CLINICAL REVIEW

Practical Guidelines for Management of Parkinson Disease

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Background: **This article describes a specialist's perspective on the challenge of caring for patients with Parkinson disease in a changing American health care environment that places increasing responsibility on primary care physicians.**

Methods: **Guidelines were developed by drawing from a combination of personal experience at a large university Parkinson disease clinic, literature review, presentations at various family practice continuing medical education conferences, and involvement as investigator in various clinical trials of drugs used in Parkinson disease treatment.**

Results and Conclusions: **From a therapeutic standpoint, Parkinson disease can be divided into three stages—early, nonfluctuating, and fluctuating. Although the same drugs, namely, carbidopa-levodopa preparations, dopamine agonists, and anticholinergic medications, are usually prescribed, their pattern of use, including frequency and dosing, varies depending on the nature of the dominant symptoms and stage of the disease. Management of Parkinson disease requires familiarity with both the disease-related and drug-related components. Optimal functional efficiency for the patient is gained through striking a delicate balance between the drug regimen and the disease-related components. (J Am Board Fam Pract 1997;10:412-24.)**

Parkinson disease remains the most treatable of all neurodegenerative diseases. According to a 1990 survey, 56 percent of all patients with Parkinson disease are cared for by primary care physicians. Because people are living longer, there is a concomitant increase in the number of persons at risk for developing Parkinson disease. For example, one study found the prevalence of Parkinson disease to be 0.3 percent in those aged 55 to 64 years, 1.0 percent in those aged 65 to 74 years, 3.1 percent in those aged 75 to 84 years, and 4.3 percent in those aged 85 to 94 years.[1] Before levodopa was available, the death rate for persons with Parkinson disease was three times the death rate of the general population. After the introduction of levodopa therapy, a distinct increase in longevity has been observed in patients afflicted with Parkinson disease.[2] This increase is even more striking in patients whose treatment was started early.[3] The net result will continue to be a growing number of patients with Parkinson disease. With the increasing emphasis on management of chronic diseases by primary care physicians, it is important that they understand the therapeutic treatment of Parkinson disease.

Parkinson disease (paralysis agitans) is a disease of unknown cause characterized by rest tremor, muscular rigidity, bradykinesia, and gait disturbance; it is associated with loss of pigmented neurons in the substantia nigra and the presence of eosinophilic inclusion bodies in the cytoplasm called Lewy bodies. Parkinsonism is a syndrome characterized by the above signs and symptoms, with or without loss of pigmented neurons in the substantia nigra, and without Lewy bodies. Parkinsonism is associated with the conditions listed in Tables 1 through 3. Although idiopathic Parkinson disease is the most common form, about 15 percent of patients with an initial diagnosis of idiopathic Parkinson disease are found to have one of the other forms after a few years.[4]

Classification of Parkinson disease has been based on pathologic changes in the brain, symptoms and clinical signs, or degree of disability. I have grouped Parkinson disease and other conditions in which parkinsonism occurs according to

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symptoms and clinical signs. Such grouping will help determine therapeutic responses to various antiparkinsonian drugs regardless of the underlying pathological abnormality. When no specific reference is made, treatment will focus on the major symptoms of the disease, namely, rigidity, tremor, gait disturbance, and bradykinesia. Postural disturbance, which develops in later stages, does not respond well to any known drug treatment. The exact cause of postural disturbance is not known, although certain theories have been postulated. Such rehabilitative measures as gait training and using devices such as a cane or walker remain the only viable aids.[5]

Methods

Guidelines were developed by drawing from a combination of personal experience at a large university Parkinson disease clinic, literature review, presentations at various family practice continuing medical education conferences, and involvement as investigator in various clinical trials of drugs used in Parkinson disease treatment.

Therapeutic Stages of Parkinson Disease

From a therapeutic standpoint, Parkinson disease can be divided into three stages: early, nonfluctuating, and fluctuating. In early-stage Parkinson disease, such symptoms as tremor, changes in handwriting, bradykinesia, and drooling begin to appear. Sometimes these symptoms become evident after a surgical procedure, an injury, or emotional trauma. Symptoms remain mild for months to years, and while they can be socially embarrassing to the patient, functionally little if any disability is experienced. Some patients require medications with mild antiparkinsonian action at this stage.

When the disease progresses to a point at which mild medications can no longer control the symptoms, patients are considered to have entered nonfluctuating Parkinson disease. At this time, adding a carbidopa-levodopa preparation to the drug regimen almost always becomes necessary. With this medication, patients should experience an 80 percent improvement in symptom control. It is important that physicians resist the temptation to improve functioning by 100 percent, because the therapeutic and toxic ranges of levodopa are very close. Patients usually continue to function well for several years, are often gainfully employed, and carry out normal daily activities, but progression of the disease and continued levodopa therapy eventually take their toll. Additional symptoms, such as difficulty with balance, dyskinesia (involuntary choreoathetotic movements), dystonia (involuntary abnormal postures), myoclonus (quick movement caused by muscular contractions), nightmares, autonomic symptoms (constipation, orthostatic hypotension), depression, and dementia, begin to appear.

Table 1. Differential Diagnosis of Parkinsonism.

