal head and torso elevation results from lessening supine hypertension, thus reducing pressure-natriuresis by the kidney and, in some patients, by increasing renin secretion.[800]

Patients and their families should be educated about the hypotensive effects of food, hot weather, and physical exertion. In patients with autonomic failure, eating can significantly lower blood pressure because the splanchnic vasodilation induced by food is not compensated for by vasoconstriction in other vascular beds. In some patients, hypotension only occurs postprandially. Thus, patients with PD should eat frequent small meals with low carbohydrate content and avoid alcoholic beverages. Caffeine taken with breakfast may be helpful. Hot baths can also induce hypotension and should be avoided. Patients should be especially careful during warm weather as heat-induced vasodilation is prone to occur in this situation and compensatory sympathetic vasoconstriction is impaired. Straining at stool with a closed glottis (i.e., producing a Valsalva maneuver), playing wind instruments, and singing can all be dangerous for patients with PD with hypotension. A high fiber diet is encouraged to prevent constipation and singing or playing wind instruments should be undertaken only when sitting. Exercise is encouraged, but it should be noted that isotonic exercise produces less hypotension than isometric exercise, and exercise in a swimming pool is particularly valuable in avoiding blood pressure reductions. The use of knee-high compressive stockings is not effective in treating orthostatic hypotension, but waist-high stockings (e.g., Jobst stockings) or abdominal binders may be effective, although these may be poorly tolerated by the patient.

Orthostatic hypotension should only be treated pharmacologically in patients who are symptomatic. Because of adaptive cerebral autoregulatory changes, patients with autonomic failure frequently tolerate

very low arterial pressures when standing and do not experience symptoms of cerebral hypoperfusion. Blood pressure levels change throughout the day and from one day to another. Thus, the patient's normal cycle of blood pressure and orthostatic symptoms should be identified before treatment is initiated. The physiologic underpinnings of orthostatic hypotension in PD guide its pharmacologic management, which consists of strategies aimed at increasing intravascular volume, increasing peripheral vascular resistance, and correcting anemia if present. Fludrocortisone (Florinef) is a salt-retaining steroid that is widely used to increase intravascular volume in patients with PD with symptomatic orthostatic hypotension. Therapy with fludrocortisone is typically initiated at a dose of 0.1 mg/d. The daily dose can be gradually increased to 0.5 mg/d as necessary, but such high doses are generally not required. Maximal clinical response occurs after approximately 1 week; dosage adjustments should include consideration that there is often a delayed onset of the treatment effect. Pedal edema and weight gain of five to seven pounds are expected consequences of fludrocortisone therapy.

Desmopressin (DDAVP) administered intranasally in doses of 5 to 40 μg at bedtime is a possible adjuvant to fludrocortisone therapy in treating orthostatic hypotension.[801] DDAVP is a synthetic vasopressin analogue that acts on the V2 receptors of renal tubular cells to promote reabsorption of water and expansion of intravascular volume. It should be noted that DDAVP can induce a severe and life-threatening hyponatremia, and that careful monitoring of serum sodium concentration is necessary during the first 4 to 5 days of treatment and at monthly intervals thereafter. Indomethacin, a prostaglandin inhibitor, has been used to treat orthostatic hypotension especially in combination with fludrocortisone,[802] but the lack of rigorous clinical data supporting the efficacy of this combination precludes a formal recommendation for its use at this time.

Sympathomimetic agents increase peripheral vascular resistance and have been used in the treatment of symptomatic orthostatic hypotension in PD. This class of compounds includes direct-acting sympathomimetics (e.g., midodrine, phenylephrine, phenylpropanolamine) and indirect-acting agents (e.g., tyramine, ephedrine). Midodrine (ProAmatine) is a selective α_1-agonist that does not cross the blood-brain barrier and does not cause central effects.[803] The blood pressure response to midodrine occurs within hours of an oral dose, making this agent potentially useful in treating patients who might benefit from an on-demand agent that increases blood pressure (e.g., postprandial and morning hypotension). Midodrine therapy is usually started at a dose of 2.5 mg and increased to no more than 10 mg TID. A typical daily regimen includes a dose before breakfast, a dose before lunch, and a third dose in the mid-afternoon. Midodrine should not be administered at bedtime. A double-blind crossover trial demonstrated benefits with midodrine that were superior to placebo in a few patients with orthostatic hypotension,[804] but there is only anecdotal information on the value of this treatment in PD.[805]

L-Threo-DOPS (the biologically active stereoisomer of the amino acid 3,4-dihydroxyphenyl serine or DOPS) is a precursor of norepinephrine that has shown promise in the treatment of orthostatic hypotension in small clinical trials.[806,807] Indeed, benefits with DOPS have been observed in patients who were refractory to treatment with other, more traditional therapies.[808] An open-label uncontrolled study in patients with MSA and other neurogenic forms of orthostatic hypotension demonstrated subjective and objective improvements with DOPS.[809] Further, clinical studies are required to determine if this promising agent will become an important treatment of orthostatic hypotension in patients with PD.

Erythropoietin can also be used to treat orthostatic hypotension based on its capacity to increase red blood cell mass and blood viscosity.[796] Erythropoietin also increases plasma endothelin, inhibits nitric oxide, and increases renal sodium reabsorption. Erythropoietin has been shown to improve blood pressure in patients with refractory orthostatic hypotension,[796] and may be beneficial for patients with PD with orthostatic hypotension, particularly if they have anemia. Treatment consists of a 6-week course of subcutaneously administered recombinant erythropoietin (4,000 units twice weekly). Other treatments for orthostatic hypotension should be continued during erythropoietin therapy. Obviously, other causes of anemia in these patients should be sought and corrected if possible.

Thermoregulation, sweating, and sialorrhea. The neurochemical and anatomic basis of temperature and sweating regulation are complex and poorly understood. Preoptic and hypothalamic areas are thought to contribute to the regulation of thermoregulatory function, and noradrenergic, serotonergic, and cholinergic systems may all play a role in thermal homeostasis. Sweating is mediated by efferent sympathetic cholinergic fibers.

Abnormal sensations of heat or cold, impaired sweating responses, and hypothermia can all occur in patients with PD. Excessive sweating of the head and neck may occur in response to external heat and is associated with poor heat dissipation. Such problems are more common than may be appreciated, being found in as many as 64% of patients with PD com-

pared with only 12% of controls.[810] Lewy bodies and cell loss have been found in the hypothalamus in patients with PD, suggesting that impaired hypothalamic function might be responsible for PD-associated sweating abnormalities. The presence of thermoregulatory disorders in patients with PD also suggests that dopamine regulation of vasomotor tone may be a contributing factor, although the precise mechanisms whereby this might occur are poorly understood. Recent studies have shown impaired sudomotor responses in the palms of patients with PD with hyperhidrosis.[811] As increased sweating in PD tends to be most pronounced over the head, face, and trunk, this may occur as a compensatory reaction to impaired sympathetic activity in the extremities.

Sweating, and even severe drenching sweats, can occur as an end-of-dose "off" phenomenon in patients with motor fluctuations, and in these cases may be satisfactorily controlled with adequate dopaminergic therapy.[812] In contrast, some patients with PD only experience sweating during "on" responses, and frequently in association with dyskinesia. Although sweating in the "on" state can be pronounced, it usually is not as severe as that which occurs in the "off" state. A reduction in dopaminergic medications may help these patients, but often at the price of more "off" time. β-Adrenergic blockers may be more useful for patients with "on"- period sweating than with "off"-period sweating. Botulinum toxin can also be an effective treatment for excess sweating, and may be helpful in individual patients with PD with focal hyperhidrosis.[813,814] DBS–STN has also been reported to ameliorate sweating during "off" periods in fluctuating patients.[815] Severe hyperpyrexia can be seen after levodopa withdrawal, probably as a manifestation of a neuroleptic malignant syndrome, and should be promptly treated by reinstitution of dopaminergic agents.

Other causes of excessive sweating should be sought and not neglected simply because the patient has PD. Some patients with excess sweating have a positive family history and a genetic basis for hyperhidrosis. Benign sweating can occur with visual, olfactory, or gustatory stimuli. Ethanol and aspirin in high doses can cause intermittent sweating. Thyrotoxicosis and the postmenopausal state can be associated with increased sweating, and endocrine evaluation should be performed and treatment instituted if appropriate. Finally, chronic infections such as tuberculosis should be considered in the differential diagnosis. A thorough history and physical examination will usually clarify these situations.

Sialorrhea or increased salivation can be a major problem for some patients with PD and has been described in up to 78% of patients.[816] Drooling is not only a social embarrassment, but can lead to skin erosion/ulceration and even aspiration pneumonia. Several studies have demonstrated decreased saliva production in PD,[817,818] suggesting that sialorrhea is primarily due to impaired swallowing. Treatment with anticholinergics may be helpful, but they are frequently associated with side effects.[819] Botulinum toxin has emerged as the most effective treatment for sialorrhea in PD. Double-blind studies have demonstrated reduced drooling and reduced disability with both botulinum toxin A and B.[820,821] Dysphagia after botulinum toxin was not a problem in these studies, but several patients did experience dry mouth.

Pain/dysesthesias. Pain is a common problem in PD and can be found in up to 50% of patients.[822] The mechanism responsible for pain in PD is unclear and the cause is probably not the same in all patients. Pain syndromes may be associated with dystonia, suggesting that PD-associated pain may arise from abnormal firing in afferent nerve fibers within dystonic muscles. A spinal cord or central origin for some pain syndromes is suggested by a pseudoradicular or thalamic distribution pattern. Pain might also ensue because of impaired capacity of the PD basal ganglia to modulate sensory information and alterations in serotoninergic pathways.[823] Many pain syndromes are worse or occur only in the "off" state, suggesting a role for dopamine-containing cells in the diencephalon, which terminate on receptors in the dorsal horn and intermediolateral column of the spinal cord.[824,825] One study investigated the effect of levodopa on pain threshold in patients with PD in the "off" and "on" states, and correlated these findings with metabolic changes on PET scan.[826] In the "off" state, pain induced significant activation in the right insula, right prefrontal area, and left anterior cingulate cortex in patients with PD, compared with a control group. Levodopa significantly reduced pain-induced activation of these areas in patients with PD. This study suggests that the pain threshold is lower in patients with PD, but returns to normal after levodopa administration. Studies have also shown that patients with PD have altered pain thresholds in nociceptive pathways, and that these are normalized with levodopa treatment.[827] This was studied using the nociceptive flexion reflex (RIII) threshold test.[827] Levodopa significantly increased the RIII threshold in patients with PD, providing evidence that dopaminergic therapy modulates an objective pain threshold in patients with PD.

Sensory symptoms in PD can also be neuritic in character, and can include paresthesias, burning dysesthesias, coldness, numbness, and deep aching within a nerve or root distribution.[828] The legs are

more often involved than the arms, with the face and neck being least frequently affected.[829] Pain is usually more severe on the side of the body where the parkinsonian symptoms are the worst.[830]

Pain related to parkinsonism may respond to adjustment of antiparkinsonian medications. If pain is linked to the "off" state, higher doses of dopaminergic therapy can be helpful. Pain may similarly be improved after DBS. Mechanical causes of radicular pain and neuropathy should to be evaluated and treated as appropriate. Pain related to arthritis is not uncommon in elderly patients with PD. In fact, arthritic pain or bursitis in the shoulder or dystonic pain in the foot are often early and even presenting features of PD, presumably related to reduced limb mobility. They may respond to the introduction of dopaminergic therapy, but a rehabilitation program with passive and active exercises incorporating a full range of movement should also be part of the treatment plan.[831]

Speech and swallowing difficulties. Speech dysfunction in PD is common, affecting as many as 89% of affected individuals.[832] PD speech is characterized by a softening of volume (hypophonia), monotonal pattern, and poor articulation with unclear intonations and a tendency for words to run into each other (tachyphemia, oral festination). Speech problems may occur early in the disease and even be a presenting manifestation, but they are usually modest at this stage of the illness. Typically, more severe speech impairment does not occur until the late stages of the disease when hypophonia may be so pronounced that it is hard to hear the patient and dysarthria so severe that speech is unintelligible. Speech impairment, like swallowing problems, occurs more often and is more severe in older patients with an akinetic rigid form of the disease. Speech impairment (except for mild hypophonia) is typically unresponsive to levodopa, and may actually be worsened by DBS. Speech therapy can be helpful in some patients, particularly the Lee Silverman Voice Treatment (LSVT) method, which is based on helping the patient to scale the speech volume upward.[833,834]

Dysphagia in patients with PD is usually, but not always, related to disease severity and eventually develops in up to 40% of patients.[835,836] Indeed, this number likely underestimates the magnitude of the problem, particularly in the earlier stages of the disease. A recently validated questionnaire identified unreported dysphagia in about 50% of patients with PD.[837] Recognition of dysphagia is important in order to refer patients for evaluation and treatment before the development of an aspiration pneumonia. Dopamine deficiency seems to play a role in the origin of dysphagia in some patients, as evidenced by the observation that many patients experience severe dysphagia only when "off," and respond dramatically to levodopa. Swallowing abnormalities can be due to direct involvement of oropharyngeal muscles as a part of the PD process with abnormal lingual control and inability to pass a bolus of food backward into the pharynx. Silent aspiration with repetitive reflux of food from the vallecula and pyriform sinuses can be a significant and potentially dangerous problem. Excessive drooling is thought to be primarily due to swallowing abnormalities, and may be annoying and cause local erosion of skin. Dysphagia with retention of medications in the vallecula is also a potential causes of erratic drug absorption, which itself may contribute to worsening dysphagia. Esophageal dysmotility is an independent problem that can occur in up to 70% of patients with PD, but it should be noted that this is a common problem in age-matched controls as well.

