In the pre-levodopa era, Parkinson’s disease was recognized as an inexorably progressive condition leading to severe disability due to bradykinesia, rigidity and tremor. Although the morbidity resulting from these symptoms has been dramatically reduced by levodopa, other neurologic impairments now commonly observed represent either adverse drug effects or neurologic signs that fail to improve with drug treatment. Management of Parkinson’s symptoms—never easy even at the earliest stage of the disease—is considerably more challenging later in the disease’s course. As the patient’s functionality diminishes, so too do the prospects for adequate symptomatic control. This feature will review the complications typical of advanced PD and will offer advice on medical and surgical interventions.

Clinical Manifestations
Although “advanced” disease typically correlates with the duration of pathology, even patients with a relatively brief history of PD can be classified as exhibiting advanced or severe presentations. In fact, 20 percent of patients treated with levodopa for less than one year and 53 percent of patients treated with levodopa for over five years have severe (i.e., stage IV or V) Parkinson’s disease.1 Patients with advanced Parkinson’s experience a variety of symptoms that are uncommon in mildly affected or newly diagnosed patients. Despite treatment with levodopa or other dopaminergic drugs, difficulties in motor, autonomic and cognitive function may develop over time that eventually overshadow symptoms that arise from tremor, rigidity or bradykinesia.

Several types of motor signs and symptoms may be recognized in patients with advanced disease. These problems, which include gait abnormalities, imbalance, dysarthria and dysphagia, differ...
from more classic “parkinsonian” symptoms in their somatotropic distribution and response to medications. Whereas tremor and bradykinesia in the upper extremities typically respond well to levodopa, axial and lower-extremity symptoms tend to respond less well to medication.2

Freezing most commonly occurs when turning, when starting to walk, and when navigating through doorways or other narrow spaces. In some patients, this occurs mainly as an “off” phenomenon, but it may occur independent of bradykinesia and tremor. In other patients, freezing occurs either unrelated to drug treatment or occurs as an adverse effect of levodopa, sometimes only with higher doses of drug. Freezing was reported in over 30 percent of patients with relatively mild disease in the DATATOP study,3 and is seen in a larger percentage of patients with more advanced disease.4

Imbalance, unrelated to freezing, develops in many patients with advanced PD. Symptoms may include unsteadiness when executing turns to severe retropulsion that prevents unassisted ambulation. Imbalance is usually unrelated to drug treatment, but can occur as an adverse effect of orthostatic hypotension secondary to levodopa or other medications. Additionally, imbalance may result from progressive postural deformities, including scoliosis and truncal flexion, which develop in patients with worsening disease.

A number of speech abnormalities may occur in patients with advanced disease, including hypophonia, dysarthria, palilalia and tachyphemia. Typically, palilalia and hypophonia are either unaffected by drug treatment or may exhibit improvement during “on” periods. Dysarthria, in contrast, may sometimes be induced by levodopa; rapid speech (tachyphemia) may also occur as an adverse effect of levodopa.5 The dysarthria may result from levodopa-induced dyskinetic movements of the mouth or tongue, but may also occur in the absence of visible dyskinesia.

Dysphagia is prevalent in severely affected patients. Like other axial motor symptoms, prominent dysphagia early in the course of the illness is atypical in idiopathic parkinsonism, but is common in patients with more advanced disease and is not at all incompatible with the diagnosis. In fact, clinically silent abnormalities in deglutition are found in virtually all patients and correlate with the severity of the disease. Physical signs observed during radiographic investigation include slowness in propelling food to the pharynx, pooling of material near the tonsillar pillars, and silent aspiration.6

Dysautonomic symptoms are numerous in severely affected patients and include orthostatic hypotension, constipation, urinary incontinence and sexual dysfunction. Like freezing and postural instability, these symptoms are uncommon in newly diagnosed patients, and their presence early in the course of the illness should prompt a search for an alternative diagnosis, particularly multiple system atrophy.