Idiopathic	Parkinson disease (paralysis agitans, shaking palsy)
Postencephalitic	Lethargic encephalitis (Von Economo disease)
	Other viral encephalitides
Drug induced	Neuroleptic medications (including metoclopramide)
	Reserpine
Toxin induced	1-methyl-4-phenyl-1,2,3,6-tetrahydropyridine (MPTP)
	Manganese
	Carbon monoxide
	Carbon disulfide
	Cyanide
Metabolic	Hypothyroidism
	Hypoparathyroidism with basal ganglia calcification
Degenerative	Bilateral striopallidodentate calcinosis (Fahr disease)
	Diffuse Lewy body disease
Genetic	Wilson disease

A patient is said to enter the fluctuating stage of Parkinson disease when motor fluctuations (marked inconsistencies in control of parkinsonian signs and symptoms) occur. Motor fluctuations are of two types. In end-of-dose deterioration or wearing-off effect, the duration of therapeutic action from a given dose of levodopa preparation lasts for decreasing periods. With time patients might have to take these preparations every 90 to 120 minutes. In the on-off phenomenon, patients fluctuate suddenly from no therapeutic benefit to complete improvement of symptoms, often with dyskinesia unrelated to the dosage or timing of levodopa preparations. The duration of the therapeutic benefit (on) or lack thereof (off) can last for unpredictable periods and cause severe disability. Not every patient develops on-off phenomenon. Some have several years without any major complications, or they experience only mild degrees of delayed adverse effects. There are no known predisposing factors to predict who might develop complications. During this stage freezing (tempo-

Table 2. Diseases With Parkinsonism Characteristics.

Progressive supranuclear palsy
Multiple system atrophy
Striatonigral degeneration
Shy-Drager syndrome
Olivopontocerebellar atrophy
Parkinson-dementia-amyotropic lateral sclerosis complex of Guam

rary, involuntary inability to move when initiating gait) can also occur.

The transformation from nonfluctuating to fluctuating is gradual. It is estimated that the incidence of adverse effects attributable to levodopa therapy, such as motor fluctuations, dyskinesia, and dystonia, is 50 percent after 5 years of continuous therapy.[6-9] Levodopa-naive Parkinson disease patients who were given either immediate-release carbidopa/levodopa (Sinemet,) or controlled-release carbidopa/levodopa (Sinemet CR) in a double-blind trial had an incidence of motor fluctuations and dyskinesia after 5 years of 20.6 percent for the immediate-release group and 21.8 percent for the controlled-release group.[10] Motor fluctuations, dyskinesia, dystonia, freezing, dementia, and depression, either singly or in combination, can greatly impair a person's ability to perform activities of daily living. In addition, evening confusion followed by agitation (sundown syndrome) and visual hallucinations can occur during the fluctuating stage; these effects usually do not disturb the patient initially, but with time can become unpleasant. As the disease progresses, difficulty with balance, combined with motor fluctuations, dyskinesia, dystonia, and freezing, can cause the patient to become dependent on a wheelchair or a walker for at least part of the day.

General Pharmacologic Management

Family physicians often recognize early-stage Parkinson disease. Patients complain of tremor, "not doing as well as before in activities of daily living" (bradykinesia), difficulty with balance or walking, or a number of vague symptoms. Physicians can elicit some of these symptoms and signs during an annual physical examination, or they might surface after a traumatic physical, emotional, or surgical event.

Therapeutic management of the three stages of Parkinson disease varies, with the management of the fluctuating stage being the most difficult. Most often, early and nonfluctuating stages can be managed by the family physician, whereas the fluctuating stage is best handled by a neurologist who has special training in movement disorders. Patients who have any atypical symptoms of the disease (Tables 1 to 3) and patients who do not respond to standard treatment should always be referred to a neurologist. Since the introduction of levodopa, the growing number of new drugs for treatment often causes confusion among physicians, who might be unsure which drug or combination of drugs to prescribe. Unlike treatment for many diseases, treatment of Parkinson disease is tailor-made for each patient. The plan should be to redefine the therapeutic goal at various stages of the disease. This plan should be discussed with the patient to promote realistic expectations. The primary goal in all stages is to attain functional improvement in the patient's condition by using the fewest drugs as infrequently as possible.

In early-stage Parkinson disease functional improvement can range from 85 to almost 100 percent. In the nonfluctuating stage, improvement can range from 75 to 85 percent; and in the fluctuating stage, a 50 to 60 percent improvement might be the highest attainable.

The choice of drug therapy varies with each patient and is dependent upon several factors. During the initial evaluation of Parkinson disease, it is important to determine whether the patient is already taking antiparkinsonian medications, and whether the patient should continue with the same drug regimen or would benefit more by a dosage change or the addition or deletion of certain drugs. To make these determinations, it is important to know the stage of the disease and the degree of disability; likewise, patient and physician expectations should be clarified. For example, a farmer whose initial major signs are resting tremor and some bradykinesia might not require therapy, because the resting tremor might disappear when the patient's hands are on the steering wheel of a tractor or are otherwise engaged in a motor activity. A corporate executive might find the same symptoms unacceptable and will want therapeutic intervention. What might be considered disabling in one profession will not be in another.

When a patient with early-stage Parkinson disease is examined, it is important that the physician assess whether the patient's symptoms interfere with any function and whether the predominant symptoms are tremor or bradykine-

sia and rigidity. Findings from this assessment can help shape therapeutic intervention strategies and determine the type of initial medications. Early-stage Parkinson disease usually lasts from several months to 2 to 3 years after symptoms develop. If a patient is not taking any drugs and is functioning well, no intervention is necessary, at least initially. The patient should be told about the various modes of treatment to consider as symptoms worsen or new symptoms develop. It is difficult to predict precisely when to begin various treatments, but most patients generally require treatment within 2 years of disease onset.