Patients with PD who experience clinically significant swallowing dysfunction should be evaluated by a speech and swallowing expert. Swallowing studies may help to define the nature of the dysphagia and exclude obstructive lesions. The presence or absence of silent aspiration must also be determined. Soft diets may be useful by making it easier to move food in the mouth and esophagus. Soft food also decreases the risk of aspiration by reducing the need for separate fluid intake. Because dysphagia is usually worse during "off" time and improved in "on" time, the initial strategy should be to try and increase "on" periods by adjusting dopaminergic therapy if possible. Patch delivery of the dopamine agonist rotigotine has been reported to be particularly valuable in treating patients with dysphagia, but this has not as yet been formally tested.[838] Patients should be specifically instructed to eat only during "on" times to reduce the risk of aspiration. Feeding gastrostomies or jejunostomies are a last resort, and are only rarely necessary for patients with idiopathic PD. However, these procedures can provide the benefit of allowing more normal food and medication intake.

Seborrhea/blepharitis. Excessive secretion of oil by sebaceous glands with seborrhea of the head, face, and neck is common in PD. Coal tar shampoos can be used as a treatment for dandruff as well as for treating the seborrhea that develops over the eyebrows and forehead. Their use should be restricted to no more than twice weekly. Selenium-based shampoos may also work in some patients when used in a similar manner. Topical hydrocortisone is most effective on the face, but needs to be applied daily. Topical ketoconazole is an alternative treatment for seborrhea in patients with PD.

Blepharitis is an inflammation of the eye that is also a common problem in PD and can potentially

lead to keratitis. In most instances, it is related to a combination of seborrhea and decreased blinking. Initial treatment consists of the use of natural tears and warm compresses, applied three to four times per day. In more severe cases, steroid creams can be effective. If blinking is severely impaired, eye patches may be necessary at bedtime to avoid corneal abrasions from local trauma.

Falls. Falls are a leading cause of morbidity and mortality in the elderly population, and frequently contribute to the need for nursing home placement.[839] Falls are extremely common in patients with advanced PD and parkinsonism routinely emerges as a major risk factor for falls in surveys of the elderly.[840–843] Indeed, in a long-term prospective study of patients with PD followed up for 15 years, falling occurred in 81% of patients, with 23% having sustained a fracture.[9] Compared with age-matched controls, patients with PD had twice the frequency of fractures, with the most common site being the femur.[844]

There are many causes of falling in patients with PD. In one study, falls in patients with PD were related to unstable posture (29.0%), freezing or festination (25.8%), sudden loss of postural reflexes (toppling falls) (25.8%), coexisting neurologic disorders (6.5%), cardiologic disorders (6.5%), and symptomatic orthostatic hypotension (3.2%).[845] Falls in patients with PD may also be related to levodopa-induced dyskinesia, other medical disorders, and local environmental factors. Risk factors include older age, longer duration of disease, advanced stage of disease, rigidity, bradykinesia, inability to rise from a chair, gait impairment, postural instability, and levodopa-induced dyskinesia. Other factors include mental status changes, vestibular dysfunction, depression, impaired fine motor control and motor planning, decreased proximal muscle strength, and fear of falling.[846] One study found that falls occurred in 68% of consecutively evaluated patients with PD, and the independent predictors of falling included previous falls, disease duration, dementia, and loss of arm swing.[847]

Falls are more likely to occur in patients with atypical parkinsonisms, such as MSA and PSP, and these diagnoses should be considered when falls are a prominent feature, particularly early in the course of the illness. The clinician confronted with a patient with PD who is falling should not assume that the cause of all falls is the same. As falls may not be readily detected on physical examination, the clinician needs to take a careful history to discern the true frequency of falling and potential causes and contributing factors. Identification of the probable cause is obviously important for developing an effective treatment plan. The following is a brief review of the major causes of falls in patients with PD, and the appropriate preventive measures for each.

Postural instability. Impaired postural responses are most likely to cause a fall when the patient changes position (e.g., when turning, getting out of a chair, or bending over). The physical examination correlate is an abnormal "pull test" in which, after backward displacement, patients need to take an extra number of steps to catch themselves or cannot maintain their balance. The examiner should be sure to be in a position to catch patients when the pull test is used to prevent them from falling and injuring themselves. Occasionally, patients may experience toppling falls, characterized as falling like a log from a standing position with no apparent cause. Toppling falls tend to occur in patients with advanced PD with marked gait and balance impairment. Should toppling falls occur early in the course of PD, other causes such as PSP, MSA, or a multi-infarct state should be considered. Postural instability may respond to drug therapy early in the disease to the extent it can be improved by improvement of rigidity and bradykinesia. However, patients with more advanced PD typically fail to improve with levodopa or other dopaminergic agents. Pallidotomy and DBS of STN or GPi have a variable effect on postural response, but this is usually not greater than can be attained with levodopa. More recently, there has been interest in the potential value of stimulating the PPN as a treatment for gait dysfunction and postural instability in advanced PD,[527] but additional studies are needed.

Exercise, physical therapy (PT), gait training, and home safety assessment may be beneficial, particularly in making the patient and family aware of the problem and how to provide assistance so as to avoid falls. A recent randomized study demonstrated that home-based exercise training can reduce falls and serious injuries and improve quality of life.[848] Patients can be trained to consciously center their feet under their body to provide themselves with a more stable platform, and thereby minimize the risk of falling particularly when arising from a chair. Recent studies indicate that patients with PD have relatively normal swing and stance phases to their gait, but have difficulty with automatic dorsiflexion of the foot.[849] Patients should be advised to initiate gait by lifting their foot off the ground rather than dragging it forward along the ground which increases the risk that they will fall. Similarly, they can be taught to turn in an arc rather than pivoting in one place. In patients with more severe postural instability, walkers may be used to provide additional support. Eventually, patients may be so incapacitated that they require total assis-

tance to avoid falling and may be effectively confined to bed or a wheelchair.

Freezing of gait and festination. Freezing of gait refers to transient arrests of ambulation, with the patient's feet seeming to "stick" to the ground.[850] Freezing episodes are transient, lasting for a few seconds to a few minutes and may occur during either "on" or "off" periods. Freezing is most likely to occur when the patient initiates walking (start-hesitation), turns (turn-hesitation), passes through a doorway, or becomes distracted. In contrast to freezing, patients may festinate (from the Latin *festinare*—to run) as a result of their feet seeming to lag behind their center of gravity causing them to run forward thereby putting themselves at risk of falling. As the patient walks, the flexed trunk precedes the lower limbs leading the patient to take increasingly fast, but short steps that often end in a fall.

Freezing of gait is more common than is widely appreciated. In a recent study of 6,620 patients with PD, 47% experienced freezing on a regular basis.[851] Freezing was more common in men than in women, and was associated with longer disease duration and a more advanced stage of the disease. In contrast, freezing was less likely to occur in patients where tremor was their predominant feature. Occasionally, manipulation of levodopa dosage or adding a dopamine agonist may help, particularly if freezing occurs during "off" episodes. Pharmacologic treatment is usually ineffective in the more advanced stages of the disease.[850] STN stimulation may improve off-period, but not on-period, freezing of gait, similar to levodopa.[852] Rare cases have also been described of freezing induced by DBS performed in the region of the STN, but improved by repositioning of the electrode,[853] suggesting that targets in the vicinity of the STN can modulate freezing. Caffeine has been reported to benefit some patients with the akinetic (as opposed to the trembling) type of freezing, presumably because of A2A antagonism,[854] but tolerance tends to develop and this is not a practical solution to the problem. Botulinum toxin injections into the calf muscles have not been shown to be helpful.[855,856] Mechanical aids such as a walker, a tripod cane, or eventually a wheelchair may be necessary to prevent injurious falls. Motor and sensory tricks may occasionally be helpful to transiently overcome freezing episodes.[857] These include redistribution of body weight, walking sideways, performing rocking movements of the body, stamping the feet, walking briskly, and taking long steps. Patients may also use sensory stimuli to help initiate a movement when in the midst of a freezing spell. These can include trying to march like a soldier, walk to music, and clap hands. Visual stimuli can include stepping over objects such as the handle of a walking stick[496] or another person's foot, the use of a specially designed cane with swing-out appendages that can be opened during freezing episodes, mirroring other people walking, and imagining a line to step over. As patients with freezing tend to fall forward on their hands and knees, knee pads, wrist guards, and helmets may prevent injury. The precise cause of freezing of gait is not known. However, recent studies suggest that in levodopa-treated patients with PD virtually all SNc dopamine neurons fire even at rest, thereby limiting the dynamic range of the SNc and the capacity of a dopamine neuron to increase its firing rate and dopamine release in a stressful situation.[227] In this regard, it is interesting that freezing in some patients is improved by lowering the dose of dopaminergic therapies. It is also noteworthy that reduced frequency of freezing has been reported in patients who received early treatment with selegiline or rasagiline.[185,443] It will be interesting to determine if more physiologic approaches to administering levodopa will reduce the risk of freezing as with other motor complications.

Levodopa-induced dyskinesia. Levodopa-induced dyskinesia is a relatively infrequent cause of falling, and as a rule, patients do better in "on" than "off" states. Occasionally, however, dyskinesia may be so severe as to cause patients to fall. Treatment is aimed at better controlling dyskinesia (see earlier). In advanced stages, though, it may not be possible to induce periods of good mobility without complicating dyskinesia. Surgical treatments that ameliorate dyskinesia may reduce the risk of dyskinesia-related falls and in addition permit the use of higher doses of levodopa so as to reduce the severity and duration of "off" time.

Symptomatic orthostatic hypotension. Orthostatic hypotension can cause falls in patients with PD. Because there are specific treatments for hypotension (see earlier), it is critical to distinguish falls due to orthostatic hypotension from other causes of falling. Orthostatic hypotension may be suspected as a cause of falling when a patient reports falling within 1 or 2 minutes of standing, often accompanied by a sensation of light-headedness.

Other neurologic deficits. Nonparkinsonian neurologic deficits should also be considered as a cause of falls in patients with PD. These might include stroke, dementia, cervical or lumbar spine problems, sensory deficits (e.g., visual, vestibular, proprioceptive), cerebellar dysfunction, and generalized weakness. If clinical signs and symptoms suggest another neurologic condition, an appropriate workup should be performed and treatment instituted. Muscular weakness, particularly in the legs or hips, can be associated with falling.[858] Weakness should be evaluated and, if

possible, improved through the use of PT and strength-promoting exercises. Aging, arthritis, physical inactivity, and cardiac disease may contribute to muscle weakness. Impaired vision should also be considered, particularly as problems such as cataracts and refractive disorders are treatable. Vestibular dysfunction, decreased proprioception, and drug effects should also be addressed in the differential diagnosis of falling and be treated if appropriate. Ataxia accompanying parkinsonism is a potential cause of falls, and should raise the possibility that the patient has MSA. Other causes of falling, such as alcohol abuse and drug toxicity, should also be in the differential diagnosis. Patients with evidence of spasticity should be evaluated for cervical spondylosis, myelopathy, and cerebral infarction. Falling should also raise the possibility of an underlying delirium or dementia. Cognitive impairment is an independent risk factor for falls in the elderly, and patients with PD with dementia are at particular risk for falling. Medications can contribute to falling by causing orthostatic hypotension, fatigue, worsened neurologic deficits, or impaired mental alertness. Indeed, the total number of medications taken by a patient correlates with their risk of falling,[859] and accordingly medications should be reviewed and unnecessary drugs eliminated.

