The ideal medication for Parkinson disease (PD) would reduce disability and halt or slow disease progression without intolerable adverse effects. Although such an agent is not yet available, current treatments offer significant symptom control for most patients. The decision about when to start therapy is highly individual; however, delaying treatment because of fear of adverse effects may not be in the patient's best interest.

Options for initial treatment of motor symptoms include levodopa, dopamine agonists, anticholinergic agents, amantadine, and selective monoamine oxidase B (MAO-B) inhibitors (Table). DOPAMINERGIC AGENTS

Since 1959, when brain dopamine deficiency was identified as a key factor in PD, medical treatment has centered on methods to enhance dopamine transmission. Dopamine agonists currently available in the United States include ropinirole (Requip), pramipexole (Mirapex), pergolide (Permax), and bromocriptine (Parlodel). Another, rotigotine (marketed as Neupro in Europe), will likely be available soon in the form of a daily skin patch. Ropinirole and pramipexole are the 2 most widely prescribed dopamine agonists. Pergolide and bromocriptine are used less because, as ergot derivatives, they have been associated with rare instances of fibrosis of the heart valves, lungs, and retroperitoneum.1 Levodopa and the dopamine agonists remain the mainstays of PD treatment. However, soon after these agents went into widespread use, reports of adverse events began to appear, including short duration of benefit and involuntary choreic movements (dyskinesia) with levodopa and abnormal psychiatric states with bromocriptine. As awareness of the adverse effects of these and other medications that were introduced later grew, it became evident that physician familiarity with the use of levodopa and 1 or 2 dopamine agonists was crucial to satisfactory patient outcomes. Levodopa and dopamine agonists complement one another and are often used together to maximize efficacy and minimize adverse effects. Probably because of its short half-life, levodopa is more likely to produce dyskinesia and other motor complications when used as monotherapy. The dopamine agonists have long half-lives and are less likely to produce these effects; however, they are not as effective as levodopa. Dopamine agonists must be introduced more slowly; they are more likely to cause adverse effects such as drowsiness, hypotension, hallucinations, and compulsive behavior. Two large-scale studies that compared initial therapy with levodopa and initial therapy with a dopamine agonist established that initial treatment with a dopamine agonist reduces or delays the appearance of motor complications—specifically dyskinesia—and end-of-dose wearing off.2,3 However, in both studies, most patients eventually received levodopa in conjunction with the dopamine agonist. Unfortunately, these results were misinterpreted by some clinicians to mean that levodopa is to be avoided, a phenomenon dubbed levodopa phobia.2–4 Clinicians who fail to prescribe levodopa withhold from their patients the single most effective agent for symptomatic treatment. According to the practice parameters of the American Academy of Neurology, treatment may be started with either levodopa or a dopamine agonist.5 To minimize the risk of motor complications, many movement disorder specialists suggest that it may be preferable to start therapy with a nonergot dopamine agonist for patients aged 65 years or younger and to add levodopa later as necessary to optimize mobility. For patients older than 75 years, levodopa may be used first and, in many cases, as monotherapy. Younger patients appear to be at greater risk for dyskinesia, and motor complications may take years to develop.

In patients aged 65 to 75 years, the choice depends on the patient. Determine whether the patient is likely to comply with the dosing changes involved in the titration of a dopamine agonist, which requires 3 to 8 weeks, or whether prompt relief of symptoms is needed. In the latter case, levodopa...
would be the appropriate choice.

**SECOND-LINE AGENTS**

Anticholinergic medications, such as trihexyphenidyl (Artane) and benztropine (Cogentin), were the mainstays of therapy before levodopa became available. However, these agents are not superior for tremor and are often associated with distressing adverse effects, such as dry mouth, blurred vision, and exacerbation of constipation and cognitive dysfunction.

*Amantadine (Symmetrel).* This agent is thought by some experts to be effective for patients with mild symptoms who do not yet require levodopa or a dopamine agonist. However, amantadine does not effectively reduce symptoms in many patients, and it has been associated with hallucinations and peripheral edema, as well as with livedo reticularis, a benign skin discoloration. Amantadine is the only medication that effectively relieves dyskinesia.6

*MAO-B inhibitors.* Agents that selectively inhibit MAO-B are far less likely to cause the adverse drug and food interactions associated with nonselective (type A) monoamine oxidase inhibitors. Selegiline, available since 1989, has been reformulated in a new freeze-dried orally disintegrating form (Zelapar), which dissolves rapidly and is absorbed directly through the buccal mucosa.7 This allows once-daily administration with a lower dose than the older tablet or capsule form. Selegiline is approved as an adjunct to carbidopa/levodopa for patients who experience a loss of effectiveness with the latter therapy.

