

Parkinson's disease

Update in diagnosis and symptom management

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Parkinson's disease (PD) is a progressive neurodegenerative disorder with a high burden of morbidity. Because no diagnostic test exists for PD, clinical knowledge and skill are key to making an early, accurate diagnosis. Diagnostic criteria for PD require at least two of three motor signs: tremor, rigidity, or bradykinesia. Levodopa and the dopamine agonists are considered first-line drug therapy. Recent studies have shown a lower incidence of dyskinesia in patients who began therapy with a dopamine agonist, although levodopa may be better tolerated by patients age 70 or older. Combinations of medications and rehabilitative, alternative, and surgical therapies can often help patients achieve adequate control of PD motor symptoms and maintain a high quality of independent living.

Marjama-Lyons JM, Koller WC. Parkinson's disease: Update in diagnosis and symptom management. *Geriatrics* 2001; 56(Aug):24-35.

Parkinson's disease (PD) is a syndrome characterized by resting and postural tremor, rigidity (muscle stiffness), bradykinesia (slowness of movement) and postural instability (imbalance). This progressive neurodegenerative disorder affects 110 in 100,000 persons in the United States and 1 in 100 persons over age 60.¹ As the older population increases, so too does the need for early, accurate diagnosis and proper treatment of PD.

Although there is no known cure for PD, new information has expanded

our treatment options and improved our ability to manage the disabling symptoms of this movement disorder, both in the early and later stages of PD. Clinically, advances have been made with respect to the role of dopamine agonists in preventing motor complications, the use of catechol-*O*-methyl transferase (COMT) inhibitors, and improvements in surgical treatments.²

This article provides a practical, updated approach to making the diagnosis of PD in primary care practice and offers guidelines for initiating and maintaining appropriate drug and nondrug therapies.

Diagnosis of PD

Making an accurate diagnosis of PD depends first on obtaining a detailed, focused history. To meet the criteria for a clinical diagnosis of PD, a patient should have at least two of three motor signs: tremor, rigidity, or bradykinesia. Because there is no specific diagnostic

test for PD, the diagnosis is based upon the physician's clinical skills.

Tremor. The clinician should have a list of questions in mind when evaluating a patient with possible PD. For example, an obvious question would be whether the patient has ever noted any tremor. The tremor of PD is more evident at rest, typically lessens with use of the affected limb, and is usually unilateral in the early stages. As many as 30% of PD patients may not have notable tremor, however, and the lack of a history of tremor should not dissuade one from considering a diagnosis of PD.

Rigidity. Some patients will complain of muscle soreness or stiffness or generalized aches and pains indicative of underlying rigidity. These nonspecific symptoms are less helpful in diagnosing PD, as they often occur in other common illnesses such as arthritis or musculoskeletal strain.

Bradykinesia. Most PD patients have some degree of bradykinesia, which the patient often misinterprets as weakness of the affected side. Bradykinesia may manifest in a variety of ways. The presence of all of the following symptoms should be sought by the treating physician during the initial history taking:

- Difficulty with simple motor tasks such as buttoning, tying shoes, putting on socks or pantyhose, getting up out of a chair or car, or turning over in bed are common manifestations.

- Bradykinesia may result in the classic shuffling gait of PD or present

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with more subtle gait disturbances such as a reduction in arm swing on one side (loss of associated movement) or dragging of one leg or simply walking at a slower rate.