Medical causes. Stable patients with PD who suddenly begin to fall or have an acute increase in the frequency of falls should undergo a complete medical evaluation. Falls are a common manifestation of acute illnesses such as pneumonia and chronic conditions such as congestive heart failure.[859] Arthritis can predispose to falls, particularly when the hips and knees are affected, and the risk of falling may be diminished with the use of symptomatic therapy for the arthritis. Foot problems, such as bunions, corns, or diabetes-related neuropathy, can cause patients to be unstable on their feet and fall. Such patients might benefit from referral to a podiatrist. Unexplained falls, particularly with loss of consciousness, should raise the possibility of a cardiac source. In postmenopausal women, concurrent osteoporosis may increase the risk of a patient sustaining fracture with falling and should be addressed independently. Appropriate referral, evaluation, and treatment are important.

Environmental causes. It is important to consider environmental factors in assessing falls in patients with PD. Patients may fall because they wear poorly fitting or nonsupportive footwear. Shoes with crepe or other nonskid soles, high heels, or open toes can contribute to falls in patients with a shuffling gait. A podiatrist may be helpful in recommending appropriate footwear. Patients using walkers, canes, or other ambulation devices who continue to fall should be referred to a physical therapist for evaluation of these aids, because their improper use can increase rather than decrease the risk of falls. In addition, a trained physical or occupational therapist can make a home visit to evaluate areas for improvement in home safety (e.g., loose throw rugs, torn carpeting, slippery surfaces, small objects on the floor, poor lighting, unsafe stairways). As the chances of falling are proportional to the number of risk factors,[851,859] everything possible should be done to correct environmental factors associated with falls.[860]

In summary, prevention is the best strategy for managing falls in the patient with PD. The underlying cause of falling should be determined and corrected if possible. For patients with postural instability or freezing, an attempt should be made to identify the relationship between falling and the timing of dopaminergic therapy, and treatment adjusted accordingly. In all falls, the possibility of an underlying medical or neurologic condition should be investigated and corrected, if possible. A thorough medication history of prescription agents, over-the-counter drugs, and health food products should be obtained. Drugs can contribute to falls, particularly psychoactive drugs, hypotensive medications, and alcohol. These should be identified and either discontinued or reduced, if possible. PT can improve strength, cardiovascular fitness, and balance. Educating the patient and caregiver about safe ambulation is likewise important. Trained physical or occupational therapists can provide home safety evaluations to correct environmental factors that increase the risk of falls.

Not all risk factors are correctable, and even after optimal treatment many patients will continue to experience falls. The use of a wheelchair may be the best solution for these patients.

Sleep disorders in PD. Sleep disturbances in PD were recognized by Parkinson[1] in his classic monograph, noting that "Sleep becomes much disturbed. Tremulous motions of the limbs occur during sleep, and augment until they awaken the patient, and frequently with much agitation and alarm." This was perhaps the first description of RBD. Patients with PD are prone to have sleep disturbances that result in EDS and require proper identification and treatment.[361,362,368,861-864] With normal aging, there is disruption of normal sleep architecture and alterations in the normal circadian rhythm leading to impaired nocturnal sleep and EDS.[865,866] These problems are accentuated in patients with PD, of whom 60% to 90% have some form of sleep disturbance, particularly in the more advanced stages of the disease.[361,861,867-869] Sleep dysfunction in PD is usually manifest by difficulty in initiating sleep, fragmented

sleep, reversal of the sleep cycle, and EDS.[862,869,870] Daytime sleepiness was assessed with the Epworth scale in 101 consecutive patients with PD and 100 age-matched controls.[374] EDS was detected in 76% of patients with PD compared with 47% of controls ($p < 0.05$). Indeed, 24% of patients with PD had scores in the diagnostic range of narcolepsy, compared with only 5% of controls ($p < 0.001$).

Sleep disturbances in PD are multifactorial and may be related to aging, parkinsonian motor dysfunction, dyskinesia, pain, nocturia, nightmares, dopaminergic and nondopaminergic medications, cognitive impairment, and a variety of specific sleep disorders, including restless legs syndrome (RLS), periodic limb movements of sleep (PLMS), RBD, and sleep apnea. Collectively, they contribute to the increase in daytime sleepiness that is so frequently found in patients with PD.[871] It is also clear that dopaminergic medications and particularly dopamine agonists can have a complex effect on sleep. Sometimes these medications cause insomnia, and their sedative properties may contribute to daytime sleepiness.[308,328,366,372-374] In other situations they may improve nocturnal immobility, and in this way improve the quality of sleep.[872,873] Thus, dopaminergic medications can either improve or worsen sleep in patients with PD.

Impaired cognition also increases the likelihood that there will be sleep problems in patients with PD. Indeed, sundowning in patients with PD can be more troublesome than in patients with AD.[874] This is reflected by the concurrence of night-time hallucinations and sleep disturbances in patients with PD. One study evaluated the relationships among hallucinations, illusions, sleep fragmentation, and altered dream phenomena in 126 patients with PD.[875] Up to 82% of those with hallucinations had a sleep disorder (15% with sleep fragmentation, 12% with altered dream phenomena, and 55% with both).[875] Conversely, daytime sleepiness in patients with PD is predictive of the development of visual hallucinations.[691] Indeed, it has been suggested that degeneration of brainstem structures in PD might be responsible for the development of both RBD and hallucinations.[876]

The anatomic basis of sleep disturbances in PD is not fully understood, but likely involves degeneration of both the dopaminergic and the nondopaminergic systems. Dopamine neurons that project from the ventral tegmental area to the cerebral cortex are thought to be involved in arousal mechanisms.[877] More recently, studies using expression of early genes suggest that brainstem dopaminergic neurons in the periaqueductal gray are primarily involved in wake and arousal cycles in rodents.[878] Dopamine itself plays a complex role in sleep. It has long been known that activation of dopamine receptors can mediate sedation and sleep.[879] Conversely, dopamine agonists can produce arousal and reduce REM sleep, whereas dopamine receptor antagonists induce sedation with increased REM sleep.[880,881] More recently, sleep has been studied in DAT knockout mice, which are characterized by high levels of extracellular dopamine.[882,883] Phenotypically, the homozygous knockout mice showed significantly reduced non-REM sleep time and increased wakefulness compared with their heterozygous and wild-type littermates. Other experiments have looked at sleep in the MPTP mouse model to assess the effect of dopamine depletion. MPTP-treated mice had a significantly greater amount of REM sleep during both light and dark phases than did controls.[884] In patients with PD, levodopa has been reported to both improve and disrupt sleep, with higher doses causing higher levels of nocturnal activity and more disturbed sleep. Similarly, high doses of apomorphine have been shown to reduce REM activity and impair sleep, whereas low doses increase total nocturnal sleep time.[885] In these studies, the extent of sleep disruption correlated more closely with the dose of the dopaminergic agent used than with disease severity. It may be that low doses of dopaminergic agents improve sleep by controlling parkinsonian dysfunction, whereas higher doses induce adverse effects that outweigh these benefits. In this regard, it is noteworthy that the patients reported to have experienced unintended sleep episodes while driving[363] were receiving relatively high doses of dopaminergic medications (see earlier). These observations highlight the importance of dopamine in maintenance of wakefulness.

Nondopaminergic neurons and systems have also been implicated in sleep dysfunction in PD. Neuronal degeneration is found in numerous nondopaminergic regions of the brainstem and hypothalamus that are thought to mediate sleep homoeostasis. These include serotonin neurons in the raphe nucleus, norepinephrine neurons in the locus coeruleus, cholinergic neurons in the PPN, and hypocretin cells in the hypothalamus, which secrete melanin-concentrating hormone.[886] Degeneration of neurons in these sleep–wake cycle-related pathways (the flip-flop switch), which are associated with thalamocortical arousal, could contribute to the development of sleep dysfunction in PD.[887] The PPN has attracted particular attention because it is intimately related to the anatomic control of sleep and is thought to play a critical role in mediating inhibition of voluntary muscles during REM.[870,888] It receives major inputs from the STN and GPi, which are markedly altered in PD, and projects to multiple basal ganglia nuclei, including the SNc. Furthermore, neuronal cell loss and gli-

osis with activated microglia have been detected in the PPN in PD.[888,889] These findings suggest that degeneration and altered regulation of the PPN and other brainstem nuclei likely play an important role in the pathophysiology of sleep disturbances in PD. Indeed, studies by Braak et al.[5] suggest that pathologic changes in the PPN and other brainstem nuclei may antedate the development of dopaminergic changes in the SNc in patients with PD. In this regard, it is interesting to note that PD pathology in the PPN is found in RBD,[889] RBD is commonly seen in PD,[82] and RBD frequently precedes the onset of motor features in patients with PD.[81]

Insomnia and sleep fragmentation. Frequent nighttime awakening is the most common sleep problem in patients with PD.[869] Difficulty with the initiation and maintenance of sleep may be a component of a primary sleep disorder or secondary to advancing PD, dementia, or depression. These may all contribute to sleep dysfunction in PD, and it is important for the clinician to assess and treat each of these components. Sleep disruption can occur during any stage of sleep, but is most common during the lighter stages (stages 1 and 2). Sleep can be disrupted in patients with PD by parkinsonian features such as akinesia, tremor, painful rigidity with stiffness, and impaired ability to turn in bed. Dyskinesia may interfere with sleep as well.

Inability to fall asleep is common among patients with PD, and a diagnosis of insomnia or fragmented sleep may be made based on the patient's or the caregiver's description. Sleep patterns can be further clarified with the use of a home diary or all-night polysomnography (PSG) or actigraphy.[863,867,870] In evaluating insomnia or other sleep disturbances in patients with PD, it is important to obtain a careful sleep history from both the patient and the bed partner to determine how the patient sleeps and the nature of any sleep disturbance. Specifically, information should be gathered regarding the ability of the patient to turn over in bed or adjust sheets without assistance, the frequency of nocturia, and the occurrence of nightmares or other parasomnias. A PDSS has been developed to assess nocturnal problems in PD, and has been shown to have good reproducibility, low floor and high ceiling effects, and to successfully discriminate between healthy controls and patients with PD.[369] Furthermore, PDSS scores were markedly different in patients with PD with early/moderate and advanced disease.

In treating patients with insomnia or fragmented sleep, proper sleep hygiene can be helpful.[375,890] Setting a regular time for rising and going to bed and providing bright light during the day and darkness at night can be important for setting and maintaining the circadian clock. Patients should be advised not to spend time in bed reading or watching television, but should use the bedroom primarily as a place of sleep. Physical aids such as satin sheets (for greater ease of movement) and condom catheters to deal with nocturnal urinary frequency and urgency may be helpful. Alcohol, caffeine, and tobacco should be avoided during the latter part of the day and liquid intake restriction before bed may reduce the frequency of nocturia. Drugs such as ditropan and detrusitol may reduce bladder hyperreflexia present in the majority of patients with PD and desmopressin nasal spray may reduce the production of urine during the night.[774] Attention should also be directed to treating nocturnal PD symptoms or drug-induced motor complications. Difficulty getting comfortable or turning in bed is often due to underdosage of dopaminergic medications or wearing off of their beneficial effects. Bedtime administration of a long-acting dopaminergic agent such as a controlled-release formulation of levodopa or a dopamine agonist may all be useful in providing more sustained antiparkinsonian benefits during the night. They may also be helpful in reducing early-morning waking because of painful dystonia. In these respects, there is considerable interest in the rotigotine patch and the extended release formulation of ropinirole which provide round the clock drug delivery and may be particularly valuable in the treatment of nocturnal problems.[347,348] Occasionally, dyskinesias can be so severe as to interfere with sleep. If such is the case, bedtime dopaminergic dosages should be decreased. If patients are taking selegiline, the last dose should be given no later than noon to avoid the possibility of insomnia related to its amphetamine metabolites. If insomnia remains a problem, consider elimination of the drug altogether or substituting rasagiline, which does not generate amphetamine metabolites. Amantadine may also produce insomnia because of its stimulatory effects and dose reduction or discontinuation of the drug should be considered.

The management of idiopathic insomnia has been reviewed elsewhere.[890] In general, long-term use of sedative hypnotics is not recommended because physical dependence may occur and cognitive side effects are common. If these types of drugs are used, shorter-acting agents are preferred. Melatonin formulations have been shown to be effective for treating insomnia in the elderly, but have not been specifically tested in PD.[891] If routine measures fail to control insomnia, the patient should be referred to a sleep specialist to consider the need for further testing with PSG to rule out a sleep disorder. Dementia may also be associated with difficulty in maintaining nocturnal sleep and disruption of the sleep–wake cycle. Patients with insomnia should be questioned

about possible depression and, if indicated, appropriate treatment should be initiated.[892] Such a program could include increased daytime activities, counseling, and the use of antidepressant medications. The soporific effects of TCAs can promote sleep onset and sleep consolidation. Typical choices include amitriptyline or nortriptyline, 10 to 25 mg at bedtime. Maximum dosages are usually less than 100 mg because of the high frequency of side effects, especially in elderly patients. An alternative approach is to treat the depression with an SSRI. Although these drugs have less sedating effects, treatment of the depression per se can improve nocturnal sleep disruption. Quetiapine has sedative properties and can help both nighttime hallucinations and insomnia.