During early-stage Parkinson disease, if the symptoms are not severe, mild antiparkinsonian drugs, such as amantadine (Symmetrel), anticholinergic medications (trihexyphenidyl or benztropine), selegiline (Eldepryl, Carbex), diphenhydramine (Benadryl), or the dopamine agonists bromocriptine (Parlodel) and pergolide (Permax) can provide up to 90 percent improvement in symptoms. If patients are taking a carbidopa/levodopa preparation, it is important that dosage and frequency be adequate. When tremor is a predominant symptom, the first drug of choice might be propranolol, especially the controlled-release formulation (Inderal LA). The second choice would be anticholinergic medications. A 70 percent reduction in tremor amplitude was reported after administration of controlled-release propranolol (160 mg/d) compared with a 50 percent reduction from administration of trihexyphenidyl (an anticholinergic), and a 25 percent reduction from amantadine.[11,12] Selegiline also has a mild antiparkinsonian effect.

Levodopa Preparations

Patients can do well on amantadine therapy, 100 mg twice daily, for several months, but controlled-release or immediate-release carbidopa/levodopa should be prescribed when symptoms worsen and amantadine is no longer effective. Controlled-release carbidopa/levodopa is believed to provide continuous stimulation to dopaminergic neurons, resulting in a possibly reduced risk of motor fluctuation onset, whereas immediate-release carbidopa/levodopa provides a pulsatile effect or intermittent stimulation. A controlled-release formulation (Sinemet CR) is available in either a carbidopa/levodopa combination of 25/100 mg or 50/200 mg. Because the bioavailability of controlled-release is less than that of immediate-release carbidopa/levodopa, dose frequency should be based on the patient's wake-up time to bedtime with 8 hours intervening. Controlled-release carbidopa/levodopa should be taken twice daily, generally between 7 and 8 AM and 3 and 4 PM, for adequate control of symptoms. If the initial 25/100-mg dose of controlled-release formulation is inadequate, it is better to prescribe one 50/200-mg tablet instead of two 25/100-mg tablets.

Because of the slow release of controlled-release carbidopa/levodopa, the interval between the time the drug is administered and the onset of therapeutic effect (kick-in) might be unacceptable for the patient. To speed up onset of action, one 50/200-mg controlled-release tablet may be broken in half (the unscored 25/100-mg tablet cannot be broken) and both halves swallowed at the same time. Breaking the tablet exposes the uncovered segment of the matrix, speeding tablet erosion in the gastrointestinal tract, facilitating absorption, and resulting in early relief of symptoms. Initially a night-time dose is not required. Immediate-release carbidopa/levodopa (available in 10/100 mg, 25/100 mg, and 25/250 mg) has a short half-life and should be taken three to four times daily, preferably before meals to enhance absorption. In a recent 5-year study involving 680 patients (about one half were taking immediate-release and the other half were taking

Table 3. Diseases With Associated Parkinsonian Features.

System or Process	Disorder or Disease
Degenerative	Alzheimer disease
	Corticobasalganglionic degeneration
	Primary pallidal atrophy
	Huntington disease (hypokinetic rigid form)
	Hallervorden-Spatz disease
	Neuroacanthocytosis
	Dystonia-parkinsonism
	Normal pressure hydrocephalus
Vascular	Multi-infarct
	Binswanger disease
	Arteriovenous malformation
Structural	Basal ganglia—tumor, abscess
Infection	Creutzfeldt-Jakob disease
Trauma	"Punch-drunk syndrome"
	Subdural hematoma

controlled-release carbidopa/levodopa), scores of activities of daily living were significantly better for the controlled-release group. There was no significant difference in side effects between the two preparations except that controlled-release carbidopa/levodopa caused more dyskinesias than did the immediate-release form (16.5 percent compared with 12.2 percent).[10]

If the patient is already taking an immediate-release preparation and the physician wants to prescribe a controlled-release form, the following formula for conversion is recommended.[13] The result gives the total number of tablets to be taken in 24 hours.

> *Multiply the milligrams of levodopa in immediate-release tablet times 1.3 divided by the milligrams of levodopa in controlled-release tablet to get the number of tablets of controlled-release carbidopa/levodopa (closest to the next higher strength), ie,*
>
> *xx mg IR × 1.3/xx mg CR = x tablets per 24 h*

In an adult the minimum amount of carbidopa required to prevent breakdown of levodopa outside the blood-brain barrier, so that the given dose of levodopa is utilized at the site of action in the brain, is 75 mg, although a smaller dose can be effective. A few patients, most often women, develop dyskinesia even on low-dose levodopa preparations. If these patients are switched to a dopamine agonist and the dyskinesias disappear, they might be sensitive to levodopa. Some physicians prescribe dopamine agonists, amantadine, or selegiline in the belief that withholding levodopa preparations for as long as possible will delay levodopa-related adverse effects, but there is no evidence to support this notion.

Dopamine Agonists

Dopamine agonists are second to carbidopa/levodopa preparations as the most effective drugs for controlling all major symptoms associated with parkinsonism. These drugs, however, are not as effective for the nonfluctuating and fluctuating stages. In one study, adding bromocriptine or pergolide to the drug regimens of patients for whom levodopa was previously prescribed resulted in substantially improved evaluation scores, but no difference in occurrence of dyskinesia, dystonia, or psychosis.[14] Dopamine agonists alone can be adequate to control symptoms in early-stage Parkinson disease, but as the disease progresses, the addition of levodopa preparations becomes necessary.