Dizziness or faintness due to orthostatic hypotension is commonly experienced in severely affected patients from degeneration of autonomic ganglia. In addition, levodopa, apomorphine and dopamine agonists have a hypotensive effect, and may exacerbate orthostatic hypotension. Frequently, blood pressure may fluctuate along with motor signs, and hypertension during “off” periods may also be observed and may lead to incorrect diagnoses of essential hypertension. Supine hypertension may be seen, but is unusual in idiopathic parkinsonism and is more suggestive of multiple system atrophy.

Constipation is a prevalent symptom, described by up to 60 percent of patients.7 Although a frequent adverse effect of many antiparkinsonian medications, it is commonly an initial symptom, sometimes predating other symptoms of parkinsonism by
months or years. Constipation is usually unresponsive to standard antiparkinsonian drug treatment. Urological symptoms are also prevalent in severely affected patients; one recent survey found that over one-fourth of men with Parkinson's disease had urinary difficulty, most often causing urinary urgency. Obstructive symptoms, such as difficulty starting and weakness of the urinary stream, are less common.

Urodynamic evaluation may reveal a number of different patterns; uninhibited bladder contractions and detrusor dyssynergia (simultaneous contraction of bladder and internal urinary sphincter) are commonly seen. As there is a poor correlation between symptoms and urodynamic findings, urologic evaluation may be needed to adequately assess bladder function. As in constipation, bladder symptoms are typically unrelated to motor effects of medications, but voiding dysfunction during “off” periods has been recognized in some patients.

Sexual dysfunction is also commonly reported in moderately or severely affected patients. Infrequent sexual activity may be due to a variety of causes and include motor symptoms such as difficulty in coital positioning, psychological symptoms such as decreased interest by the patient or partner, and autonomic symptoms (e.g., decreased mucosal lubrication, premature or delayed ejaculation, and erectile dysfunction). A less common but bothersome symptom is hypersexuality or sexual delusions. These symptoms may result from levodopa or dopamine agonists and can occur in isolation or may represent a prodcome to a more severe drug-induced psychosis.

Although the motor and autonomic aspects of Parkinson's disease are the most readily recognized, a large proportion of patients with later-stage disease develop cognitive difficulties, the prevalence rising with worsening motor symptoms. The cognitive symptoms are variable and range from mild, short-term memory difficulty to frank dementia. In patients without dementia at onset, nearly 40 percent develop dementia over a 10-year period.

The pattern of dementia, though, differs from that of Alzheimer's disease. Whereas Alzheimer's patients experience prominent aphasia and apraxia, language function and praxis remain largely unaffected in Parkinson's disease. Instead, patients with Parkinson's disease develop selective difficulties in memory, slowing of cognition and frequent depression. There is evidence that, in some patients, memory may depend on the motor state. In a study of nondemented patients, impairments in learning by association were noted, and these improved by administration of levodopa.

Depression and other psychological symptoms are prevalent in patients with Parkinson's disease; in one recent study, only 12 percent of patients were free of depression, anxiety, sleep disorder, fatigue or sensory symptoms. Hallucinations and psychosis can also develop, and tend to affect older and more severely affected patients. In a recent prospective study, 26 percent of patients with Parkinson's disease experienced either hallucinations or delusions, and four percent had drug-induced delirium.

Differential Diagnosis
A large number of conditions other than Parkinson's disease may produce bradykinesia and rigidity, and together are thought to represent approximately 25 percent of all cases of parkinsonism. Of these other causes, a set of illnesses grouped together and referred to as “Parkinson plus” or “atypical parkinsonism” are the most common, comprising approximately 12 percent of patients with parkinsonism. Although diseases in this category are characterized by degeneration in pathways other than the nigrostriatal tract, these conditions may be confused with idiopathic parkinsonism until the later stages of illness. Other causes of parkinsonism are uncommon and include vascular disease, sequelae of trauma, cortical degenerative illnesses, hydrocephalus, intoxications and metabolic diseases.