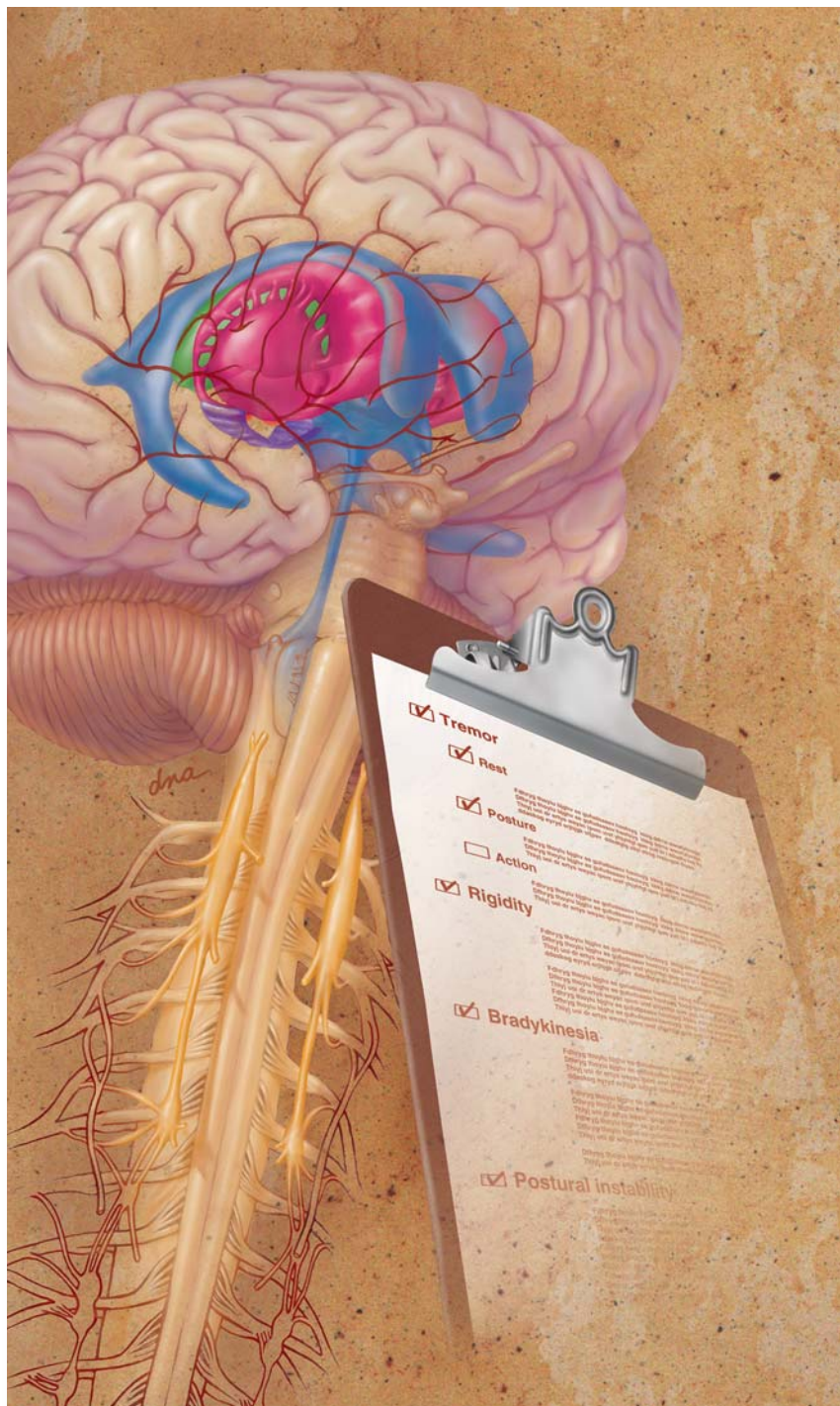
- Micrographia, or small handwriting, is very suggestive of PD.
- Bradykinesia-related reduced facial expression and hypophonia (a reduction in the volume and clarity of one's voice) may be misinterpreted by family members or health care professionals as depression or anger.

Postural instability. PD patients may have trouble with balance and report frequent falling, stumbling, or near-falls. Imbalance occurs more often when a patient is attempting to stand up or turn. It is extremely important to ask the patient about balance problems due to the potential injuries that may result from falling, such as hip or wrist fractures. These problems, however, are uncommon in early PD.

Autonomic dysfunction. The autonomic nervous system (ANS) can be affected in PD, and a host of symptoms related to autonomic dysfunction may occur, such as constipation, drooling, dysphagia, blurry vision, postural hypotension, and impotence. Severe ANS symptoms suggest other parkinsonian syndromes.