Dopamine agonists should be prescribed in high doses for the few patients who cannot tolerate levodopa even when combined with high doses of carbidopa. For example, bromocriptine, 60 to 80 mg/d in three to four divided doses, with the dosage increased gradually, can be effective. The efficacy ratio of pergolide to bromocriptine is 10:1, which means that one 0.25-mg tablet of pergolide equals one 2.5-mg tablet of bromocriptine. Pergolide can have a faster onset and longer duration of action than bromocriptine. The adverse effects of pergolide and bromocriptine are almost identical, and patients should be monitored for peptic ulcer disease and livido reticularis (a discoloration of the skin). Care should be exercised when prescribing dopamine agonists for patients with known coronary artery disease.

Early therapy combining bromocriptine with levodopa did not prevent motor fluctuations, and the overall adverse effects were the same for the group taking levodopa alone as for the group taking a levodopa/bromocriptine combination.[15] There have been several studies comparing levodopa/dopamine agonist combination therapy with dopamine agonist monotherapy to evaluate whether motor fluctuations and dyskinesia can be delayed or reduced.[16-24] Whether early use of dopamine agonists in combination with levodopa will prevent or delay onset of motor fluctuations and dyskinesia remains controversial, however. The differences in the results of some studies are likely due to the study methods and the problems relating to open-label trials and the use of historically matched treatment control groups.[25]

Selegiline

Whether to use selegiline is a question that baffles physicians and patients. Failure to induce parkinsonism in experimental animals exposed to MPTP (1-methyl-4-phenyl-1,2,3,6-tetrahydropyridine) after pretreatment with selegiline (a monoamine oxidase type B inhibitor) led researchers to speculate that selegiline might have a neuroprotective effect.[26] In several studies selegiline was evaluated in patients with Parkinson disease, but whether the drug provided any neuroprotective effect could not be firmly concluded.[27-30] The mild symptomatic antiparkinsonian action of selegiline delays the need for levodopa treatment, but this delay does

not mean it has a neuroprotective effect. The degree of antiparkinsonian effect produced by selegiline is not cost effective when compared with levodopa preparations, dopamine agonists, or amantadine. All that could be concluded from a large study comparing selegiline (earlier generic name was deprenyl) with placebo in patients with newly diagnosed Parkinson disease[29] was that selegiline might delay the need for a more powerful antiparkinsonian drug, such as levodopa. Amantadine could also delay the need for treatment with levodopa.

The decision to prescribe selegiline rather than amantadine for early stage Parkinson disease before the patient requires levodopa preparations is based on the severity of symptoms, what the treating physician and the patient expect from selegiline therapy, and an understanding of cost effectiveness. When selegiline is discontinued, a few patients might experience deterioration in mood, level of energy, or performance. Although these responses are considered a placebo effect, there could be a pharmacologic explanation, as selegiline is metabolized to amphetamine products.[31]

Management of Symptoms

Tremor

For some patients with Parkinson disease tremor is the major symptom, and rigidity and bradykinesia are minimal or absent. Tremor can be incapacitating. In early-stage Parkinson disease, if tremor is the major symptom and there is a considerable postural component, distinguishing Parkinson disease from essential tremor can be difficult and require the assistance of a specialist.

Treatment of tremor is often challenging. Carbidopa/levodopa preparations do not reduce tremor but must be prescribed if there is associated mild rigidity. Propranolol, a centrally acting adrenergic β-blocking agent, is considered more effective for controlling tremor than are anticholinergic drugs.[11,12] Controlled-release propranolol confers sustained benefit as a single daily dose and, when taken in the morning, can provide uninterrupted benefit throughout the wakeful period. Tremor is not manifest during sleep. The recommended initial dose for controlled-release propranolol is 60 mg in the morning; depending on the response, the dosage may be increased to 80, 120, or 160 mg daily. Ideally, this dose should be taken as a single tablet. The patient's heart rate should be monitored, as β-blockers adversely affect heart rate. The usual contraindications for using β-blockers, such as bronchial asthma, bradycardia, and congestive cardiac failure, should be kept in mind.

If the patient cannot tolerate propranolol, then anticholinergic drugs would be the next choice. Although dementia is much less likely when tremor is predominant, if the patient has dementia, anticholinergic drugs should be avoided, because they can precipitate confusion. Anticholinergic drugs can also precipitate urinary retention in subclinical benign prostatic hypertrophy. Dry mouth and throat secondary to anticholinergic drug therapy usually improve after a few days.

Anxiety can be associated with and provoke tremor. Diphenhydramine, which produces both a sedative and anticholinergic effect, would be the drug of choice for those patients who experience anxiety in addition to tremor. Diphenhydramine would also be the hypnotic of choice for patients whose tremor causes difficulty falling asleep. A starting dosage regimen of 25 mg 4 times daily can be increased as necessary. Elderly patients should be monitored for confusion. In a few patients, diphenhydramine might not control exaggerated tremor resulting from anxiety. In such cases a combination of anticholinergic drugs or propranolol and a tranquilizer, such as diazepam (Valium) or alprazolam (Xanax), can be effective. Patients who are taking propranolol should be observed for signs of depression. If tremor is not controlled adequately with the above-mentioned drugs prescribed at the maximum tolerated dosages, then the patient is unlikely to benefit from pharmacologic therapy. The only choice available to control tremor would be a surgical procedure such as thalamotomy.