Additional neurologic symptoms or signs are expected in these other diseases and allow a diagnosis to be made. The diagnosis of “severe Parkinson's disease” as an explanation of dementia, dysautonomia, dysarthria or other axial motor symptoms should be made cautiously and should include a careful search for signs of other neurologic diseases. Early, prominent dysautonomia, for example, is highly unusual in idiopathic parkinsonism, and should suggest multiple system atrophy; also suggestive of multiple system atrophy is rapid disease progression, symmetric disease, lack of tremor and an equivocal response to levodopa. Evidence of postural instability early in the disease and vertical eye movement disorders, in particular, are frequently early signs in progressive supranuclear palsy. Ophthalmoplegia, at any stage of parkinsonism, is also inconsistent with idiopathic disease and may suggest the possibility of progressive supranuclear palsy. Similarly, long tract signs, focal weakness, distinct reflex asymmetry and ataxia are all signs that are inconsistent with the diagnosis of idiopathic parkinsonism.

The quality and magnitude of the response to levodopa may be helpful in recognizing these other illnesses. The majority of patients with Parkinson's disease exhibit an objective improvement following administration of levodopa, whereas a poor or absent response to levodopa is typical in progressive supranuclear palsy, multiple system atrophy, or other secondary causes of parkinsonism. This feature, though, is not absolute, and the sensitivity and specificity of a clear response to levodopa has been estimated as only 80 to 90 percent.

Diagnostic Work-up
The diagnosis of Parkinson's disease as a cause of dementia, dysautonomia or axial motor symptoms should be viewed as a diagnosis of exclusion. In addition to suspecting other neurolog-
ic diseases, coexistent medical conditions and drug interactions and adverse effects should be ruled out.

One initial step in approaching dysautonomic symptoms is to consider adverse drug effects. Anticholinergics, in particular, can cause urinary retention or urgency or worsen constipation, and a brief period of reducing the dose or withdrawing these medications should be considered. Many other medications have some degree of anticholinergic-like effects, including tricyclic anti-depressants, hypnotics, benzodiazepines, beta-blockers and even amantadine, and trials of reducing or eliminating these medications may be needed.

Similarly, adverse drug effects should be also suspected in recent-onset behavioral or cognitive symptoms. Anticholinergics are notorious in flaring or causing amnesia or confusion, sometimes only in combination with other medications. Other dopaminergic agents, including amantadine, deprenyl, levodopa and dopamine agonists, are well known to cause agitation, confusion, hallucinations and other behavioral disturbances, and a trial of withdrawing or reducing the dose of each of these medications may be necessary.

There is less likelihood that adverse drug effects underlie the worsening of motor symptoms. However, dysarthria, imbalance and freezing may each represent dopaminergic toxicity, and a careful history should be obtained as to how each of these symptoms appear following each dose of levodopa or other medications.

Cerebral imaging should also be considered in patients with severe parkinsonism who fail to improve with levodopa. Brainstem or cerebellar atrophy, focal white matter disease, hydrocephalus or striatal infarction are all changes that would indicate a secondary cause of parkinsonism and serve as major clues to diagnosis. Although MRI is more accurate, the high incidence of nonspecific white matter disease in the elderly may be confusing. Interestingly, one study found a high incidence of periventricular white matter abnormalities in a group of 102 patients with Parkinson's disease without dementia and without risk factors for vascular disease. It also found these patients had evidence for more rapidly progressive parkinsonism than those patients without white matter disease.19

**Medical Management**

The approach to patients with advanced Parkinson's disease is generally complex, and the multitude of symptoms each require different approaches that frequently interact and may limit therapy.

Treatment of motor symptoms should emphasize producing predictable periods of mobility without producing unacceptable dyskinesias or “off” dystonia. Wearing-off, unpredictable “off” periods, failures of levodopa doses to take effect, and periods of severe “on,” diphasic, or “off” dyskinesias or dystonias should be identified as these will influence the dose and frequency of levodopa dosing.

The first step is to optimize the effects and absorption of levodopa. Patients who describe failures of individual doses to take effect or who have a short “on” period should try higher individual doses of levodopa and should take the medication at least 30 minutes before or two hours after meals. Parcopa, a rapidly dissolving tablet of carbidopa and levodopa, has the advantage of being able to be taken without water and may be useful in some patients with dysphagia.