Nightmares and parasomnias. Parasomnias, including nightmares, vivid dreams, night terrors, somnambulism, vocalizations, hallucinosis, panic attacks, and RBD, frequently complicate nighttime sleep in patients with PD.[893] These may occur secondary to medication, be idiopathic, or be associated with dementia. It is important to distinguish between vivid dreams or nightmares and RBD, as there are differences in treatment. Nightmares are typically reported by patients who may be frightened by them, whereas patients themselves are usually unaware of RBD-related problems and complaints are usually voiced by bed partners. Aggressive behavior with injury to the patient or the bed partner suggests RBD. Dopaminergic medications may improve symptoms of RBD, but these drugs frequently induce vivid dreams and nightmares in patients with PD. Patients with PD often note a return of previously absent dreaming shortly after initiation of levodopa therapy. Generally, it is only after several years of treatment and with the use of higher doses of levodopa that vivid dreams become problematic.[894] A reduction in the use of dopaminergic drugs at night can alleviate nightmares in some patients. Elimination or reduction of TCAs can also be beneficial. If optimal motor function necessitates the nighttime use of dopaminergic drugs that produce psychosis or nightmares, treatment with a low dose of a selective, "atypical" neuroleptic such as quetiapine can be helpful. Treatment may only be required 3 to 4 nights per week.

RBD and PD. RBD is characterized by vigorous and potentially injurious motor and vocal behaviors during REM sleep that are thought to represent an attempted enactment of vivid, action-filled, dreams.[895-897] Normally, there is a loss of muscle tone during REM sleep with the exception of respiratory, sphincter, extra-ocular, and middle ear muscles. Thus, in the normal situation, dreaming during REM sleep is not accompanied by motor activity or physical reenactment of dreams. The cause of violent behavior in RBD is the loss of muscle atonia that normally accompanies REM sleep, allowing people to "act out" their dreams. It is interesting that in patients with PD, speech and speed of movements are improved during REM episodes as shown by PSG and by the report of bed partners.[896,898] It has been suggested that the restored motor or cognitive. control during REM sleep represents a transient reestablishment of the basal ganglia loop, or that parkinsonian features may be mitigated by a REM sleep-related disconnection between the pyramidal and extrapyramidal systems.[898]

It is now appreciated that there is a strong relationship between RBD and α-synucleinopathies, such as PD, MSA, and DLB, and that RBD frequently precedes the onset of the more classic motor or cognitive features of these degenerative disorders. In one study, RBD was found to have preceded the onset of PD symptoms in 52% of patients, whereas a detailed motor examination of patients with RBD without PD revealed subtle impairments in motor function that may turn out to be a harbinger for the subsequent development of PD.[899] In a prospective trial, 11 of 29 patients with RBD (all 50 years of age or older) developed PD with a mean interval of 3.7 years after diagnosis of RBD and a mean interval of 12.7 years after symptom onset.[81] In another, 57% of 93 patients with RBD had coexisting neurologic disorders, with 86% of these being PD, dementia, and MSA.[82] RBD in patients with PD is frequently seen in association with visual hallucinations.[900] The presence of RBD in patients with PD is also frequently associated with neuropsychiatric problems and cognitive impairment. In a study of 79 patients with PD, visual hallucinations were found in 58% of those who had RBD, whereas RBD was found in 55% of those with visual hallucinations.[91] RBD is also commonly seen in association with DLB,[901] and the presence of RBD in a patient with PD without dementia predicts the subsequent development of cognitive impairment.[902]

The etiology of RBD in PD is uncertain, but neurodegenerative processes affecting brainstem cholinergic, serotonergic, and noradrenergic regions, such as the PPN and locus coeruleus-subcoeruleus complex, may be responsible.[888,903] Neuropathologic examination of the brainstem nuclei in patients with RBD but no motor disturbances reveals neuronal loss, depigmentation, gliosis, and even Lewy bodies in the locus coeruleus-subcoeruleus complex as well as in the SNc, a pathologic pattern suggestive of early PD.[757,904,905] A relationship between RBD and PD is further supported by neuropathologic data from the studies of Braak et al.,[5,906] which indicate that there is early involvement of the lower brainstem in the PD neurodegenerative process. It should be appreciated that RBD can also be seen

in other α-synucleinopathies such as multiple systems atrophy and Lewy body dementia.[901,904,907,908]

RBD in patients with PD may be effectively treated with low-dose clonazepam (0.25 to 1.0 mg nightly). Tricyclic drugs and MAO inhibitors may precipitate or unmask RBD and should not be used.[909]

RLS, PLMS, and akathisia. RLS is relatively common in elderly individuals (approximately 5% to 15% occurrence) and can contribute to nighttime sleep difficulties in patients with PD.[910] Clinicians should be aware of the varied manifestations of RLS, which may include uncomfortable sensations in the legs, paresthesias, aches, cramping, and an overwhelming need to move or walk. Symptoms tend to be worse in the evening or in the early nighttime and to improve when the patient is up and walking, stretching, or exercising. Symptoms can occasionally persist into the daytime, and the upper extremities can be involved in some cases. RLS can be familial and has been linked to five different loci, although no specific gene mutation has yet been identified.[911] It may also be associated with a variety of medical conditions, including chronic renal failure, neuropathy, pregnancy, and iron deficiency.[912] Persons whose RLS symptoms begin before the age of 45 years are more likely to have a family history of RLS and to have a more slowly progressive course. There is some debate as to whether or not RLS occurs more frequently in patients with PD. Most reports suggest that RLS does occur with increased frequency in patients with PD compared with the general population,[913] and it is not uncommon for RLS symptoms to begin after the diagnosis of PD has been established.[914] In one case-control study, RLS had a weak association with PD and was six times more likely to occur in patients with PD than controls, but was not a major contributor to sleep dysfunction in these patients.[915]

The pathophysiologic basis of RLS is not known, but dysfunction of dopamine neurons in the striatum, spinal cord, and A1 neurons of the hypothalamus have been implicated as they modulate spinal excitability and sensory processing of leg afferents, and because dopaminergic therapies are effective in the treatment of this disorder.[916] This of course has led to speculation on a possible relationship between RLS and PD,[917] although as indicated above this has not as yet been conclusively established.

In idiopathic RLS, dopaminergic agents are the treatment of choice, and dramatic benefits have been observed with bedtime doses of numerous dopamine agonists, including pergolide, pramipexole, ropinirole, cabergoline, and rotigotine.[918-924] Lower doses are generally recommended, as they are effective and higher doses increase the risk of augmentation.[925] There is a particular risk of augmentation with levodopa, which may relate to its short half-life. However, levodopa-induced augmentation is associated with increased CSF dopamine levels, which may reflect overstimulation of D1 receptors in the spinal cord.[926] It is not known how or if dopaminergic alterations reported in RLS contribute to the pathophysiology of the condition, or if levodopa treatment aggravates RLS in patients who do not have PD.

Dopamine agonists are the first-line therapy for RLS in PD as well, but not all patients respond and many patients with PD develop augmentation with levodopa. In these cases, other treatment options like low-dose gabapentin, clonazepam, or opiates (e.g., codeine, 30 to 60 mg nightly) should be considered. TCAs may exacerbate RLS and should be avoided. The effect of long-acting therapy in the treatment of RLS in PD such as patch rotigotine or the extended release formulation of ropinirole is currently being investigated. It is noteworthy that pathologic gambling and hypersexuality have been described with the use of low-dose dopamine agonists in the treatment of RLS.[927]

Approximately 50% of patients with RLS have associated PLMS,[928] but PLMS can occur in isolation and interfere with nighttime sleep. Termed "nocturnal myoclonus" in the past, this syndrome can be so mild that it can only be detected with PSG or so severe that it forces the bed partner to sleep in a separate room. The movements can resemble fragments of the triple flexion or Babinski response, last 0.5 to 6 seconds, and may occur at 20- to 40-second intervals. These movements can profoundly disrupt normal sleep architecture, leading to insomnia and EDS. They tend to respond dramatically to levodopa and dopamine agonists, implying that they are somehow related to reduced dopamine activity in the brain or spinal cord. However, the specific neuronal systems that are responsible for these movements have yet to be determined. It has also not been established if the incidence of PLMS is higher in patients with PD compared with age-matched controls, although PLMS have been reported to occur in as many as one third of patients with PD.[895] Although RLS and PD can both respond to dopaminergic agents, neuroimaging and neuropathology suggest they are distinct entities.

Akathisia is characterized by excessive, usually repetitive, movements, and a feeling described as if "you are going to come out of your own skin if you don't move." It is usually seen as a side effect of neuroleptic medications but may also occur in PD and must be distinguished from RLS. In PD, it is most often related to underdosage or wearing off of the levodopa effect.[929] If akathisia is suspected, adjust-

ment of antiparkinsonian medications or treatment with clozapine may be helpful.[930]

Sleep apnea. It is generally believed that sleep apnea is not a major or frequent cause of sleep disruption in PD. However, recent evidence suggests that sleep apnea in PD may be more frequent than was previously suspected. In one study, 20% of patients with PD tested had moderate to severe sleep apnea despite normal body mass index.[931] Another study based on PSG revealed that there was an increased incidence of obstructive sleep apnea in patients with PD compared with age-matched controls.[932] As sleep apnea is a potentially treatable disorder that may be associated with additional medical problems, physicians should be aware of this possibility in patients with PD with sleep dysfunction and evaluate and treat accordingly.

Excessive daytime sleepiness and unintended sleep episodes. Because of the many potential problems that can interfere with nocturnal sleep in patients with PD and the tendency of dopaminergic medications to induce sedation, EDS is a common problem.[933,934] Indeed, polysomnographic recordings indicate that the average patient with PD obtains only 4 to 5 hours of documented sleep per night, instead of the approximately 8 hours that are normally required.[893,894] In one study, 76% of consecutive patients with PD reported EDS, compared with 47% of age-matched controls ($p < 0.05$), and 24% had sleep scores in the range of patients with narcolepsy, compared with only 5% of controls ($p < 0.001$).[374] Patients with EDS have a tendency to fall asleep in unintended situations. Typically, these occur in relatively benign situations that are conducive to falling asleep such as while watching TV, listening to a lecture, or reading quietly. However, in extreme situations patients may fall asleep during a meal, while in conversation, and in potentially dangerous situations such as when driving a motor vehicle or operating heavy machinery. The problem is complicated by the fact that many patients are not aware they are sleepy before falling asleep because they have become tolerant to the sensation of chronic sleepiness, and do not remember their sleepiness before falling asleep because of the amnestic effects of sleep. To identify sleepiness in an individual patient, it may be necessary to use sleep questionnaires such as the ESS,[368] which do not rely on subjective estimates of sleepiness, but rather on a measure of the propensity of the patient to fall asleep. The ESS has been shown to correlate with more expensive and time-consuming tests such as the Multiple Sleep Latency Test (MSLT) in patients with sleep apnea.[368]

The importance of addressing EDS in PD was highlighted by a report of eight patients who suddenly fell asleep while driving a motor vehicle.[363] These episodes were termed sleep attacks by the author because they seemed to have occurred without warning, and were attributed to dopamine agonists because they disappeared when the drugs were withdrawn. This report generated intense interest in the nature and frequency of sleep disturbances in PD and a debate as to how these episodes are related to the use of dopamine agonists. Indeed, sudden onset of REM sleep, which may occur with hallucinations, has been described in patients with PD, raising the possibility that alterations in neural mechanisms in PD may contribute to sudden onset sleep episodes.[935] However, others have suggested that sleep attacks in patients with PD are more likely to represent an extreme form of EDS due to the combination of a sleep disturbance and the sedative effects of dopaminergic medications.[366] Sleep attacks in which patients fall asleep without an antecedent warning of sleepiness are not known to occur either physiologically or in association with pathologic conditions.[368] For this reason, the concept of a "sleep attack" has been abandoned even in narcolepsy and is not included in the classification of sleep abnormalities recognized by the American Sleep Disorder Association.[936] Rather, it was proposed that sleep attacks represent an extreme form of sedation in patients who were sleep deprived and on sedative medications, and would be better termed "unintended sleep episodes." The concept of a sleep attack implies that the events are inevitable and occur without any warning whatsoever. The notion of unintended sleep episodes implies that at-risk individuals can be identified and the episodes prevented by instituting appropriate treatment measures.