Rigid Form of Parkinson Disease

Some patients with Parkinson disease complain of bradykinesia and rigidity as the predominant symptoms and have minimal or no tremor. Although many of these patients will have idiopathic Parkinson disease, which is diagnosed at autopsy, some will have one of the other forms of parkinsonism listed in Table 1. In many patients the initial clinical symptoms and signs suggest idiopathic Parkinson disease, but additional symptoms and signs that appear with time often lead to a more precise diagnosis. Older age at onset and

bradykinesia, rigidity, and postural instability can be associated with considerably more intellectual and motor impairment and greater progression of the disease than is found in tremor-predominant, younger-onset patients.[32] Regarding treatment, carbidopa/levodopa preparations are the first drugs of choice for controlling rigidity; dopamine agonists and amantadine are second. Anticholinergic drugs do not help alleviate rigidity.

Asymmetric and Hemiparkinsonism

A few patients will manifest asymmetric parkinsonism, meaning that one side of the body shows a more severe degree of involvement than the other. Although it is advantageous to the patient to have fewer signs and symptoms on one side, treatment is a challenge. A given dose of a drug such as carbidopa/levodopa might inadequately control the symptoms on one side while overloading the less affected side, resulting in dyskinesia. Achieving optimal control by titrating the dose can be difficult. In hemiparkinsonism the symptoms persist on one side for several years, if not permanently, and tremor might be the major visible symptom. Otherwise, the management of asymmetric and hemiparkinsonism is identical to that of bilateral Parkinson disease.

Care of Patients Intolerant to Levodopa

Some patients cannot tolerate levodopa. Severe nausea (and vomiting) occurs despite their taking the usual combination of carbidopa and levodopa. Adding carbidopa, which is available as 25-mg tablets, 1 hour before taking the carbidopa/levodopa preparation can alleviate this problem. Certain other patients will develop chorea, even with very small doses of levodopa preparation. Symptom control in this group can be managed with dopamine agonists, though a very few patients will be intolerant to both dopamine agonists and levodopa treatment.

Management of Treatment-related Complications

Dyskinesia

Dyskinesia occurs with two different conditions. For a small group of patients, especially women, even the smallest dose of levodopa causes dyskinesia. In this case, the dyskinesia is an enhanced dopaminergic reaction, and the exact cause is not clear. For most patients dyskinesia develops after taking the same dosage of carbidopa/levodopa for several years. A reduction in the dosage often results in disappearance of dyskinesia without loss of therapeutic benefit. Dyskinesia can occur during the on phase of on-off phenomenon. It can also occur briefly at the onset of therapeutic effect and before the next dose is due (dyskinesia-improvement-dyskinesia), or at the peak effect of levodopa action, about 2 hours after dosing (improvement-dyskinesia-improvement).

When patients complain of dyskinesia, they are often taking a high-dose carbidopa/levodopa preparation or a combination of carbidopa/levodopa and dopamine agonists. The first step is to discontinue the dopamine agonists. If dyskinesia does not abate, then the dosage of carbidopa/levodopa should be reduced. If dyskinesia does not disappear or is not minimized without reducing therapeutic benefit, and if the patient is taking a sustained-release carbidopa/levodopa preparation, which increases the incidence of dyskinesia compared with an immediate-release preparation, then treatment may be switched to the immediate-release form. When all efforts fail, and reducing the carbidopa/levodopa dosage results in inadequate control of symptoms, a dosage compromise must be worked out to maintain adequate functional improvement despite some degree of dyskinesia. Adding anticholinergic drugs has been advocated, but they are not always effective. Patients often prefer to have control of parkinsonian symptoms with dyskinesia rather than a dyskinesia-free state with parkinsonian symptoms on subtherapeutic dosages of carbidopa/levodopa preparations.

Motor Fluctuations

In patients taking immediate-release carbidopa/levodopa who have wearing-off effect, the immediate-release preparation may be replaced with a sustained-release preparation every 3 or 4 hours. In any case, sustained-release preparations should not be taken more often than every 2 hours because of the extended duration of action. This approach is generally effective in most patients for a few years. With time, if this approach does not work, sustained-release carbidopa/levodopa should be replaced with immediate-release carbidopa/levodopa (10/100 mg), every 2 or 3 hours (1.5 hours for some patients) during the wakeful hours. If necessary, one or two doses can be taken during sleeping hours for optimal control.

In patients with on-off phenomenon, management is more difficult, and treatment achieving complete control is not available. The treatment goal is to increase "on" time (there is almost always dyskinesia) and reduce "off" time. Most patients seem to benefit more from sustained-release carbidopa/levodopa, and some patients take the drug as often as every 1 to 3 hours. Adding dopamine agonists, selegiline, or other drugs has not proved beneficial.

A new class of drugs is undergoing investigation as an alternative approach to manage wearing-off phenomenon and to alleviate frequent dosing. Levodopa and dopamine are catabolized by catechol *O*-methyltransferase (COMT), and drugs that potentially inhibit this enzyme would lengthen the plasma half-life of levodopa. Two such drugs, entacapone and tolcapone, are currently undergoing clinical studies and might be available in the near future.[33,34]

There is interest in whether a protein redistribution diet is of any benefit for symptom management. A low-protein regimen during the day, with the evening meal providing the recommended daily allowance of protein, could be an important step in controlling motor fluctuations. Many patients past middle age find it difficult to change dietary habits, however, and often comply with such a meal plan for only a short time. Despite following a protein redistribution diet plan, some patients find no improved change in their pattern of on-off phenomenon.