Rasagiline (Azilect) has recently been approved as monotherapy for mild PD and as an adjunct to levodopa for patients who are experiencing symptom fluctuations.8,9 This once-daily formulation is currently being investigated as a possible disease progression-slowing agent. Both selegiline and rasagiline may interact with other medications. Concomitant use of either drug with antidepressants may be problematic or dangerous. Neither drug should be used within 14 days of administration of meperidine, tramadol, methadone, or dextromethorphan; neither drug should be used concomitantly with over-the-counter (OTC) cold and allergy remedies. Although the "cheese effect" of tyramine-containing foods is less likely to occur with MAO-B inhibitors, rasagiline carries a warning about this effect.

*Catechol-O-methyltransferase (COMT) inhibitors.* Attempts to address the short half-life of levodopa include concurrent administration of COMT inhibitors, which inhibit a degradative pathway of levodopa. The COMT inhibitors entacapone (Comtan) and tolcapone (Tasmar) increase the effective plasma half-life of levodopa, allow enhanced delivery to the CNS, and prolong the efficacy of levodopa. Entacapone has been combined with levodopa and carbidopa in one tablet that is marketed as Stalevo.

*Cholinesterase inhibitors (ChEIs).* Patients with cognitive impairment may benefit from ChEIs. A review of data on ChEI therapy for cognitive impairment in PD concluded that rivastigmine (Exelon) and donepezil (Aricept) are modestly beneficial.10 However, of the ChEIs, only rivastigmine has been examined in a large trial of patients with PD and dementia.11 Although it was modestly effective in some patients, it was also associated with nausea, vomiting, and increased tremor. It was recently approved for the treatment of mild to moderate dementia in patients with PD. A new patch form of rivastigmine that may cause fewer adverse effects will soon be available.

*Coenzyme Q10 (CoQ10).* Many patients inquire about CoQ10, an OTC supplement that has received a great deal of attention based on the results of one well-designed but small study.12 The study demonstrated apparent slower progression of early PD in patients who were otherwise untreated for 16 months. The outcome reached statistical significance only at the highest dosage studied (400 mg/tid). The results of this study require corroboration. A larger trial that has been organized and is being funded by the NIH has not yet begun. Pending additional results, we neither encourage nor discourage the use of this agent by our patients.

**WHEN TO START TREATMENT**

Traditionally, medical treatment for PD has not been started until the patient and clinician have judged that the symptoms are sufficiently troublesome to warrant therapy despite potential adverse effects. This strategy remains reasonable and is widely practiced. However, 2 recent studies of levodopa13 and rasagiline14 have led to a reexamination of this practice. In the former study, participants with early PD were assigned to placebo or levodopa, 150, 300, or 600 mg/d, divided into a thrice-daily regimen.13 They were observed for 9 months and reexamined after the medication had been discontinued for 2 weeks. Even after the discontinuation, patients in the levodopa group scored significantly higher on the Unified Parkinson's Disease Rating Scale than those in the placebo group. In the rasagiline study, participants originally assigned to placebo were switched to rasagiline after 6 months, but they did not improve to the same extent as patients who started in the rasagiline group.14
Clinical Pearls on the Management of Parkinson Disease
Published on Physicians Practice (http://www.physicianspractice.com)

These 2 studies of medications with different mechanisms of action, as well as some earlier evidence,¹⁵ raise the concern that a delay in treatment because of a patient's fears about adverse effects or desire to wait until the patient deems that his or her symptoms are intolerable may not be an optimal strategy and may even be deleterious. The question of when to start therapy is not easily answered. We suggest that potential benefits and adverse effects of medication be discussed with patients in a realistic way. In our practice, we also explore the concerns of patients who are already taking medication for dyslipidemia, hypertension, or diabetes and are reluctant to begin another drug regimen.

ADVERSE EFFECTS
Among the many adverse effects associated with PD medications, several warrant special emphasis. Sleep disorders and somnolence. Sleep disorders are common in PD, and daytime somnolence sometimes is a symptom of PD. However, PD medications, particularly the dopamine agonists, may induce sudden, severe drowsiness, and this raises concerns about motor vehicle safety. Patients who experience drowsiness should exercise at least the same level of caution when driving as they would with any medication that has this adverse effect. Although no formal guidelines exist, evidence suggests that patients with PD—other than those with the mildest symptoms—are at greater risk for automobile accidents than are unaffected age-matched peers.¹⁶ Visual hallucinations and delusions. Visual hallucinations are relatively common; they are often benign initially but are likely to be disruptive within 2 or 3 years of onset.¹⁷ Patients may be untroubled if they see insects or small animals, but are likely to be agitated if they believe they are seeing burglars entering the house. Similarly, dopaminergic and anticholinergic medications may produce delusions. Patients may begin to suspect spousal infidelity or become paranoid about personal safety and financial matters. These delusions are frightening, agitating, and disruptive for the entire household.