Sometimes, combinations of immediate- and controlled-release levodopa may be useful. However, adverse effects of levodopa such as hypotension, ataxia or mental effects such as sedation, euphoria, confusion or hallucinations limit the size of individual levodopa doses.

Several adjunctive medications are also useful in improving motor fluctuations. These medications can prolong the duration of “on” periods, decrease the severity of “off” periods, and may allow the dose of levodopa to be lowered. These include the dopaminergic agonists pergolide, bromocriptine, pramipexole and ropinirole. The number of dose-limiting side effects is common, though, and includes nausea, sedation and more serious CNS effects such as sudden sleep attacks, confusion, hallucinations and psychosis. In addition, pergolide has recently been recognized to carry a risk of causing restrictive valvular heart disease similar to anorectic drugs. Therefore, it has been recommended that pergolide either not be used or that patients should be monitored with periodic echocardiographic studies. Long-term use of the ergot derivatives pergolide and bromocriptine can result in retroperitoneal and pleural fibrosis and pleural effusion. Although these complications are rare, side effects can result in renal insufficiency or restrictive lung disease and may be irreversible.

Apomorphine, a dopamine agonist administered by subcutaneous injection, is quick acting but its effects are brief, usually lasting 60 to 90 minutes. It is, therefore, best suited as a “rescue” drug for patients with marked motor fluctuations and severe “off” symptoms, such as painful dystonia or immobility.

The catechol-O-methyltransferase inhibitor entacapone delays the metabolism of levodopa, prolonging its effects. In some patients, the dose of levodopa can be lowered and is generally well tolerated. A second COMT inhibitor, tolcapone, is sometimes more effective than entacapone but is potentially hepatotoxic. Patients must be monitored by frequent liver function tests.

A third class of medications is made up of MAO-B inhibitors. The first MAO-B inhibitor developed, selegiline, is minimally effective in most patients with motor fluctuations, but a new formulation of this medication with improved absorption and improved efficacy is being developed. Rasagiline, another MAO inhibitor, has recently been introduced under the brand name Azilect and has been reported to be helpful in the
reduction of motor fluctuations and in improving “off” time in patients. Other adjunctive medications, including selective adenosine antagonists, are under clinical development and appear promising.

Tremor refractory to levodopa may be difficult to treat. High doses of pramipexole and ropinirole have been reportedly effective in some patients, but a large number of patients do not respond to any drug treatment. Although clozapine has been reported to be effective in patients with refractory tremor, neurosurgical treatment may be necessary.

Management of levodopa-induced dyskinesias is also difficult. “Off” dystonias may improve with the addition of a dopamine agonist, COMT inhibitor, anticholinergic, benzodiazepine or gabapentin. “On” dyskinesias may improve by lowering the dose of levodopa; however, this generally results in poorer control of parkinsonism unless a dopamine agonist or COMT inhibitor is added. In occasional patients, amantadine can substantially reduce both “on” and “off” dyskinesias. Other drugs that have been observed to reduce dyskinesias include clozapine, and in small studies, dextromethorphan and riluzole.

Surgical Management

A number of neurosurgical procedures may be appropriate in patients with advanced disease and can improve refractory tremor, motor fluctuations, “on” dyskinesias and “off” dystonias. Lesioning of the ventral intermediate nucleus of the thalamus can eliminate or dramatically reduce tremor, and when performed unilaterally, is generally well-tolerated. There is an unacceptable risk of dysarthria, dysphagia and cognitive side effects when performed bilaterally, though, and in patients with bilateral tremor, thalamic stimulation may be preferable. Stimulation can be administered bilaterally, or may be administered on the side contralateral to a previous thalamotomy.

In patients with disabling unilateral or asymmetric dyskinesias, lesioning of the internal segment of the globus pallidus can be effective. This procedure greatly attenuates dyskinesias and can allow patients to take doses of levodopa higher than previously possible. It can also improve other aspects of parkinsonism, although these effects are somewhat inconsistent. Like thalamotomy, bilateral lesioning can produce adverse effects in mood, cognition and balance, and is generally not performed. As this surgery is destructive, pallidotomies are much less commonly performed, and are being replaced by deep brain stimulation.