Drug-induced symptoms. Obtain a complete list of the medications the patient is taking to rule out the possibility of drug-induced parkinsonism. All dopamine receptor-blocking drugs can cause parkinsonism. These agents include the antipsychotics (eg, haloperidol, chlorpromazine), antiemetics (eg, metoclopramide, prochlorperazine, promethazine) and dopamine-depleting drugs such as reserpine and tetraabenazine. Some of the newer atypical antipsychotics (eg, clozapine, quetiapine) are less likely to induce parkinsonism.³

True drug-induced parkinsonism should be reversible, but parkinsonian symptoms may not resolve for weeks to months after a patient stops taking the offending agent. The finding of striatal lesions on MRI may correlate with a slow recovery rate.⁴



Diagnosis of Parkinson's disease (PD) is based upon the physician's clinical skills because there is no specific diagnostic test. To meet the criteria for PD, a patient should have at least two of the three motor signs: tremor, rigidity, and bradykinesia.

Illustration for Geriatrics by David Baker

Physical examination

Tremor. In very early PD, a postural tremor with no resting component may exist. Some PD patients may not have tremor, however, and the lack of tremor does not exclude the diagnosis.

The tremor of PD is typically a 4- to 6-Hz resting tremor involving the arm and/or leg that lessens with use of

the affected limb.⁵ Tremor usually begins on one side and remains more severe on the initially affected limb. Tremor can also involve the chin but typically does not involve the voice or head as occurs in essential tremor.

The examiner should always observe for tremor in the three phases of rest, posture (limbs extended and held

against gravity), and action (finger to nose and heel to shin). A common mistake is to misdiagnose postural tremor as resting tremor while the patient's arms are resting on the arms of a chair. The examiner should always reposition the arms onto the patient's lap or have the patient recline in the supine position on the exam table to observe for true rest tremor.

Essential tremor may be misdiagnosed as PD but in most cases is easily distinguishable. With essential tremor, there is no resting tremor but rather an increase in tremor with use of the affected limb. Essential tremor may involve the head and voice, which is rare in the tremor of PD. Patients with essential tremor lack the other motor signs and symptoms of PD, and they usually have a family history of essential tremor, as it is an inherited, autosomal-dominant disorder. Less than 1% of cases of PD are thought to be familial in origin.⁶

Bradykinesia. Bradykinesia can be examined in a variety of ways. First, simply observe the patient get up out of a chair and walk into the exam room. The patient may have to rock upward several times, use his/her arms to push off, or ask someone for assistance. Also observe for a decrease in arm swing on one or both sides, mild dragging of one leg, small shuffling steps, and stooped posture.

PD patients may freeze suddenly while walking (especially when going through doorways or tight spaces) or hesitate after standing and be unable to initiate ambulation. Turning may be more cumbersome and may require taking several extra small steps and result in an arc-shaped or semicircle pattern. The patient's rate of facial expression, eye blink, and spontaneous gesturing may be reduced and more evident by comparison to someone else in the room.

Test micrographia by having the patient repeatedly sign his or her name five to ten times vertically down unlined paper. A significant decrease in the amplitude of the letters and the

width of the name is characteristic of true micrographia (figure).

Another useful technique to elicit bradykinesia is to have the patient perform rapid repetitive movements, such as opening then closing the hand at least ten times in a row. In PD, an inability to fully extend the fingers and a reduction in the speed and amplitude occurs with repeated movements. Another useful test is to ask the patient to sit in a chair, raise one foot about 3 inches off the floor with the toe slightly raised, and tap the heel on the floor again and again. For each test, repeat with the other hand or foot; it is always important to look for asymmetry, with one side appearing slower than the other.

Rigidity. Rigidity must be felt by physically moving a patient's limb about a fixed point, such as flexing and extending the forearm about the elbow or slowly rotating the wrist in a circular motion. As with tremor, initial rigidity is more pronounced on one side. The rigidity may have a ratchet-like quality called "cogwheel" rigidity.

Postural instability. To test for postural instability, stand behind the patient who is also standing and quickly tap the front of the patient's shoulders back toward the examiner. Patients with postural instability may not move their feet and may fall backwards like a stiff board. The examiner must be able to fully support the patient should he fall. Postural instability is usually absent in early PD.