Although sleep attacks were initially described in patients receiving pramipexole and ropinirole, it is clear that sedative effects and unintended sleep episodes can be seen with any of the dopaminergic agents, including levodopa,[364,365,937,938] and that these effects are dose related, occurring with greater frequency in patients taking relatively high doses. Thus, somnolence is more likely to occur in patients taking higher doses of dopaminergic medications and is greatest when a given dose reaches its maximal concentration. Indeed, patients who had unintended sleep episodes while taking pramipexole were receiving larger daily doses (3.5 to 4.5 mg)[363,938] than those shown in clinical trials to provide maximal clinical benefit (1.5 mg).[328]

It is generally thought that EDS in patients with PD results from impaired nocturnal sleep. However, not all studies confirm this concept. The "FAST TRACK" study evaluated daytime sleepiness with MSLT. In 27 patients with PD, MSLT scores did not correlate with quantity and quality of previous night's sleep or other sleep architecture measures

such as sleep stage percentages and total sleep time.[939] Similarly, in another study, no correlation was found between MSLT score and total sleep time, sleep efficiency, arousal index, apnea-hypopnea, or periodic leg movement indices.[931] These studies suggest that the quality of night time sleep may not be the only factor responsible for daytime sleepiness.

Whatever the mechanism, EDS is present in a large number of patients with PD. Varying estimates have been reported, ranging from 15% to 75%.[370,374,940-946] The wide variation in the prevalence of EDS in patients with PD is probably due to the different populations studied and the tools used to assess the presence of EDS. The most commonly used tools are the ESS, Scales for Outcomes in PD (SCOPA-SLEEP), PDSS, MSLT, and PSG. In one study comparing 419 patients with PD and 150 controls, EDS was detected in 43% of patients with PD, compared with only 10% of controls.[947] A nationwide survey for evaluating EDS and dozing off behind the wheel was carried out in France, using the ESS questionnaire.[946] Of the 1,625 patients with PD who completed the ESS questionnaire, EDS was reported in 29%, dozing off behind the wheel in 0.8%, and sudden onset of sleep episodes while driving in 0.5% of patients.[946] The possibility that dopaminergic medications, and especially dopamine agonists, may aggravate EDS has attracted considerable attention, again driven by the observation that all patients who fell asleep while driving in the seminal 1999 report of this problem were receiving high doses of dopamine agonists.[363] In a controlled study involving 100 consecutive patients with PD, 21% of patients with PD had fallen asleep at the wheel in the past 3 years compared with 6.5% in the control group.[374] Among patients with PD, the daily dopaminergic load was almost twice as high in those who had experienced sleep episodes while driving compared with those who had not. All dopamine agonists seem to have a similar capacity to induce EDS and sleep episodes, with dose being the primary factor. PSG studies have similarly demonstrated that total dopaminergic dose rather than the specific dopaminergic agent was the best predictor of EDS, as MSLT scores of patients on the different dopaminergic therapies were similar.[940]

The relative contributions of dopamine agonists and the disease process have not been established. In an 8-year longitudinal study, there was a steady increase in the rate of EDS in patients with PD, from 5.6% at baseline to 22.5% at 4 years and 44.9% at 8 years.[943] However, similar increases were noted in those who did, and did not, receive dopamine agonists. Another study similarly showed that patients on levodopa alone had MSLT scores similar to those receiving both levodopa and a dopamine agonist.[933] These observations suggest that while dopamine agonists may induce or exacerbate EDS, there are other contributing factors. Autonomic dysfunction has also been implicated, with 70% of dysautonomic patients with PD reporting sleep attacks compared with 17.8% of nondysautonomic patients with PD.[948] Table 23 summarizes studies that have reported on

Table 23 Studies on EDS in PD patients

Year	Author	PD (n)	Controls (n)	EDS-PD (%)	EDS-Controls (%)	Sleep attacks PD (%)
2007	Ghorayeb et al.[946]	1,625	—	29	—	—
2008	Verbaan et al.[947]	420	150	43	10	0.5
2007	Amick et al.[945]	21	—	24	—	0
2007	Boddy et al.[949]	31	37	42	16	—
2006	Gjerstad et al.[943]	89	—	44.9	—	—
2006	Shpirer et al.[950]	46	30	50	—	—
2006	Ferreira et al.[942]	176	174	33.5	16.1	27.5
2006	Monaca et al.[951]	222	—	43.2	—	28.4
2005	Wegelin et al.[952]	22	16	59	31	—
2004	Razmy et al.[940]	80	—	43	—	0
2004	Körner et al.[953]	6,620	—	—	—	42.9
2003	Kumar et al.[954]	149	115	21.47	3	—
2003	Brodsky et al.[374]	101	100	76	47	20.8
2003	Schlesinger and Ravin[955]	70	—	—	—	34.3
2003	Högl et al.[956]	99	44	33	11.4	—
2003	Paus et al.[371]	2,952	—	—	—	16
2002	Hobson et al.[370]	638	—	51	—	3.8

PD = Parkinson disease; EDS = excess daytime sleepiness.

Table 24 Causes of excessive daytime sleepiness in patients with PD

Age-related changes in sleep architecture and circadian rhythm
PD-related disturbance in sleep–wake regulation
Disturbed nocturnal sleep as a result of PD-related motor symptoms (akinesia/bradykinesia, tremor rigidity)
Parasomnias with vivid dreams, nightmares, hallucinations
Sleep disorders such as RLS, RBD, sleep apnea
Coexisting medical and psychiatric conditions such as urinary frequency and depression
Medications that can cause sedation
Dopaminergic drugs (dopamine agonists, L-dopa, selegiline)
Other antiparkinsonian agents (anticholinergics, amantadine)
Sedative medications; benzodiazepines, antidepressants, neuroleptics, and anxiolytics
Endocrine dysfunction such as hypothyroidism

PD = Parkinson disease; RLS = restless legs syndrome; RBD = REM behavior disorder.
Reproduced with permission from Olanow et al.[15]

Table 25 Management options for excessive daytime sleepiness and unintended sleep episodes[375]

Ensure correct diagnosis: rule out syncope, seizures, cardiac disorder
Assess with validated sleepiness scale (e.g., Epworth)
Counsel patients on risks of daytime sleepiness and sudden sleep episodes
Consider need for polysomnography and possibility of sleep disorder (e.g., sleep apnea, RLS) and treat where appropriate
Teach patients how to improve sleep hygiene
Improve management of parkinsonian motor symptoms with dopaminergic agents
Reduce, eliminate, or reschedule concomitant sedating medications (e.g., benzodiazepines, antidepressants) or medications that interfere with drug metabolism
Use lowest dose of dopaminergic agent that provides good clinical response
Reduce dosage of dopaminergic agent if patient has evidence of excessive daytime sleepiness
Evaluate for possible contributing medical conditions (e.g., hypothyroidism)
Evaluate for depression and treat accordingly

RLS = restless legs syndrome.

EDS in patients with PD. Factors that can contribute to excessive daytime sleepiness in PD patients are shown in table 24.

Management approaches to the treatment of EDS and unintended sleep episodes are listed in table 25.[375] The first step is to identify at-risk patients. To accomplish this, the physician or ancillary personnel must inquire about EDS from both the patient and a caregiver who might provide a more objective assessment of the patient's sleep habits. Furthermore, patients may not recognize that they are sleepy, as they may have become tolerant to the sensation of chronic tiredness. As described above, the ESS provides a quick and reliable assessment of sleepiness based on the propensity of the patient to fall asleep in unintended situations, and does not rely on the patient's subjective awareness of whether or not they are sleepy. ESS scores greater that 10 are considered to be in the "sleepy" range, and such patients are at higher risk for experiencing unintended episodes of falling asleep. This should alert the physician to consider potential contributing factors (table 23) and take corrective action. Management options include introducing proper sleep hygiene, eliminating unnecessary sedative medications, using the lowest dose of dopaminergic medication that provides satisfactory clinical control, and identifying and treating sleep disorders.

If alterations in dopaminergic medications fail to help EDS, one can consider adding a wakefulness-promoting agent like modafinil (Provigil). This is a nonamphetamine drug that is used in narcolepsy. Early open-label reports were promising,[957,958] but double-blind, controlled studies showed only modest benefit[959,960] or failed to provide benefit.[961] In the clinic, the drug may be useful in treating EDS in individual patients with PD. It should be started at a dose of 100 mg and increased to 200 to 400 mg/d as necessary. Side effects include headaches and insomnia.

Patients with EDS should not drive a motor vehicle until this problem has been corrected. Indeed, European agencies have suggested that patients with PD taking dopamine agonists should not drive at all, although we believe that this recommendation is too harsh and that patients may safely drive, subject to the treatment guidelines described in table 25.

NONPHARMACOLOGIC TREATMENTS FOR PD

Nonpharmacologic interventions are fundamental elements of the overall management of patients with PD. It is important for physicians, who tend to concentrate on pharmacologic and surgical approaches to the disease, to also recognize the importance of these essential aspects of the management of patients with PD. They include education, support services, professional, legal and financial counseling, management of emotional needs, exercise, nutrition, help in the home, and need for respite care. It is also important to consider the needs of the caregiver. Caregivers perform an average of 23 tasks per day on behalf of patients with stage III PD, and 30 for patients in stage IV/V of the disease,[962] underscoring the physical burden they bear. In the early stages, it may only be necessary to provide educational and support ser-

vices. Later, the clinician may have to evaluate the need for home health care and/or respite services.[963,964] Physicians should also recognize that pessimism among caregivers can predict poor outcomes for both the patient and the caregiver.[965,966]

Education. Education provides the patient with PD and their caregiver with an understanding of their disease and a sense of control even as the disease continues to progress.[962] Conversely, patients and caregivers should be aware that in the early stages of PD, knowledge of the potential consequences of the disease can be alarming and anxiety provoking. At this stage, selective or at least filtered information is generally more helpful. Patients and families can be referred to the PD literature that is available through the national PD organizations, books written for the lay public, patient/family symposia, and information on the Internet. Patients should, however, be aware that PD is a heterogeneous disorder and that information obtained may not be applicable to their specific situation, or may be incorrect. Patient with PD tend to be well educated about their disease and often bring new treatments to the attention of their physician. However, one must take care to ensure that the information being disseminated is reputable and has been scrutinized by PD authorities, particularly if it is derived from the Internet. Misinformation, can lead to unauthorized, inappropriate, and potentially harmful treatments, diets, exercise programs, etc. Web sites associated with the major PD foundations provide an important educational resource (see later). Some books on PD that are intended for lay persons are listed below:

Caring for the Parkinson Patient: A Practical Guide. Second edition (1999)
J. Thomas Hutton and Raye Lynne Dippel, eds.
Prometheus books

American College of Physicians Home Medical Guide: Parkinson's Disease (2000)
David R. Goldmann and David A. Horowitz, eds.
DK Pub Merchandise

Parkinson's Disease and the Art of Moving (2000)
John Argue
New Harbinger Publications

Parkinson's Disease: Questions and Answers, Fourth Edition (2003)
Kelly E. Lyons, Rajesh Pahwa, Theresa A. Zesiewicz, Lawrence I. Golbe, Robert A. Hauser, eds.
Merit Publishing International

What Your Doctor May Not Tell You About Parkinson's Disease: A Holistic Program for Optimal Wellness (2003)
Jill Marjama-Lyons, Mary J. Shomon
Warner Books

Parkinson's Disease: 300 Tips for Making Life Easier (2006)
Shelley Peterman Schwarz
Demos Publishing

Parkinson's Disease: A Complete Guide for Patients and Families (2007)
William J. Weiner, Lisa M. Shulman, Anthony E. Lang
Johns Hopkins Press

Parkinson's Disease for Dummies (2007)
Michele Tagliati, Gary Guten, Jo Horne, eds.
Wiley Press

Support services. Patients and their families frequently need help in living with and adapting to a chronic, progressive illness. There are a number of useful support strategies that help patients and families cope with PD.