Stimulation of the subthalamic nucleus and the internal segment of the globus pallidus are effective treatments for many patients with severe Parkinson’s disease. Stimulation of either of these structures may greatly reduce motor fluctuations and improve “off” symptoms. In a recent study, neurostimulation of the STN combined with medication use was more effective than medical therapy alone in improving quality of life as measured by the PDQ-39 and motor symptoms as measured by the UPDRS-III. DBS typically allows for a reduction in medication use in the short term and possibly the longer-term as well.

Although subthalamic nucleus and globus pallidus stimulation both improve motor signs, there are some important differences in their effects. Whereas globus pallidus stimulation atten-
Advanced Parkinson’s

uates dyskinesias directly, subthalamic nucleus stimulation does not reduce dyskinesias in patients given a standardized dose of levodopa.27 However, subthalamic nucleus stimulation does have a levodopa-sparing effect, and dyskinesias are able to be reduced as the dose of levodopa is lowered. In clinical experience, subthalamic nucleus stimulation seems to produce a larger benefit. However, a blinded trial found roughly similar effects with stimulation of each site,28 and a large, multicenter trial comparing the effects of these two targets is now being conducted in the United States. Stimulation of both sites has demonstrated sustained benefits over several years.

Patient selection is extremely important in ensuring success; patients with a poor response to levodopa, who have significant cognitive impairment, who have persistent freezing or gait problems, or who have severe dysarthria do not generally improve adequately and may even worsen from the procedure. Although there is a risk of depression and memory problems with deep brain stimulation, in experienced hands, both globus pallidus and subthalamic nucleus stimulation are generally safe and do not affect cognitive function in most patients.29

Non-Dopaminergic Symptoms

A number of other symptoms occur commonly in patients with advanced Parkinson’s disease. Unlike tremor and bradykinesia, these other symptoms do not improve substantially with levodopa or other dopaminergic drugs and are, therefore, thought to represent degeneration of non-dopaminergic pathways.

One of the most common symptoms is speech impairment. This is usually due to a combination of problems, including hypophonia, rapid speech (tachyphemia) and slurred speech (dysarthria). These problems may be approached most effectively by a speech therapist. In addition, speech problems in some patients are worsened by dopaminergic drugs, and these may require adjustment of the dose or timing of medications in order to improve communication.

Dysphagia is difficult to adequately treat, and aspiration should be ruled out in patients with difficulty swallowing. Clues to aspiration may include coughing after swallowing, but aspiration may be silent, and barium swallow or cine-esophagography may be needed to adequately address the safety of eating different textures of food. Weight should be monitored, and gastrostomy may be needed in some patients to adequately maintain nutrition. Many patients with dysphagia also have excessive salivation. Some patients improve with the addition of anticholinergics, but systemic side effects may limit the use of these medications. Botulinum toxin injections in the salivary glands are an option and have been shown to be effective in blinded trials.30

Unfortunately, little effective treatment is available for imbalance and freezing. Patients may sometimes improve by walking over an inverted cane to visually pace walking, but such measures are usually inadequate. In patients at high risk for falls, ambulation without assistance should be discouraged and physical therapy should be used to teach the optimal use of walkers or wheelchairs. In patients with freezing, wheeled walkers tend to be more helpful than folding walkers, as the latter may worsen freezing.

Problems related to dysautonomia, including impairments in bladder function, constipation, gastroparesis, and orthostatic hypotension are also prevalent in patients with advanced Parkinson’s disease.

Bladder dysfunction may include urinary urgency, frequency, incontinence and urinary retention. The most common problem is detrusor hyperreflexia, but other urodynamic abnormalities such as detrusor-sphincter dysynergia, detrusor areflexia and mixed patterns are also seen. A progressive increase in postvoid residual urine volume is seen with advancing disease.31 Assuming that urinary retention has been ruled out, urinary frequency may be helped by a peripherally active anticholinergic such as propantheline and oxybutynin.