PD versus parkinsonism

The patient who answered yes to some of the questions you asked during history-taking and had at least two of the three motor signs of tremor, rigidity, or bradykinesia on physical exam has parkinsonism. The next question to attempt to answer is whether this is primary PD or some other parkinsonian syndrome, such as progressive supranuclear palsy, multiple systems atrophy, or diffuse Lewy body disease. Specialists rely heavily on a few guidelines when answering this question.⁷⁻⁹ Signs

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Figure. Micrographia, or small handwriting, in a series of signatures by a patient with suspected PD. Bradykinesia is associated with a decrease in the amplitude of the letters and width of the name when a patient repeatedly signs her name vertically down unlined paper.

Source: Provided by Jill M. Marjama-Lyons, MD, and William C. Koller, MD, PhD

that should raise the suspicion that the patient may have a parkinsonian syndrome other than PD include:

- lack of a clinical response to levodopa or a dopamine agonist
- lack of asymmetric motor signs
- rapid decline over several months to 1 year
- presence of clinically significant dementia early in the course or pre-dating the parkinsonian motor signs.

In addition to parkinsonian syndromes, other diagnoses commonly confused with PD include arthritis, essential tremor, depression, and physical changes associated with advanced age. When the diagnosis is uncertain, consider referring patients to a neurologist whose specialty is PD.

Imaging. It is not necessary to order a brain scan in patients who appear to have PD based on the above criteria. The pathologic loss of dopaminergic neurons in the substantia nigra compacta is a microscopic finding that will not be evident with brain neuroimaging.

continued

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Table 1 Medications for treatment of symptoms in Parkinson's disease

| Medication | Starting dose | Potential side effects | Clinical indication |
|---|--|--|---|
| Levodopa | | | |
| Carbidopa/levodopa, immediate-release (Sinemet) | 25/100 mg bid to tid | Hypotension, nausea, confusion, dyskinesia | First-line or add to dopamine agonist |
| Carbidopa/levodopa, controlled-release (Sinemet CR) | 50/200 mg bid | Same as above | First-line or add to dopamine agonist |
| Dopamine agonists | | | |
| Bromocriptine mesylate (Parlodel) | 2.5 mg tid | Hypotension, nausea, livedo reticularis, edema, confusion | First-line or add to L-dopa |
| Pergolide mesylate (Permax) | 0.05 to 0.25 mg tid | Same as bromocriptine | First-line or add to L-dopa |
| Pramipexole (Mirapex) | 0.125 mg tid | Nausea, hypotension, sleep attacks, sedation, hallucinations | First-line or add to L-dopa |
| Ropinirole HCl (Requip) | 0.25 mg tid | Nausea, hypotension, sleep attacks, sedation | First-line or add to L-dopa |
| Amantadine HCl (Symmetrel) | 100 mg bid to tid | Same as bromocriptine | Second-line therapy for motor fluctuations |
| Anticholinergics | | | |
| Benzotropine mesylate (Cogentin) | 0.5 mg bid | Confusion, hallucinations, blurry vision, dry mouth, urinary retention, nausea | Second-line therapy for tremor |
| Trihexyphenidyl HCl (Artane) | 1 to 2 mg bid | Same as benzotropine | Second-line therapy for tremor |
| MAOB inhibitor | | | |
| Selegiline HCl (Eldepryl) | 5 mg bid (maximum dose; no titration) | Agitation, insomnia, vivid dreams, hallucinations | Third-line therapy; little role for PD |
| COMT inhibitors | | | |
| Entacapone (Comtan) | 200 mg with each dose of L-dopa (maximum 8 tabs or 1,600 mg/d) | Hematuria, diarrhea | Add to L-dopa; second-line therapy for wearing-off symptoms |
| Tolcapone (Tasmar) | 100 mg tid | Same as entacapone, plus hepatotoxicity (liver monitoring required) | Add to L-dopa; third-line therapy for motor fluctuations |