Dystonia

Dystonia can occur in patients who have been taking levodopa preparations a long time. Although dystonia is uncommon, when it occurs, patients feel acutely uncomfortable because many of the spasms can be painful. For a few patients the foot draws inward. Often these spasms occur early in the morning, when the level of dopa is lowest or absent. This condition is referred to as early morning dystonia and disappears after levodopa is taken. A nighttime dose of controlled-release carbidopa/levodopa will usually avert the problems well.

Sometimes generalized dystonia occurs even when the patient has an adequate amount of drug or when the drug is at peak levels. Treatment with baclofen or anticholinergic medications might alleviate this problem.

Freezing

Freezing is believed to be secondary to the disease itself, not the result of drug therapy. Generally, freezing is unresponsive to any known pharmacologic agents. Patients must be trained to lift one foot at a time in a marching fashion and then propel themselves forward to overcome this disability. Sometimes marching to loud music is beneficial. Some patients initially take a few steps backward then walk forward, but this approach is unwise if they are unable to turn to see where they are going before walking even a few steps backward.

Surgical Treatment

An autologous adrenal medullary transplant to corpus striatum has been performed in more than 200 patients worldwide. Although some improvement in parkinsonian symptoms has been reported, no posttransplant reduction in the need for antiparkinsonian medications occurred.[35] Substantial postoperative morbidity and mortality have been reported with no definite evidence of survival of graft tissue.[36] This procedure has been almost abandoned.

A fetal dopamine neuron transplant, using ventral mesencephalic tissue from aborted human fetuses stereotaxically implanted to the putamen, has resulted in improvement in parkinsonian symptoms. In one study reduction in frequency and disability caused by "off" periods peaked at 4 to 5 months, and there was evidence of survival of the grafted tissue.[37] This procedure remains experimental. It is not widely available, is complicated, and requires long-term immunosuppression therapy.

Thalamotomy can reduce contralateral tremor and, to a lesser extent, rigidity, though ipsilateral tremor, bradykinesia, and postural instability are not improved. The procedure is helpful in tremor-predominant parkinsonism if pharmacotherapy is ineffective or cannot be tolerated. Tremor can return after a few years. Thalamic electrical stimulation is being investigated as an alternative approach.[38]

Bilateral posteroventral pallidotomy, a relatively less complicated procedure compared with fetal tissue transplant, involves creating a lesion between the medial and lateral segments of the globus pallidus. Improvements in rigidity, tremor, levodopa-related motor fluctuations, dyskinesia, and

dystonia result. The complication rate is low, but the procedure is available in only a few centers, and a long-term benefit has not been established.

Management of Secondary Effects of Parkinsonism

Anxiety

Many patients suffer from anxiety associated with Parkinson disease. Bradykinesia causes patients to fall behind normal companions in such activities as walking, talking, or dining, provoking anxiety in addition to that associated with having an incurable illness. Anxiety can manifest as increased tremor, gait disturbance, fear of falling, drooling, difficulty with speech, dysphagia, and insomnia, as well as a host of other symptoms that might not adequately respond to the usual antiparkinsonian drugs unless treatment is supplemented with an antianxiety agent. When patients develop on-off phenomenon and freezing, the superimposed anxiety can make these symptoms even worse. Anxiety, if mild, responds to diphenhydramine, but moderate to severe anxiety requires treatment with tranquilizers and counseling the patient about the relation of parkinsonian symptoms to anxiety.

Constipation

Constipation is a common autonomic manifestation of Parkinson disease. Studies have shown a paradoxical anal sphincter muscle contraction[39] with impaired squeeze response, secondary to involvement of the pelvic floor musculature by Parkinson disease process.[40] Treatment should include mild stimulant laxatives, such as senna alkaloid taken in dosages of 1 to 4 tablets at night on a regular basis. Bulk laxatives do not help, but of course patients should maintain adequate liquid and fiber intake.

Daytime Sleepiness

Parkinson disease results in lack of motivation. Because most patients are disabled to some extent, they tend to sit in a chair or watch television and fall asleep, especially after a meal, often to the annoyance of the spouse. Contributing to this tendency could be disturbed sleep at night as a result of depression or frequent micturition. Levodopa taken late in the evening can also cause sleep disturbance. Stimulants, such as methylphenidate (Ritalin), dextroamphetamine (Dexedrine), and pemoline (Cylert), have been tried with mixed success. A few patients have benefited from selegiline taken during the daytime. Daytime sleepiness is not easy for a physician to remedy. It is important to talk to a family member to ascertain the cause. Some patients require help developing hobbies, or they can be encouraged to spend the daytime in a senior center to keep occupied. Activity keeps patients awake, but sleep is safer than a stimulant drug.

Dementia

Dementia occurs with idiopathic Parkinson disease, but it occurs more often and progresses more rapidly in those who have additional neurologic disorders, such as extensor plantar response, or who have cerebellar signs such as those found in olivopontocerebellar atrophy or paralysis of downgaze. Profound dementia will occur with progressive supranuclear palsy. In one study the age-specific prevalence of dementia for patients older than 70 years was more than twice that of younger patients.[41] The Folstein Mini Mental State Examination[42] or Blessed Short Form[43] evaluation can be administered to assess degree of dementia. Pseudodementia can be caused by depression, and patients show dramatic improvement when suitable antidepressants are prescribed. Causes of treatable dementias should be evaluated and treated before concluding that the dementia is due to Parkinson disease. Rarely does Parkinson disease coexist with Alzheimer's disease.