When hallucinations or delusions become disruptive, it is best to gradually lower medication dosage, especially that of dopamine agonists, and perhaps simultaneously add an antipsychotic agent, such as quetiapine (Seroquel) or clozapine. Abrupt discontinuation of any PD agent may result in sudden and dangerous worsening of rigidity. Patients who experience psychiatric adverse effects often do best with levodopa monotherapy.

Other adverse effects. Amantadine and the dopamine agonists may cause leg edema. Entacapone and tolcapone can cause diarrhea as well as a benign change in urine color that may upset some patients if they are not forewarned. Dopamine agonists also can result in compulsive behavior that may be destructive.¹⁸,¹⁹ We have observed compulsive gambling, eating, and shopping in our patients with PD. We caution our patients about these phenomena and ask that they notify us if they occur. We have found that elimination of the responsible medication is required when compulsive behavior occurs; the substitution of one agent for another (eg, ropinirole for pramipexole) does not solve the problem.

SURGICAL TREATMENT
Surgery has had a recrudescence in the treatment of PD. Surgical intervention has been practiced in some form since the accidental discovery in the 1950s that tremor could be reduced by partial infarction of the thalamus.²⁰ The most common current treatment, deep brain stimulation (DBS), entails permanent placement of an electrode in the subthalamic nucleus, usually on both sides of the brain. Application of an electrical current to this location reduces tremor, stiffness, and slowness of the contralateral limbs. This technique does not generally eliminate the need for medication (although a small number of patients are able to discontinue medication, at least temporarily) and is unlikely to be effective for patients who do not have any discernible response to levodopa.

DBS works best for carefully selected patients,²¹ such as those who respond well to dopaminergic agents but for too short a period (2 hours or less), those who have dyskinesia that causes functional impairment, and those who are in their 60s or younger (although advanced age alone is not a restricting factor).

The procedure carries a small risk of symptomatic stroke from a hemorrhage that may occur at the time of electrode placement.²¹ The devices sometimes break and require repair or become infected and need to be removed. Moreover, DBS will not ameliorate symptoms that do not improve with medications, such as impaired balance and freezing of gait. Some symptoms, such as those that involve speech and cognition, may be exacerbated by DBS.²¹ The technique also requires substantial commitment from the patient and physician alike for adjustment of the implanted stimulator settings and medications. For carefully chosen candidates, the procedure can be life-enhancing for years. Although DBS clinics have sprung up in various parts of the country, the procedure requires careful
consideration that should include an extensive evaluation by a neurosurgeon who regularly collaborates with specialists in the diagnosis and treatment of PD.

**OTHER MODALITIES**

Although clinical data are sparse, it appears that physical activity, particularly aerobic exercise, helps patients maintain optimal mobility.22 Walking on a level surface, pedaling a stationary bicycle, and participating in pool aerobics are reasonable options for many. Exercises that require mild exertion, such as Tai Chi and qigong, also appear to be beneficial.23,24 Such activities as daily stretching, Pilates, and yoga are enjoyable and helpful for many patients. We routinely refer patients to physical therapists for assessment of balance, training to reduce the risk of falls, and development of a realistic exercise regimen. Group programs can help sustain patients’ enthusiasm and adherence.

To address symptoms such as dysarthria and dysphagia that do not respond well to medication, we often refer patients to speech pathologists with experience in PD for recommendations and treatment. Rehabilitative therapies draw upon diverse expertise that allows for an optimal level of care that cannot be achieved by a single practitioner.

We also encourage intellectual exercise—crossword puzzles, card playing, socializing, participating in community activities, and keeping up with the news. Support groups can be quite helpful but are not suitable for all patients. Younger patients, in particular, feel that conventional support groups, most of whose members are older, do not address their needs. Patients in an earlier stage of disease may be unsettled by seeing those at a more advanced stage.

**WHAT THE FUTURE HOLDS**

Researchers are investigating such promising areas as gene therapy, neurotrophic factors, and stem cell therapy.25 The ultimate "cure" may involve identifying persons at risk for PD and arresting the disease process before it becomes clinically evident. This strategy is currently being explored.

**Editor’s Note:** A version of this article was published in the October 2006 issue of Consultant.

**REFERENCES**


Examples of evidence-based medicine related to this article include:


References:

REFERENCES


Clinical Pearls on the Management of Parkinson Disease


Links:
[1] [http://www.physicianspractice.com/authors/neal-hermanowicz-md](http://www.physicianspractice.com/authors/neal-hermanowicz-md)