MAOB: Monoamine oxidase B

COMT: Catechol-O-methyltransferase

Source: Prepared for Geriatrics by Jill M. Marjama-Lyons, MD, and William C. Koller, MD, PhD

Treatment decisions

Once the clinician has made a clinical diagnosis of parkinsonism and suspected PD, the next step is to decide how to treat the patient. The first and most important question is whether the motor symptoms are disabling. The an-

swer, of course, will depend on the individual. For example, a 42-year-old nurse who is unable to start IV lines and to chart her patient notes due to bradykinesia may need pharmacotherapy to remain gainfully employed. A 78-year-old retired policeman who has

mild resting tremor of his left hand and no other PD motor symptoms may not want or need medication.

If the patient's symptoms warrant medication, the next decision is which of the many available medications to prescribe. This once relatively simple

task is becoming increasingly complicated as the number and classes of drugs for the treatment of PD grows. Since the discovery of levodopa in 1967, eight additional medications for the treatment of PD have been released in the United States, four of these in the last 2 years.

Medications for the treatment of PD are listed in table 1, along with dosing guidelines, clinical indications, and side effects. A step-wise approach to the management of PD, as recommended in recently published guidelines,² is summarized in table 2. The discussion that follows will attempt to simplify prescribing by outlining some general rules for initiating medication in the patient with newly-diagnosed PD.

Medications

Which agent first? Levodopa combined with carbidopa (immediate-release [Sinemet] and sustained-release [Sinemet CR]) remains the gold standard for the treatment of PD. However, long-term use of levodopa is associated with the development of motor complications in as many as 80% of PD patients. The most disabling of these motor complications are the dyskinesias (choreiform, athetotic, and dystonic posturing of the limbs and trunk).

Recent studies comparing the dopamine agonists with levodopa therapy have clearly shown a lower incidence of dyskinesia in patients treated with dopamine agonist monotherapy compared with levodopa monotherapy.^{10,11} In addition, patients treated with dopamine agonist monotherapy had a greater reduction in "off time" (when parkinsonian motor symptoms are disabling) compared with the levodopa monotherapy group.

The motor symptoms of tremor, rigidity, and bradykinesia were well-controlled with dopamine agonists for up to 5 years in 30% of the patients, such that they did not need to add levodopa to their medication regimen. These findings support the use of dopamine agonists as monotherapy in

Table 2 Step-wise approach for managing Parkinson's disease

Ensure that correct diagnosis is made

Consider neuroprotective therapy (eg, selegiline) as soon as diagnosis is made

Initiate symptomatic therapy with a dopamine agonist as appropriate

Supplement with levodopa when dopamine agonist monotherapy no longer provides satisfactory clinical control

Consider introducing supplemental levodopa therapy in combination with a COMT inhibitor to extend its elimination half-life

Consider surgical intervention when parkinsonism cannot be satisfactorily controlled with medical therapies

COMT: catechol-O-methyltransferase

Source: Reprinted with permission from Olanow CW, Watts RL, Koller WC. An algorithm (decision tree) for the management of Parkinson's disease (2001): Treatment guidelines. *Neurology* 2001; 56(11[suppl 5]):S4.

newly-diagnosed, early mild-to-moderate PD and adding levodopa therapy when the patient's motor symptoms are not adequately controlled by dopamine agonists alone or intolerable side effects develop.

Dopamine agonists are appropriate first-line therapy for older patients in generally good health and with normal cognition. Levodopa may be the preferred initial therapy for patients over age 70 or 80, particularly those with dementia. These patients may be intolerant of the side effects of dopamine agonist medications, such as confusion including hallucinations, hypotension, nausea and vomiting, and daytime sedation. Similar side effects may be seen with levodopa but tend to occur less frequently.

Of the available forms of carbidopa/levodopa and the four dopamine agonists (bromocriptine mesylate [Parlodel], pergolide mesylate [Permax], pramipexole (Mirapex), and ropinirole HCl [Requip]), no one drug has been proven to be superior to others in its class. Bromocriptine, the oldest dopamine agonist, is not used as much as others because of its side effect profile. Preferential use varies among clinicians.¹²⁻¹⁴ Some general administration rules are listed in table 3.