Emotional needs assessment. Healthcare providers should routinely assess the emotional status and needs of the patient, the caregiver, and family members. Particular attention should be addressed to the coping abilities of the caregiver. Patients and family members should be questioned about the presence of depression, anxiety, stress, anger, and worry. The needs of patients and family members can be very different and should be assessed separately. Families often have the least amount of support from healthcare providers, but may desperately need help because of the impact of PD on their own lives.[967] Problems may include physical strain, sleep deprivation, depression, stress, financial problems, and concern about nursing home placement. A healthy and well-informed caregiver is a valuable resource for the patient with PD. A better understanding of the caregiver's needs allows for more appropriate intervention on the part of the healthcare professional.[948] Emotional needs and coping strategies for patients and caregivers change as the disease progresses, and this assessment should be an ongoing process.[968]

Peer and group support. Support groups can offer psychological and social benefits to both patient and family. The value of peer support and support groups has been well established in chronic neurodegenerative diseases.[964,969] Studies have shown that interaction with others who have had similar experiences can positively affect the psychological well-being of patients and caregivers and reduce the overall amount of interpersonal stress.[969–971] Practical tips on how to deal with specific problems can be invaluable. It is noteworthy that caregivers who have larger num-

bers of back-up caregivers in their support network have lower depression scores.[971,972]

Patients and families should be questioned about their support networks. If they do not know others with PD, an introduction to people with the same problems can be extremely helpful. One caveat for patients with early-stage disease is that support groups can actually have a negative impact. Seeing people with advanced stages of the disease can be frightening and depressing for the early patient. A one-on-one peer support opportunity or a support group that is designed specifically for the newly diagnosed patients or those with young-onset PD may be more helpful than immersion into a group of patients dealing with the consequences of late-stage disease. Information regarding local support organizations and educational materials can be obtained by contacting:

American Parkinson Disease Association, Inc.
1250 Hylan Blvd, Suite 4B
Staten Island, NY 10305
1-800-223-2732
www.info@pdaparkinson.org

European Parkinson Disease Association
215 Vauxhall Bridge Road
London, United Kingdom SW1V 1EJ
enquiries@parkinson.org.uk

National Parkinson Foundation, Inc.
1501 NW Ninth Avenue NW, Bob Hope Road
Miami, FL 33136-1494
1-800-433-7022
www.parkinson.org

The Parkinson's Disease Foundation
1359 Broadway, Suite 1509
New York, NY 10018
1-800-457-6676
www.pdf.org

The Michael J. Fox Foundation for Parkinson Research
Church Street Station
PO Box 780
1-800-708-7644
New York, NY 10008-0780
www.michaeljfox.org

The Parkinson Foundation of Canada
4211 Yonge Street
Suite 316
Toronto, Ontario, Canada M2P2A9
www.parkinson.ca

Professional counseling. When the stress of living with PD or living with someone who has PD becomes so challenging that coping skills begin to reach their limit, a referral should be made for psychiatric or psychological counseling. Clinicians managing patients with PD should have a list of local psychiatrists or counselors who specialize in chronic illnesses such as PD so that appropriate referrals can be made. Counseling needs for spouses should be assessed separately from those of the patient. Stresses are different for the spouse, and counseling may be helpful for a spouse at a time when it may not be necessary for the person with PD.

Legal/financial counseling. Clinicians should encourage patients to seek out expert advice from attorneys or estate planners who specialize in the area of elder law and are skilled in the financial and legal issues of chronic illness and disability. This kind of preparation by patients and their families early in the course of the disease can be helpful in coping with some of the anxiety that comes from living with the possibility of developing increasing physical disability.

Occupational counseling. Where appropriate, clinicians should inquire about performance of the patient with PD in the workplace. Work can be an important source of self-esteem and independence, and adaptations often can be made so that the patient can maintain employment. These might include changes in job requirements, number of work hours, or workplace environment in an effort to prevent the need for termination or premature retirement.[973,974] Occupational therapists are trained to visit the workplace and consider adaptations that can be made to improve productivity and reduce stress. The ability of the patient to continue in the workplace and the need for disability insurance should also be considered.

Exercise. Exercise is an important adjunctive therapy for PD and can be beneficial for patients in all stages of the disease.[975] Although exercise has not been shown to directly improve the cardinal features of PD such as bradykinesia, tremor, postural instability, or rigidity, it can help to prevent the impairment in mobility or functional activity that results as a consequence of these problems.[976,977]

Patients with PD frequently receive PT for extended periods based on anecdotal experience, but there have been few studies examining the efficacy of PT in a rigorous, scientific manner.[978] One controlled study demonstrated that patients with PD randomized to receive a regular exercise program had fewer total falls and fewer injurious falls at 6 months compared with a control group.[848] Exercise in this study was also associated with an enhanced quality of life. Other studies similarly suggest that exercise may augment the effects of levodopa[979] and improve the patient's perception of quality of life.[980] Studies also suggest that combining visual cues with gait training provides enhanced and more sustained responses compared with visual cues alone.[981] A randomized, controlled trial with a crossover design compared PT

plus best medical therapy with best medical therapy alone. This study found that patients who received PT in addition to best medical therapy had significant benefits with respect to the total UPDRS score, the ADL subscore, and the mobility section of the Sickness Impact Profile.[982] Although such studies are difficult to blind properly, they suggest that patients with PD may derive benefit from short-term PT. Other studies have demonstrated benefits of exercise on UPDRS and quality of life, but showed comparable results for patients who received formal PT vs those who followed a self-administered home exercise program.[983] This study suggests that exercise is important, but how it is administered is less so.

PT with gait training and teaching visual cues, may also have a role in the management of freezing. It is a common clinical observation that auditory and visual cueing may benefit patients with freezing.[984] The mechanism and neural circuits through which sensory cuing improves rhythmic movements and freezing of gait in PD are unknown. Auditory cuing was evaluated in a clinical study using [18F]-fluorodeoxyglucose-PET.[985] Improvement was detected in gait as well as in repetitive movements such as finger tapping. These changes were accompanied by significant metabolic increases in the right cerebellum and right parietal and temporal lobes. As these areas are involved in sensorimotor processing, they may provide an explanation for the improvement. The Rehabilitation in PD: Strategies for Cueing (RESCUE) study reported that home training in sensory cuing provided significant improvements in the severity of freezing, gait speed, step length, and timed balance test.[986] However, the effects were short-lived and diminished considerably after 6 weeks.

The best form of PT to use in PD has not been established, but a few studies have tried to compare different modalities. One study compared body weight-supported treadmill training with conventional PT, and concluded that the body weight-supported treadmill training group had significantly greater improvement in short-step gait problems.[987] Another small study compared a high-force eccentric resistance training program with standard PT.[988] Greater improvements in muscle volume, force, and functional status were observed in persons receiving high-force eccentric resistance training. Significant benefits were also observed in scores for muscle structure, stair descent, and walking. In contrast, a small open-label study found that constraint therapy did not benefit hemiparkinsonian patients.[989]

There is also some evidence suggesting that alternative approaches provide some benefit for patients with PD. The ancient Chinese medical exercise Qigong was reported to be beneficial in a randomized, controlled study.[990] At 12 months, there was a sustained difference between the groups in change from baseline in UPDRS motor scores. Taiji (T'ai Chi) is an ancient Chinese martial art that emphasizes slow and graceful movements. In a small study, this exercise was reported to improve balance and benefit six of eight patients with PD.[991]

Finally, there is some evidence suggesting that exercise may prevent cell death and induce plastic changes in cortical and basal ganglia neurons that enhance motor function. Exercise has been shown to increase longevity in animal models of neurodegenerative diseases, possibly by inducing the production of neurotrophic factors such as IGF-I.[992] In MPTP-lesioned mice, exercise has been found to be associated with increased dopamine neurotransmission,[993] and to protect dopamine neurons.[994]

Overall, there is considerable anecdotal and some research evidence indicating the benefit of exercise for patients with PD. Patients should be educated about the positive effects of exercise on mobility and mood. An exercise program should include aerobic, strengthening, and stretching activities. One does not replace the other. Aerobic exercise should be done at a training heart rate of 60% to 70% of maximum. Stretching exercises should be done when muscles are warm, and strengthening exercises should be performed with light weights. The goal should be to improve flexibility and strength, not to add bulk. Emphasis should be placed on the extensor muscles to counteract the flexor postures that tend to develop in PD. A reasonable goal is a 20-minute exercise session, three times a week. Patients with advanced disease can also benefit from regular, focused exercise sessions. Most patients can still exercise regardless of the stage of PD. Because fatigue is an important feature of later-stage PD, it may be helpful to refer patients to PT so that they can learn energy conservation techniques designed to help reserve their energy for the most important activities of the day. Patients should not exercise to the point of exhaustion.

Before an exercise program is started, potentially complicating medical problems such as heart disease should be excluded. Other limitations such as decreased range of motion in a particular joint should be identified to focus PT and minimize the risk for injury. Non–weight-bearing exercise (e.g., water aerobics) may be particularly beneficial for patients with PD. Patients who are interested in an exercise program but are not sure how to get started should be

referred to a physical therapist or a PD exercise group. In considering the long-term need for PT, cost should be a consideration. One study estimated that spa therapy was more effective and less expensive than conventional PT treatment in the management of PD.[995]

Speech therapy. As discussed above, up to 90% of patients with PD develop a speech or voice disorder with impairment of laryngeal, respiratory, and articulatory functions.[832] Standard neuropharmacologic and neurosurgical approaches do not consistently improve speech and voice, and DBS of the STN may worsen dysarthria and dysphonia.[996]

The LSVT method of speech therapy is based on efforts to increase the loudness of the voice to improve "calibration." The aim of increasing vocal loudness is to increase the coordination and modulation of the speech production system.[997] By incorporating sensory awareness training, LSVT provides the ability to self-monitor vocal loudness. LSVT has been reported to provide short-term and long-term benefits on speech production in PD.[834,998] This concept of increasing speed and amplitude of movement has also appeared promising when applied to large muscles in patients with PD.[999]

Nutrition. Good nutrition is essential to the well-being of patients with PD. It is important to establish and maintain good eating habits throughout the course of the disease. Patients with PD are at increased risk for having poor nutrition, weight loss, and loss of muscle mass compared with healthy controls,[1000,1001] and are four times more likely than age-matched controls to have weight loss of greater than 10 pounds.[1000] Conversely, obesity may become a problem because of the sedentary lifestyle and poor eating habits that may accompany PD. These problems can lead to a generalized weakness and an increased risk of falling.

Clinicians should obtain a thorough dietary history from patients with PD and define their current eating habits. Assessment of nutritional status begins with a careful history to identify patients who are losing weight and factors that might interfere with proper nutrition. These might include insufficient caloric intake, chewing or swallowing difficulties, poor dentition, impaired ability to prepare meals, and use of nontraditional diets. One study demonstrated significant weight loss during 10 years of follow-up in both patients with early and advanced PD compared with controls.[1002] Although worsening of parkinsonism was the most important factor, visual hallucinations and dementia were also associated with weight loss. Depression, cognitive impairment, inadequate social support, low income, and other psychosocial factors can also contribute to poor nutrition.

The relationship between weight loss and dyskinesia is complex. Although some studies have found that severe dyskinesias can contribute to weight loss,[1003] others have not found this association.[1002] It is also important to recognize that the weight loss that occurs in PD may result from patients receiving higher dosages of levodopa per unit of body mass, which tends to aggravate dyskinesia, thereby setting up a vicious cycle.[1004]

Helping patients become aware of their dietary habits and educating them about the elements of a balanced diet and the techniques to successfully alter poor eating habits is essential. Although no specific diet is required, it should be balanced, containing sufficient fiber and fluid to prevent constipation and enough calcium to maintain bone structure. Dietary amino acids can compete with levodopa for absorption from the gastrointestinal tract and for transport into the brain, and may thus cause erratic and unpredictable responses to levodopa therapy. Patients with advanced PD should be aware of this interaction as it can lead to delayed "on" and no "on" responses if levodopa is taken with a meal. Ideally, patients with PD should take levodopa on an empty stomach to facilitate absorption, but nausea may necessitate the administration of levodopa with some food. In this case, it is preferable for patients to take levodopa with low-protein containing food. A protein-redistribution diet in which all protein is taken with the evening meal may be helpful for a limited period of time, but rarely provides a long-term solution to the problem. In general, this is an unpleasant and possibly improper diet and it is usually sufficient for patients simply to take levodopa on an empty stomach, 1 hour before or 1 hour after meals. Pharmacists may label prescriptions for levodopa with a warning to take the medication with food, but this is not desirable, particularly for patients with motor fluctuations.

A proactive approach should be taken to preventing constipation. Patients should be encouraged to increase the amount of fluid and fiber in their diets.[1005] Patients who have difficulty maintaining a balanced diet may be candidates for a supplemental multiple vitamin with or without calcium supplementation. There is a large body of literature supporting a role for oxidative stress as a contributing factor in the pathophysiology of PD.[1006] However, there is currently no evidence to suggest that a diet rich in antioxidants (e.g., α-tocopherol or ascorbate) alters the course of the disease[163,1007] and supraphysiologic or megadoses of vitamins and other "nutritional" agents are costly and potentially dangerous. Patients have used fava beans to treat Parkinson

symptoms because the beans contain levodopa and have been thought to be a safe adjunctive therapy. However, large amounts of fava beans are required to provide adequate levels of levodopa, it is hard to titrate the dose with dietary formulations, and abrupt discontinuation of fava beans in patients with PD may lead to a dangerous clinical situation resembling neuroleptic malignant syndrome.[1008]

Many patients with PD take supplements without the recommendation of a physician. In one study, 63% of the patients took nutritional supplements, with vitamin E being the most commonly used.[1009] Fewer than half consulted with their doctor before taking them, and only 4% were aware of their possible side effects. Alternative or complementary therapies are most likely to be taken by Asian patients and those with more severe motor dysfunction.[1010] With the exception of tocopherol, which had no effect, and coenzyme Q10 and creatine, which are currently being evaluated in double-blind trials, neutraceuticals have not been well studied and their role in the treatment of PD, if any, is limited.[1011] Greater awareness of supplement use in patients with PD is warranted to avoid potentially harmful effects and drug interactions.