Several newer anticholinergics, with reduced side effects, have been developed. These include tolterodine, trosipium and darifenacin. Obstructive symptoms, in general, are poorly responsive to any pharmacological manipulation. Though unusual, some patients have “off” period anuria, and a schedule of voiding timed with levodopa treatment may be needed. Surgical treatment of obstruction may also be helpful, but there is a high incidence of postsurgical incontinence. Sometimes, intermittent catheterization may be needed to avoid obstructive uropathy.

Constipation is best approached by a “stepped” treatment. If mild, constipation may be improved by exercise, adequate intake of fluids and the inclusion of fresh or dried fruits or bran in the diet. Stool softeners and bulk-forming agents may be helpful, with the proviso that adequate hydration is maintained. Other measures that may be helpful are osmotic agents, such as oral sorbitol or lactulose, or glycerin suppositories. Bowel stimulants such as bisacodyl, senna, cascara or phenolphthalein are effective but may lead to dependence. A number of treatments are available for impotence, and are best addressed by a urologist.

Treatment of orthostatic hypotension may also be challenging. Levodopa and other dopaminergic drugs commonly induce hypotension and the dose of these drugs may have to be reduced or the medication eliminated, even at the expense of motor functioning in some patients. Reduction or elimination of other medications that can worsen hypotension, such as hypnotics or antidepressants, may be necessary. Selegiline may worsen levodopa-induced hypotension and may take some time to resolve after it is discontinued. Other treatments for orthostatic hypotension include a high-sodium diet, pressure stockings, flu-drocortisone and midodrine. Other medications that have been reported to be helpful include nonsteroidal anti-inflammatory
medications, clonidine, ephedrine, domperidone and propranolol, but these medications are generally inadequate.

Cognitive and behavioral problems are some of the most challenging symptoms to treat. As in other patients with severe parkinsonism, adverse drug effects and coexistent medical conditions need to be carefully excluded. Even focal impaction, for example, may present by worsening of behavior in patients with severe parkinsonism. Hypersexuality, visual hallucinations, paranoid ideation and reversal of sleep-wake cycles are early signs of dopaminergic toxicity, and should prompt either reduction of the dose or elimination of antiparkinsonian drug treatment, particularly dopamine agonists. Even some drugs not commonly considered as causing drug toxicity, such as digoxin, propranolol, oxbytunin or diphenhydramine, could cause confusion.

Patients and spouses should be carefully questioned about sleep disorders. Several parasomnias are quite common in patients with Parkinson’s disease and may include restless leg syndrome and periodic limb movement disorder, sleep apnea, and REM behavior disorders. These disorders may contribute to or cause nocturnal agitation and vivid dreaming, and may also cause daytime somnolence and worsening of memory and concentration.

Treatment options vary as to the specific problem, but may include additional night-time doses of levodopa or dopamine agonists, benzodiazepines, reduced doses of dopamine agonists during the day, or adjunctive CNS stimulations such as modafinil. 11,32

Drug treatment of agitation and psychosis include sedatives and anxioytics and sedating antidepressants. In patients with dementia in particular, though, these medications are not well tolerated and may worsen agitation, and an antipsychotic medication is needed.

The choice of antipsychotic medications is limited. Standard, older antipsychotics such as haloperidol and thioridazine worsen motor function and are not useful. Of the newer, atypical antipsychotics, the best tolerated drug seems to be clozapine; this medication has few extrapyramidal effects and can even improve tremor and is well tolerated and effective in reducing psychosis. 33 However, it can cause agranulocytosis and is only used with frequent blood monitoring.

Quetiapine is a useful alternative; it is generally effective and is tolerated well long term, although it can worsen parkinsonism to a mild extent in up to 34 percent of patients. 34 Olanzapine is less well tolerated than the other drugs; its use in patients with Parkinson’s disease carries a risk of worsening motor function. 35

Donepezil may be another option; it has been shown to improve cognition in patients with Parkinson’s disease 36 and some small studies and case reports have described an improvement in psychosis as well. 37 In addition, rivastigmine was recently granted FDA approval to treat PD dementia. PN

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