Adjunctive medications. Although carbidopa/levodopa and the dopamine agonists are the most efficacious med-

ications for the treatment of the motor symptoms of PD, several other classes of medications may be used as adjuncts. These include:

- amantadine HCl (Symmetrel)
- anticholinergics such as benzotropine mesylate (Cogentin) or trihexyphenidyl HCl (Artane)
- the monoamine oxidase B inhibitor selegiline HCl (Eldepryl)
- and the COMT inhibitors entacapone (Comtan) and tolcapone (Tasmar).^{15,16}

Detailed discussion of the use of adjunctive medications is beyond the scope of this article but has been published elsewhere.² The reader is referred to table 1 for an overview of the uses, dosing, and side effects of these agents.

Nonpharmacologic treatment

Physical and occupational therapy. Patients who report difficulty with balance or are stumbling or falling should be referred for physical and occupational therapy. Services may include safety-proofing the patient's home, consideration of the use and need for a cane or walker and other assistive devices, and balance therapy to minimize the risk for serious falls and injury.

Speech therapy. Patients experiencing dysphagia and or hypophonia may benefit from a thorough diagnostic evaluation, including a dynamic video

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Table 3 Recommendations for administering dopamine agonists and carbidopa/levodopa for patients with Parkinson's disease

- Start only one new drug at a time, and monitor for a clinical benefit or intolerable side effects
- Begin with the lowest dose (eg, pergolide, 0.05 mg, or carbidopa/levodopa, one 25/100 mg tablet)
- Dose dopamine agonists three times daily and carbidopa/levodopa two to three times daily, spaced evenly throughout the day
- To allow maximal GI absorption, avoid dosing carbidopa/levodopa close to meals; advise patient to take tablets at least 30 minutes before eating or 1 hour after eating
- Slowly titrate dopamine agonists no faster than doubling the lowest dose every 1 to 2 weeks (eg, pramipexole, 0.125 mg tid in week one; 0.250 mg tid in week two or three)
- Be aware of potency differences among the dopamine agonists (0.5 mg pergolide is approximately equivalent to 0.5 mg pramipexole and 5.0 mg bromocriptine); ropinirole is much less potent, and individual doses of 8 to 12 mg may be needed to produce clinical benefit
- Titrate carbidopa/levodopa by increasing by one-half 25/100 tablet with each dose every 2 weeks (eg, carbidopa/levodopa immediate-release 25/100, 1 tablet tid in week one, 1½ tablets tid in week three, 2 tablets tid in week five)
- No maximal dose exists for the dopamine agonists and carbidopa/levodopa; choose the lowest dose that achieves satisfactory clinical benefit while avoiding unacceptable side effects

Source: Prepared for Geriatrics by Jill M. Marjama-Lyons, MD, and William C. Koller, MD, PhD

swallow study and therapy by a speech therapist with expertise in PD.

Nutritional therapy. A well-balanced diet with plenty of fruit and fiber with adequate hydration is recommended for all persons, but is particularly important to prevent severe constipation in the PD patient. In addition, supplementation with vitamin C, 1,000 mg/d; vitamin E, 400 to 1,000 IU/d; beta-carotene, 15,000 IU/d; coenzyme Q10, 100 mg bid; selenium, 200 mcg/d; and multivitamins should be considered. Although no change in the progression of PD has been demonstrated with the use of these supplements, they are known antioxidants and may reduce the presence of free radicals, which are potentially toxic to dopaminergic brain cells.

Exercise and complementary therapies. Exercise in any form that does not put the patient with PD at high risk for falling is highly recommended. Exer-

cise can improve and maintain flexibility, posture, and balance; reduce the risk of falling; and enhance overall mental and general physical health. Yoga, tai chi, and water aerobics may be especially helpful in the PD patient and can be performed to some degree even by persons with advanced disease.