In summary proper nutritional status is important in the management of patients with PD. Patients may occasionally benefit from a home health evaluation and may need assistance to develop a program that improves their eating habits and nutritional status. Patients should be made aware that many commercially available dietary supplements are high in protein, and they should become accustomed to reading labels before purchasing these products. Referral to a nutritionist for evaluation and dietary recommendations may occasionally be valuable. Patients with dietary problems due to depression or cognitive impairment should be treated appropriately.

FUTURE DIRECTIONS—WHAT'S IN THE PIPELINE In the 7 years since the writing of the last "algorithm," there have been important advances in our ability to treat patients with PD in all stages of the disease. Nevertheless, important unmet medical needs remain, and even more effective therapeutic interventions are required for the successful management of the patient with PD. Current therapeutic research directions are presented in table 26.

Table 26 Future research directions

Treatment of early PD
Treatment of dyskinesias and motor fluctuations
Interventions that restore function for patients with advanced PD
Interventions that treat nondopaminergic features of PD
Neuroprotective treatments

PD = Parkinson disease.

Treatment of early PD. Symptomatic therapy for the classic motor features found in patients with early PD is usually satisfactory and does not represent a major need at this time. Rather, there remains a need for therapies that provide antiparkinsonian benefits that do not induce motor complications. An early treatment strategy that prevents the development of motor complications would enhance the quality of life of patients with PD and greatly simplify their later management. Much effort has been directed toward achieving this goal. As discussed in detail above, current evidence suggests that motor complications are related, at least in part, to the downstream consequences of non-physiologic, pulsatile stimulation of dopamine receptors. On the basis of these observations, it is hypothesized that the risk of inducing motor complications would be lower with therapies that provide more CDS.[233] It is now evident that initiating symptomatic therapy with a long-acting dopamine agonist reduces the risk of motor complications compared with short-acting agents such as levodopa. However, dopamine agonists have relatively limited efficacy, and patients eventually require levodopa, which increases the risk of motor complications even if administered with a dopamine agonist. Much effort, therefore, has been focused on developing more effective dopamine agonists that induce even less pulsatile stimulation than the existing long-acting agents. Transdermal formulations of rotigotine or lisuride, and the extended release formulation of ropinirole, provide relatively stable plasma levels of these drugs and should, therefore, be associated with relatively continuous stimulation of dopamine receptors and a low risk of dyskinesia. However, existing dopamine agonists have very little tendency to induce motor complications, and no additional advantage with respect to dyskinesia has been detected with cabergoline, which has a very long half-life (approximately 48 hours). Furthermore, no dopamine agonist has been shown to prevent the need for levodopa. Therefore, it remains to be determined if new dopamine agonists and new delivery systems for dopamine agonists can provide any additional benefit compared with available agonists.

More interest has focused on the possibility that a long-acting formulation of levodopa will reduce dyskinesia associated with the standard short-acting form of the drug.[231] Although it has proven difficult to develop such a formulation, it has been shown that levodopa administered in combination with a COMT inhibitor at 3-hour intervals provides a plasma pharmacokinetic profile that resembles

a levodopa infusion, and reduces the risk for motor complications in MPTP monkeys compared with levodopa alone.[419] The STRIDE-PD study failed to show any advantage of administering levodopa in combination with a COMT inhibitor at 3.5 hour intervals. It is possible that this study failed because this dosing schedule did not achieve CDS and that better results might have been attained with more frequent dose administration as suggested by pharmacokinetic studies. More promising are attempts to develop patch formulations of levodopa, continuous oral delivery formulations of levodopa, and levodopa prodrugs that can be administered 1–3 times daily and provide continuous availability of the drug.

Studies in the relatively near future should also help to clarify the issue of when to introduce therapy. There is an increasing trend toward initiating therapy early in the course of the disease, and perhaps even at the time of diagnosis.[440] This approach has been facilitated by the development of symptomatic agents such as MAO-B inhibitors that can be administered once a day and are well tolerated. Current studies are testing whether any of these agents have disease-modifying effects by way of neuroprotection or stabilization of basal ganglia networks. The ADAGIO study has shown that early treatment with rasagiline 1mg/day provides benefits that cannot be achieved with later introduction of the same drug. It will be important to determine if this change in UPDRS score at 18 months will translate into reduction in cumulative disability at later stages of the illness. A demonstration that benefits in the ADAGIO study persist or even become greater would strongly support early introduction of therapy. The development of an oral formulation of levodopa that mirrors the plasma pharmacokinetic profile of an infusion could permit early introduction of this drug so as to maximize its benefits without motor complications. Studies trying to define at-risk individuals[85] are intriguing and raise the possibility that soon we may even be able to introduce therapy before the onset of motor symptoms and achieve better long-term results.

Treatment of dyskinesias and motor fluctuations. Levodopa-induced dyskinesia can be an important source of disability for some patients, and perhaps more importantly, limit the utility of dopaminergic drugs to optimally control PD symptomatology. The development of an effective antidyskinetic agent might permit dopaminergic agents to be administered in larger doses and thereby provide better control of parkinsonian motor features without fear of inducing worsened dyskinesia. The development of such a treatment might also obviate the need for surgical intervention in many patients because surgery is performed primarily to treat motor complications. Currently, amantadine is the only medical agent that reliably reduces dyskinesia without worsening parkinsonism, but the drug is associated with impaired cognition and benefits are often transient.

CDS-based therapies have attracted attention as a treatment to prevent motor complications, but these approaches might also have a role in reversing established motor complications. Improvement in both dyskinesias and "off" time has been observed with continuous delivery of a dopamine agonist or levodopa.[416,492] However, infusion therapies are not currently approved in the United States (although they are available in some other countries). Continuous subcutaneous infusion of apomorphine and lisuride are currently being pursued for regulatory approval in the United States. It is anticipated that continuous levodopa infusion will provide even greater benefits. Continuous intraintestinal infusion of methyl ester levodopa has been shown to dramatically reduce "off" time and dyskinesias.[416] Continuous intrajejunal infusion of Duodopa, a specially formulated levodopa gel, is currently being investigated. Furthermore, Duodopa infusion has been found to be superior to optimized combinations of conventional oral and subcutaneous medications in patients with motor fluctuations.[225] Continuous infusion of a dopaminergic agent offers an alternative to DBS that avoids the risks associated with intracranial surgery. Such treatments, however, use an infusion system that is cumbersome for both patient and caregiver, and in the case of levodopa, a surgical intervention is also required. Infusions are also typically only administered during the waking day, and problems of nighttime akinesia and dystonia will have to be addressed. A pharmaceutical therapy would be preferable. The development of more compact infusion systems that use insulin pumps are being pursued.

Several new pharmacologic approaches are currently being investigated as possible treatments for dyskinesia. These include adenosine A2A antagonists, opioid antagonists, 5HT2A agonists, 5HT2C antagonists, CB-1 antagonists, α-2 antagonists, atypical neuroleptics, dopamine uptake inhibitors, antagonists of NMDA receptor subunits, selective muscarinic and nicotinic agonists, as well as novel and more traditional dopamine agonists.

Adenosine A2A receptors are localized to cholinergic interneurons and cell bodies of D2 receptor-bearing striatal output neurons in the indirect pathway,[1012] and have the capacity to influence acetylcholine, GABA, and dopamine release. In the dopamine-lesioned state, adenosine A2A antagonists reduce overactivity in D2-bearing striatal neurons that are thought to contribute to dyskinesia,[1013] and

prevent dyskinesia associated with the introduction of levodopa in the MPTP monkey.[1014] The adenosine A2A antagonist KW6002 (istradefylline) has now been tested as add on therapy to levodopa in a 12-week, double-blind, placebo-controlled study in patients with advanced PD with dyskinesias and motor fluctuations.[503] Surprisingly, istradefylline reduced "off" time by 0.7 hr/d compared with placebo, but did not reduce dyskinesias. These disappointing results may reflect that in animal models the drug reduced dyskinesia when it was initiated along with levodopa, whereas in the clinical trial the drug was administered only after dyskinesias had already emerged. Other more potent and selective A2A antagonists are being developed, and it is hoped that they will provide antidyskinesia and antiparkinsonian benefits if used in a manner that more closely replicates studies in animal models.

Glutamate receptor antagonists and release inhibitors have also attracted attention as possible antidyskinetic agents. The NMDA receptor antagonists amantadine and dextromethorphan are associated with reduced dyskinesia in MPTP monkeys, and have been reported to improve dyskinesia in PD patients.[475,477,1015,1016] These drugs are, however, associated with cognitive side effects that limit their utility as a treatment in patients with PD. Rimantadine is the α-methyl derivative of amantadine, and has been shown to have motor benefits in PD in an open-label study and to be better tolerated than amantadine.[1017,1018] It has not yet been studied as a treatment for dyskinesia. AMPA receptor antagonists are also being studied based on their capacity to block excessive glutamatergic neurotransmission and to reduce dyskinesia in MPTP monkeys. Talampanel has been shown to reduce levodopa-induced dyskinesias in the MPTP-treated monkey model without the toxic effects associated with NMDA receptor antagonists,[1019] and is currently being studied in a phase 2 clinical trial. Perampanel is another AMPA receptor antagonist that is also being studied in PD. However, a recently completed, but as yet unpublished, placebo-controlled, double-blind study testing perampanel as an adjunct to levodopa showed no improvement in either "off" time or dyskinesia compared with placebo.[1020] Perampanel was well tolerated with no significant safety issues. Two additional phase 3 studies of perampanel in PD are ongoing.

Perhaps most interesting are drugs that inhibit the NR2B subunit of the NMDA receptor, which has been shown to play a key role in the pathogenesis of dyskinesia in experimental models.[292] This subunit is localized to the striatum, and inhibitor drugs are not anticipated to induce cognitive side effects. Unfortunately, preliminary clinical trials with this agent did not show any antidyskinesia benefit (oral communication, Nutt). Improvement in established levodopa-induced dyskinesia was seen in MPTP monkeys when NMDA and AMPA receptor antagonists were combined, and this approach warrants further clinical consideration.[1021] Riluzole, which blocks activated sodium channels and inhibits glutamate release, has also been reported to reduce dyskinesia in patients with PD,[1022] but is not being studied at present.

Striatal opioid binding is reduced in dyskinetic patients with PD patients consistent with the presence of raised enkephalin and dynorphin levels.[1023] This suggests that opioid antagonists might be effective in the treatment of dyskinesia. Small clinical trials showed that the opioid antagonist naloxone,[1024,1025] but not naltrexone,[1026,1027] had some antidyskinetic effects, but so far this has not been further pursued.

Nicotine has complex interactions with the basal ganglia, and nicotinic cholinergic activity has been shown to regulate dopamine release.[457] In an experimental study in MPTP monkeys, nicotine pretreatment markedly reduced peak and total levodopa-induced dyskinesias.[1028] This suggests that either nicotine or nicotine agonists may have a role in the prevention of levodopa dyskinesia.

Alpha 2 adrenergic receptor antagonists are also being explored as possible antidyskinetic agents. Activation of α-2 adrenergic receptors facilitates movements produced by activation of the direct pathway, and it has been speculated that this might contribute to levodopa-induced dyskinesias.[1029] The α-2 adrenergic receptor antagonist fipamezole has been reported to reduce levodopa-induced dyskinesias without counteracting the antiparkinsonian effects of levodopa in the MPTP-lesioned marmoset model of PD.[1030] This drug is currently in phase 2 studies.

Docosahexaenoic acid (DHA) is an omega-3 essential fatty acid that is found in fish oil. There is some evidence that a reduction in DHA may be associated with lowered serotonin levels in the brain and that this might reduce the risk of dyskinesia. In one experiment, DHA reduced dyskinesia in MPTP-treated parkinsonian monkeys without diminishing the effect of levodopa.[1031] These promising results have not yet been tested in clinical trials in patients with PD.