When dementia occurs, the therapeutic goal of improving motor control should be reduced. A few patients with dementia have sundown syndrome in which they become agitated and have hallucinations with the onset of evening. If the agitation is frequent, clozapine (Clozaril), in doses of 25 to 75 mg, will control these symptoms satisfactorily, but bone marrow function should be monitored for adverse effects through weekly blood tests. If the agitation is occasional, such drugs as thioridazine (Mellaril) could be used. If patients are unable to take oral thioridazine, intramuscular haloperidol (Haldol) might help. Frequent administration of haloperidol should be avoided because of the risk of an added drug-induced parkinsonism. Centrally acting anticholinergic medications (including amantadine and diphenhydramine) should also be avoided, as they can precipitate confusion. Levodopa prepa-

rations should be avoided between 6 PM and 3 AM. Complications of dementia, such as agitation and hallucinations, can be controlled and are discussed separately.

Depression

Depression is common in Parkinson disease, occurring in more than 47 percent of patients.[44] It appears to be part of the disease itself rather than a reactive manifestation. Depression can take the form of worrying, brooding, loss of interest, suicidal tendencies, social withdrawal, loss of libido, or insomnia. Psychomotor retardation can often be masked by underlying bradykinesia. Mild depression does not require any treatment except for patient education, but moderate depression requires pharmacotherapy. An ideal drug for Parkinson disease-related depression is amitriptyline because of its anticholinergic effect. Taken at night, amitriptyline helps with sleep. Most cases of Parkinson disease-associated depression can be managed in a primary care practice; however, some patients who develop severe depression that does not respond to antidepressants will require electroconvulsive therapy. Electroconvulsive therapy, in addition to improving depression, might require a reduction in the dosage of antiparkinsonian drugs; hence, close monitoring is necessary.

Dizziness

Patients with Parkinson disease often report a history of vague dizziness. With questioning, however, this dizziness often turns out to be unsteadiness of gait. A few patients have orthostatic hypotension, which causes light-headedness when standing quickly from a lying or sitting position. Blood pressure measurements while supine and then erect are diagnostic. Having patients rise slowly and sit for a minute before standing up will manage the condition if the symptoms are mild. Some patients require salt-retaining drugs, such as fludrocortisone. If, however, the patient has concomitant congestive heart failure or hypertension, for example, and cannot take these drugs, mechanical devices to promote better venous return, eg, Jobst stockings, can help. Many patients resent these stockings, because they are difficult to impossible to put on or take off unassisted. Indomethacin and other milder drugs are not effective, and Ted hose cannot prevent venous pooling in the lower extremities when the patient stands up.

Drooling

Drooling is due to early impairment of the swallowing mechanism. Saliva, instead of draining posteriorly, drools anteriorly. No drug, including the anticholinergic medications, seems to be effective in controlling this symptom. Frequently wiping saliva with dry tissues can result in angular stomatitis. During the night it is best to place a thick cotton Turkish hand towel over the pillow so it can be changed every morning; occasionally the patient will require a bib.

Dysphagia

Dysphagia is common in the later stages of Parkinson disease, and adequate antiparkinsonian drug therapy must be ensured. Dysphagia requires treatment because patients generally tend to give up solid food and adopt semisolid and liquid diets. Patients with advanced disease will require a feeding tube.

Hallucinations

When Parkinson disease is associated with dementia, visual hallucinations, which are often benign, are common and usually do not require any specific treatment. If the hallucinations occur during the latter part of the day, the last dose of levodopa preparation should be given no later than 4 PM. Controlled-release carbidopa/levodopa should not be prescribed for these patients because of its long half-life. Even with preventive measures, some patients will develop considerable agitation associated with hallucinations. In this case, the hallucinations can be effectively treated with clozapine.

Sleep Disturbance

Sleep disturbance is common in Parkinson disease. In a study of 220 patients, 215 reported difficulties at night or upon waking. The most common problem was an inability to turn over or get up to use the bathroom during the night. Two thirds of patients considered their quality of sleep to be acceptable, however.[45] Causes of sleep disturbance are many and include the disease itself. When the patients go to bed, even searching for a comfortable sleeping position can interfere with falling asleep. For patients who have trouble