Patients with PD use a variety of complementary therapies, such as acupuncture, meditation, craniosacral massage, and herbal remedies including *Mucuna pruriens* (an herb containing levodopa),¹⁷ evening-primrose oil (*Oenothera biennis*), passion-flower (*Passiflora incarnata*), milk thistle (*Silybum marianum*), ginger (*Zingiber officinale*) and St. Johnswort (*Hypericum perforatum*). St. Johnswort, which is a mild antidepressant, should not be used with most other antidepressants, nor should it be used to treat major depression in a patient with PD.

Many PD centers in the United States

are using these therapies, and some formal studies are underway in an effort to validate their use and benefit in PD. It is the authors' opinion that many of these approaches are potentially beneficial in the treatment of PD. In our own patients, we have observed improved balance and reduced tremors and rigidity in patients who practice yoga and tai chi. In some cases we have been able to lower the dosages of patients' parkinsonian medications after they have adopted nontraditional therapies.

Potential drug interactions with herbal remedies are unknown due to a lack of controlled studies. Because herbs and supplements are not regulated by the Food and Drug Administration, physicians and patients may have legitimate concerns about the purity of these substances. It would be wise to obtain them from nationally known corporate manufacturers who have an investment in ensuring the purity and safety of their products. Advise patients to avoid any substance that is advertised as a "cure" for PD or its symptoms. Consultation with a licensed herbalist or doctor of oriental medicine may be helpful.

Surgical therapies

A greater understanding of the neuroanatomy and physiology of the basal ganglia, coupled with recent advances in the technology of stereotactic surgery, has led to effective and safer neurosurgical procedures for PD. The two most effective and widely used procedures are pallidotomy and deep brain stimulation. Studies comparing those procedures are attempting to define the more effective treatment for patients with PD.

Pallidotomy uses thermocoagulation to place a small lesion into the medial segment of the globus pallidus. Procedure-related morbidity, which occurs in 1 to 8% of patients, may include hemiparesis, visual field defects, depression, hypophonia, dysarthria, and seizures. Bilateral pallidotomy is generally not recommended due to a higher rate of morbidity. Patients may experi-

ence up to a 50% reduction in rigidity, bradykinesia, "off" time, dyskinesia, and tremor, and studies have shown benefit persisting from 6 months to 4 years.¹⁸⁻²⁰

Deep brain stimulation involves placing a small quadripolar electrode into the brain at a specified site and then continuously stimulating the brain at frequencies between 100 and 180 hertz. This technique has been applied to the ventral intermediate nucleus (VIM) of the thalamus, the subthalamic nucleus (STN), and the globus pallidus internus (GPI). Overall morbidity has been estimated at 2% for permanent neurologic deficits; minor side effects are often reversible with electrode reprogramming.

In 92% of PD patients, stimulation of the VIM causes a significant reduction in tremor that persists more than 8 years.²¹ However, VIM stimulation does not result in marked reduction of rigidity or bradykinesia. Recent studies with STN stimulation have reported an 80% reduction in tremor, a 65% reduction in rigidity, and a 51% reduction in bradykinesia. Similar, although less dramatic findings occur with deep brain stimulation of the GPI.²²⁻²⁴

Referral decisions. Deciding when to refer a PD patient for neurosurgical treatment may be a difficult task. Neurosurgery is generally recommended for patients with severe motor fluctuations or disabling dyskinesia. Evaluation for a neurosurgical procedure should be done at a center with a neurologist who specializes in PD and a neurosurgeon with stereotactic training.

Conclusion

Parkinson's disease affects more than 1 million persons in the United States. It is a progressive neurodegenerative illness that can cause significant medical disability and a large socioeconomic burden. Although the cause of PD has not been identified and no cure has been found, effective treatments exist. Pharmacologic therapy, rehabilitation therapies, alternative treatments, and surgical approaches can have a dramatic positive impact on the patient's

symptoms and functional ability.

In many cases, primary care physicians can make an early diagnosis of PD in the office practice by asking targeted questions during history-taking and performing a physical examination to elicit tremor, rigidity, and bradykinesia. It is appropriate to consider referral to a specialist in movement disorders to assist with accurate diagnosis and treatment of this often unpredictable and disabling illness. **G**

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