There also continues to be interest in the potential of dopamine agonists to provide enhanced antiparkinsonian effects with less dyskinesia in patients with advanced PD. It has long been speculated that selective patterns of activation of dopamine receptors might have different effects on motor function and dyskinesia. Short-acting D1 and D2 receptor ago-

nists have both been shown to induce dyskinesia in animal models of parkinsonism.[303] However, in MPTP monkeys the pure D1 agonists A-86929 and A-77636 provide motor benefits with reduced dyskinesia,[1032,1033] and there is renewed interest in studying these agents in patients with PD. Recent studies have implicated the D3 receptor in the induction of dyskinesia,[305] and the partial D3 agonist BP897 ([N-[4-(4-(2-methoxyphenyl)piperazinyl)butyl]-2-naphthamide) has been shown to provide antiparkinsonian effects and reversal of dyskinesia in both macaque and squirrel monkeys.[1034] These types of agents warrant further investigation in patients with PD. The dopamine agonist SLV308 (Pardoprunox) is a partial agonist at dopamine D2 and D3 receptors and a full agonist at the serotonin 5-HT(1A) receptor.[1035,1036] The drug is currently in phase 3 trials for the treatment of early and advanced PD as a means of preventing and reversing motor complications. Lisuride is a short-acting ergot dopamine agonist that is a nonhallucinogenic congener of LSD. It is approved for the therapy of PD in Europe but not in the United States. Transdermal formulations of lisuride (lisuride TTS) have been developed to try and provide continuous delivery of the drug and to mirror the benefits of infusion. Lisuride TTS has been reported to reduce motor fluctuations in patients with unpredictable "on-off" phenomena in a small open-label trial.[1037] As with other patches, transient skin irritation was common.

Lisuride TTS is currently being tested in phase 2 trials in the United States and Europe, with the goal of reducing levodopa-induced dyskinesias. Despite being ergot-derived, lisuride is devoid of 5-HT(2B) agonistic activity and to date has not been shown to induce fibrotic changes in heart valves as seen with other ergot-derived agonists.[1038]

Finally, there is interest in antidyskinesia treatments directed at interfering with signal transduction pathways activated by nonphysiologic pulsatile stimulation of dopamine receptors. These are thought to be associated with upregulation of striatal kinases that phosphorylate NMDA receptor subunits leading to altered plasticity and dyskinesia.[474,1039] Indeed, inhibition of the serine kinase cyclic AMP-protein kinase A by Rp-cAMPS and of tyrosine kinase calcium/calmodulin-dependent protein kinase II (CaMKII) by KN-93 have been shown to reverse levodopa-induced response alterations in dopamine-lesioned rodents.[1040] Similarly, the tyrosine kinase inhibitor genistein reverses motor complications associated with levodopa in the rodent whereas the tyrosine phosphatase inhibitor okadaic acid potentiates these alterations.[473] More recently, it has been shown that dyskinesia associated with levodopa treatment in denervated rats induces extrasynaptic translocation of the NR2B subunit of the NMDA receptor.[293] Interestingly, agents that manipulate the translocation of the NR2B subunit can induce or reverse dyskinesia, suggesting that this could be an important target for developing an antidyskinetic drug. These observations support the notion that interference with signaling mechanisms that promote dyskinesia are logical candidates for testing as antidyskinetic agents in PD.

Surgical interventions that restore function in patients with advanced PD. Surgical therapies have now become a part of the routine management of patients with advanced PD who experience disability related to levodopa motor complications that cannot be satisfactorily controlled with currently available medical therapy. Striking benefits, particularly with respect to dyskinesia, were initially observed with pallidotomy. This procedure has largely been replaced by DBS–STN and DBS–GPi, which avoid the need to lesion the brain and thereby avoid side effects associated with bilateral ablative procedures. Both DBS–STN and DBS–GPi seem to provide comparable benefits. Formal studies directly comparing stimulation of these two targets are being performed and their results should be available shortly. DBS–STN is the more widely performed procedure at most centers and may be the more effective, but recent studies suggest that there may be fewer serious adverse effects with DBS–GPI.[601] It should be noted that neither of these procedures have demonstrated improvement of "on" functions beyond what can be achieved with levodopa, and that their primary role is in the management of uncontrolled motor complications. Furthermore, DBS is not a benign procedure, and side effects can occur in relation to the surgical procedure, the stimulation system, stimulation itself, and the periodic need to replace the battery. Future research is focusing on new targets for stimulation such as the PPN for gait dysfunction and a variety of cortical brain targets that might improve psychiatric problems, including depression and compulsive behaviors.

Current evidence suggests that continuous infusion or long-acting formulations of levodopa or a dopamine agonist (apomorphine, lisuride) might produce benefits comparable to those obtained with DBS and avoid the necessity of an intracranial procedure. Such a treatment would potentially avoid the need for an intracranial procedure. Attempts to commercialize infusion therapies or develop long-acting formulations of these drugs, and particularly levodopa, constitute a major focus of current pharmaceutical research (see discussion earlier).

Transplantation strategies have generated considerable enthusiasm based on their potential to achieve

physiologic dopamine reinnervation to the striatum without disrupting any component of the basal ganglia system. However, double-blind, controlled trials of fetal nigral transplantation failed to demonstrate significant benefit compared with placebo,[508,623] and transplantation was complicated by a previously undescribed form of dyskinesia that persisted even after the levodopa dose was lowered or stopped (off-medication dyskinesia). In addition, double blind trials of fetal porcine nigral cells and retinal pigmented epithelial cells have failed to demonstrate any advantage of the transplant procedure. Although these results are discouraging and have largely halted clinical trials for the present, post-hoc analyses suggest that transplantation of larger numbers of cells distributed more diffusely throughout the striatum, with more prolonged use of immunosuppressants, might lead to improved results in patients who are younger and have milder disease.[625] Stem cell therapies have captured the imagination of researchers and the lay public because of the potential of stem cells to provide an unlimited supply of optimized dopamine neurons. Although preliminary studies show benefits in dopamine-lesioned rodents and monkeys, many obstacles remain to be overcome before clinical trials can be considered. These include determining the type of stem cell to be used, the optimal properties of the dopamine nerve cell to be used for transplantation, and the transplant protocol. In addition, it remains to be determined if transplanted cells can survive in adequate numbers, provide benefits superior to what has been achieved with fetal cells, and if stem cell transplantation is associated with a satisfactory safety profile.[644] Furthermore, societal concerns regarding the use of embryonic tissues must be resolved. The use of autologous stem cells has provided some optimism, but results to date are inferior to what can be obtained with ES cells. Realistically, it does not seem that a cell-based therapy will be available for commercial use in the near term. It is also unreasonable to expect that any of the current dopaminergic cell-based therapies will satisfactorily address the many nondopaminergic aspects of PD.

Trophic factors have attracted great interest in PD based on their potential to rescue damaged dopaminergic neurons in both in vitro and in vivo model systems. GDNF has been shown to repair the damaged nigrostriatal system in animal models of parkinsonism; however, benefits were not observed in a double-blind, placebo-controlled trial,[650] possibly because point source delivery through a catheter does not permit adequate diffusion throughout the target area. Gene delivery offers a unique opportunity to provide continuous availability of a therapeutic protein throughout the target region. Gene delivery of neurturin, a trophic factor in the GDNF family, showed dramatic behavioral and histologic benefits in MPTP monkeys,[655] and AAV-2 delivery of neurturin to the striatum provided significant clinical benefit to patients with advanced PD in an open-label trial.[656] This therapy is particularly appealing because it not only has the potential to restore physiologic dopaminergic function, but might protect remaining dopamine neurons from future neurodegeneration. However, a double blind trial comparing AAV2 delivery of neurturin failed to provide benefits superior to placebo. This may have been due to inadequate gene expression, and further investigations are planned. Gene therapy also offers the potential of delivering other therapeutic proteins as they are deemed to be relevant in PD. For example, gene delivery of parkin might effectively "cure" patients with a parkin mutation. Although the concept of gene therapy is promising, it remains to be established that this type of procedure is safe and well tolerated in patients with PD.

Interventions that treat nondopaminergic features of PD. The development of nondopaminergic features, such as dementia, postural instability, gait disturbances, and autonomic dysfunction, are among the most disabling aspects of PD for many patients. Yet, we have very little in the way of effective treatment for many of these important problems. Dementia is perhaps the most important source of disability for patients with advanced PD. Cholinesterase inhibitors offer only limited benefit in the treatment of PD-D and DLB.[676,678] There is some optimism that treatment of patients with PD with MCI will achieve benefits superior to those obtained for patients with MCI in the general aging population, and studies testing this hypothesis are anxiously awaited. Safinamide is the first agent to test the potential of a drug to influence the executive dysfunction that characterizes PD, but the magnitude of benefit seems to be small and may be common to other dopaminergic therapies. Even cholinesterase inhibitors have yet to be tested in patients with PD with executive dysfunction but without frank dementia. Clearly, newer and more effective therapies are required.

There are effective treatments for the psychosis that frequently precedes PD-D, and this might represent an interesting population in which to test agents for treatment of early cognitive impairment. Symptomatic therapies exist for some of the features of autonomic dysfunction such as orthostatic hypotension, constipation, and urinary dysfunction, but there are no effective treatments for patients with gait dysfunction and postural instability that does not respond to levodopa. Preliminary data with stimulation of the PPN offers some promise, and is currently being investigated. More insight into the basis of the

locomotor defect that occurs in PD might provide new opportunities for novel therapies. The development of therapies to treat effectively or prevent these nondopaminergic features remains one of the major unmet medical needs in the management of PD. To facilitate achieving this goal, an animal model that replicates the nondopaminergic features of the disease would be of enormous value.

Neuroprotective treatments. Perhaps the single most important unmet challenge in the management of PD is the development of a neuroprotective therapy that slows or stops disease progression. Laboratory clues have provided us with many rational approaches to protecting or restoring function to nerve cells that degenerate in PD. Candidate targets include oxidative stress, mitochondrial dysfunction, excitotoxicity, and signals associated with apoptosis. Proteolytic stress has attracted considerable attention because protein accumulation characterizes PD pathology. This might occur as a consequence of the increased production or impaired clearance of misfolded proteins, and may be diminished by agents that prevent the formation of misfolded proteins or promote their clearance through the proteasomal or autophage system. Genetic studies lend considerable support for the possibility that protein and/or mitochondrial abnormalities play a key role in cell death in PD, and thus present additional targets for novel drugs. Recent studies have also focused attention on the potential of calcium channel blockers to provide neuroprotection in PD. They demonstrate that dopamine neurons have an unusual reliance on L-type Ca(v)1.3 calcium channels to drive their pacing, which increases with age and makes them vulnerable to neurodegeneration.[125] Blocking these channels induces a reversion of these neurons to a more juvenile form of pacemaking and protects them in both in vitro and in vivo models of PD. This provides another exciting new target for development of a neuroprotective drug.

However, developing a disease-modifying therapy for PD has proven an elusive task. Antioxidants (vitamin E), trophic factors (immunophilins, GDNF), antiapoptotics (TCH346, mixed lineage kinase inhibitors), and antiglutamatergic agents (riluzole) have failed in clinical trials, whereas MAO-B inhibitors (selegiline, rasagiline) and dopamine agonists (pramipexole, ropinirole) have demonstrated benefits compared with placebo, but could not be established to be neuroprotective because of possible confounding symptomatic and pharmacologic effects. Clinical trials are currently testing the potential neuroprotective benefits of dopamine agonists (pramipexole), bioenergetics (coenzyme Q10, creatine), trophic factors (neurturin), and antiapoptotic agents (rasagiline), but there is no assurance that positive results in these studies will be any more definitive.

Problems in attaining a neuroprotective therapy include uncertainty as to the precise etiopathogenesis of PD and, therefore, what to target; lack of an animal model that precisely reflects the etiopathogenesis and pathology of PD; difficulty in determining the precise dose of the agent to use in clinical trials; and clinical end points that accurately reflect disease progression.[1041] Indeed, it is possible that multiple gene and environmental events are responsible for cell death in PD, and a cocktail of neuroprotective agents may be required to prevent neurodegeneration.[1042] Despite these hurdles, there is some optimism that these problems can be overcome. Gene mutations associated with familial or sporadic cases of PD are beginning to provide critical information on the pathways that lead to neurodegeneration in PD.[12] They further permit the development of transgenic animal models that carry these or related gene mutations, which hopefully will more closely reflect the pathology and clinical course of PD than current models. In this regard, it is essential to develop a model where positive results in the laboratory are more likely to predict benefits in patients with PD than has been achieved to date with models based on 6-OHDA and MPTP toxicity. Finally, there are new trial designs such as the delayed start and "long-term simple" study, which offer opportunities to test the effect of a putative neuroprotective drug on disease outcome without necessarily understanding its precise mechanisms. The ability to perform studies that lead to drug approval by regulatory authorities with a neuroprotective label is crucial if pharmaceutical companies are going to continue to provide the necessary resources to investigate promising drugs, and for clinicians to know that a given intervention has meaningful benefits for their patients. The potential to identify patients at a "preclinical" stage of the disease would further permit the introduction of a potential disease-modifying agent at a stage when it might be more likely to be effective, to protect ongoing compensatory mechanisms, and slow or prevent the emergence of the classic motor features of PD. Thus, the development of a therapy that can slow or stop disease progression and effectuate a cure for PD is the ultimate aim of research, and would be a landmark in the management of this disorder. Hopefully, that day is not too far in the future.

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