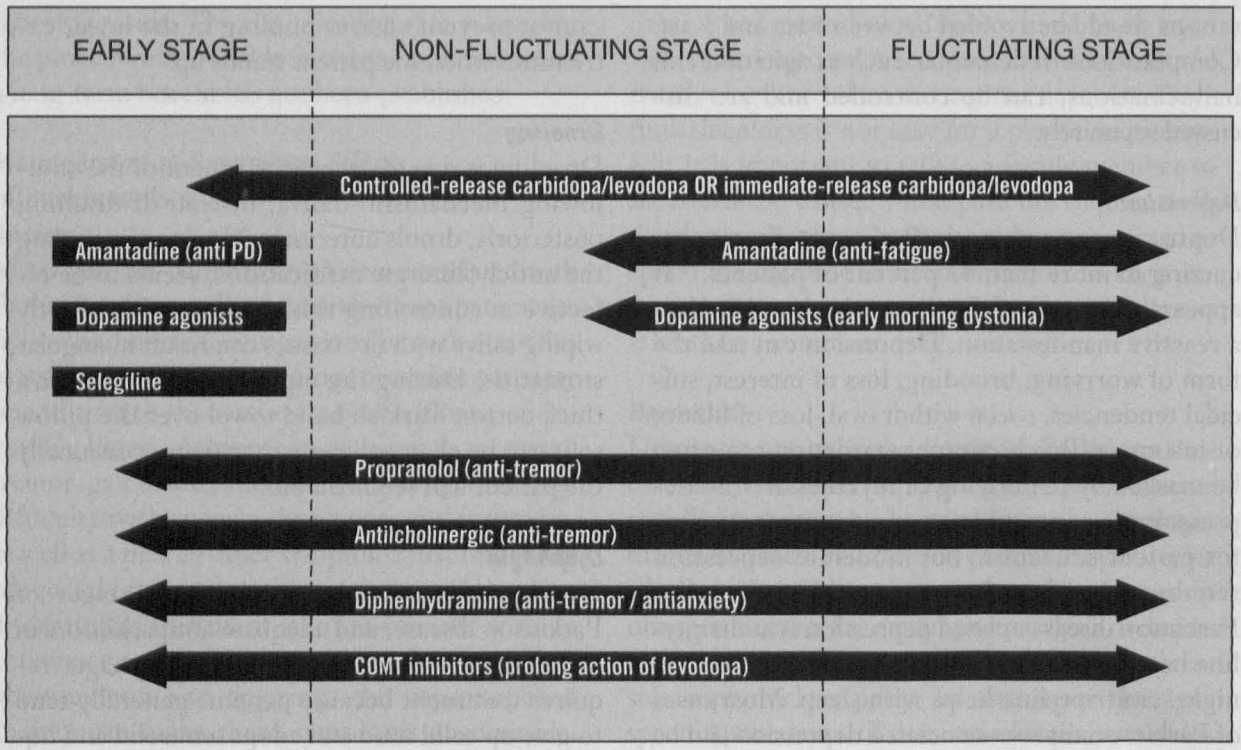

Figure 1. Drugs for Parkinson disease at various stages of disease.
PD - Parkinson disease, COMT - catechol *O*-methyltransferase.

turning around in bed, satin sheets can be helpful because they are slippery.

Severe tremor, which can prevent sleep, is best treated with diphenhydramine; its anticholinergic effect suppresses tremor and its sedative effect induces sleep. Because levodopa is a stimulant, it could stimulate the bladder, which would require getting up several times during the night. Patients on levodopa therapy are also more susceptible to myoclonus, in which case methysergide will be effective. Nightmares are not uncommon, as levodopa and dopamine agonists are known to induce vivid dreams. Depression can disturb sleep in various ways.

Treating sleep disturbance depends on its cause. Adhering to a daytime exercise program can be beneficial, as physical exertion induces sleep. If parkinsonian symptoms cause sleep disturbance, a dose of controlled-release carbidopa/levodopa (diphenhydramine, if tremor is the major symptom) before going to bed might help. On the other hand, if levodopa causes sleep disturbance through its stimulant effect, the last dose of controlled-release carbidopa/levodopa should not be taken after 4 PM, and the last dose of a standard carbidopa/levodopa preparation should not be taken later than 7 PM. A very few patients will benefit from a mild hypnotic, preferably prescribed for periodic use.

Speech Disturbance

Vocal loudness, articulation, rate of speech, and content are affected in Parkinson disease as the disease progresses. Hypophonia develops as a result of abduction of the vocal cords. Moderate hypophonia might require a speech amplifier, whereas severe hypophonia will require treatment with an injection of collagen into the vocal cards.

Conclusions

Parkinson disease is a neurodegenerative disorder. As it progresses, additional signs and symptoms occur because of the disease itself and as a complication of long-term treatment. All available treatments are symptomatic. Several factors influence drug selection and dosing. The main goal is always to maintain activities of daily living for as long as possible. Family physicians and neurologists caring for patients with Parkinson disease should be aware of the patients' occupations and expectations and should educate patients and their families on the merits and limitations of available drugs. Dosing of levodopa

preparations and anticholinergic drugs should be timed to the patients' routine of waking and sleeping. Selegiline should not be administered later than 8 hours before bedtime because it can interfere with onset of sleep. All other antiparkinsonian drugs can be administered at standard times. The timing for various drugs that are important at the three different stages of the disease is schematically displayed in Figure 1.

Although the overall management of Parkinson disease can appear to be complex, the family physician will be involved in all stages of the disease, so a basic knowledge of treatment and its limitations is important. There are times when referral to a neurologist specializing in Parkinson disease becomes necessary. If the family physician or neurologist cannot successfully manage such symptoms as depression, dysphagia, and hypophonia that occur during the course of the disease, referral to other specialists will be necessary. For example, depression can be so severe that a patient will require referral to a psychiatrist for possible electroconvulsive therapy, or a patient with dysphagia that occurs in the late stage of the disease might require referral to a gastroenterologist to exclude local causes or to place a feeding tube. Similarly, the patient might be referred to a urologist if urinary frequency occurs either as a result of levodopa therapy or other local causes.

Several newer drugs—the catechol *O*-methyltransferase inhibitors tolcapone (Tasmar) and entacapone (Comtess), and the dopamine agonist ropinirole (Requip)—are expected to be available in the near future, and the dopamine agonist pramipexole (Mirapex) has just been approved, so it is important to stay abreast of new strategies for managing Parkinson disease.

Brissaud said in 1895: "Parkinson disease remains so utterly inexplicable that we are constantly drawn to it by the lure of the mysteries." It is not surprising that even after 100 years modern science is still trying to solve the many mysteries of this disease.

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