VIEWPOINT

Management of Parkinson Disease in 2017
Personalized Approaches for Patient-Specific Needs

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Parkinson disease (PD) has been described as one of the most complex syndromes encountered in clinical medicine. Long-term treatment with dopaminergic agents, the mainstay of therapy, necessitates constant recalibration and possibly additional pharmacological, behavioral, and surgical therapy. Numerous motor and nonmotor PD symptoms may complicate the diagnosis and present therapeutic challenges (**Figure**).

Diagnosis and Multidisciplinary Care

The diagnostic criteria for PD have been recently broadened to consider premotor disease features. Symptoms such as anosmia, constipation, and rapid eye movement sleep behavioral disorder commonly predate the occurrence of the typical and recognizable motor features of tremor, rigidity, bradykinesia, and shuffling gait. Depression, anxiety, apathy, sleep disorders, bladder dysfunction, and other nonmotor features have now been recognized as part of the PD symptom complex. Although dopamine transporter imaging has been approved by the US Food and Drug Administration (FDA) to separate PD from essential tremor, this technique is expensive and rarely necessary.

A multidisciplinary approach to PD treatment including physical, occupational, and speech and swallowing therapy; neuropsychology; counseling psychology; and social work therapy is likely beneficial. Patients with PD require ongoing management of comorbidities such as hypertension, hypotension, diabetes, and heart failure, particularly because many patients die of diseases other than PD. Patients with PD have a substantial risk of falls and increased risk of osteoporosis; therefore, both men and women should have bone mineral density screening based on general geriatric guidelines. Patients with PD also have increased risk of melanoma unrelated to dopamine therapies, and yearly skin examinations are also recommended. There is an expanding palliative care movement to better help patients in advanced stages of PD and to assist their caregivers.

A substantial shift in the management of patients with PD has been the introduction of widespread use of exercise therapy, with recent studies suggesting a benefit. Aerobic exercise, resistance strength training, and tai chi are a few approaches with positive outcome data.

Pharmacologic Therapy

Two decades of debate on the early use of levodopa created significant treatment uncertainty. However, 2 trials suggest there is no reason to withhold early levodopa therapy.[1,2] Levodopa is considered the safest and most efficacious medication for treatment of PD, and its use early following diagnosis should be considered. Dopamine agonists, such as ropinerole and pramipexole, are also considered safe; however, there is a 2- to 3-fold increase in the odds of emergence of impulse control disorders,[3] reducing previous enthusiasm for early agonist initiation, particularly in the absence of stringent monitoring. Frequent adjustment of drug dose and delivery interval are needed to address motor fluctuations and dyskinesia.

Two common clinical questions are what medication to initiate in early PD treatment and whether any therapies may slow disease progression. In a study of 800 patients with PD, the monoamine oxidase type B (MAO-B) inhibitor selegiline did not slow disease progression but did have a small symptomatic effect on medication wearing off and PD motor symptoms.[4] Rasagiline, a newer MAO-B formulation, was recently tested in a delayed-start trial of 1176 patients to test the possibility of disease modification. The results were controversial, with the 1-mg dose but not the 2-mg dose meeting the primary motor score end point; thus, this drug failed to achieve criteria for slowing disease progression.[5] The Movement Disorders Society evidence-based medicine review recommends using one of many generic or brand formulations of MAO inhibitors in patients with early PD to address symptoms of primary PD and of wearing off of the drug.[6] MAO-B inhibitors in low doses can usually be combined safely with antidepressants.

Levodopa is a short-acting medication (half-life of 1-2 hours) when administered in combination with carbidopa. Levodopa-induced dyskinesias are associated more with total levodopa dose and disease duration rather than by timing of levodopa initiation. Within 5 years, half of patients treated with levodopa develop motor fluctuations and possibly dyskinesia. These issues can be addressed by changing drug dose, adjusting medication intervals, and possibly by adding an MAO-B or a catechol-O-methyl transferase inhibitor, although the latter may increase dyskinesia. Several randomized trials have shown that amantadine can suppress PD-related dyskinesia, and recent evidence-based guidelines suggest it is likely efficacious.

Dopamine agonists such as pramipexole and ropinerole are longer acting than levodopa (6- to 8-hour half-life) and have less dyskinesia but are not as potent for treating motor symptoms. Based on evidence published in the last 3 years, it is now common to use combinations of low-dose levodopa and dopamine agonists early in the disease to capitalize on synergistic effects and to delay dose-dependent adverse effects of both medications. Ergot-based dopamine agonists, such as bromocriptine and pergolide, are no longer used because of associated heart valve and pulmonary fibrosis. Apomorphine subcutaneous injections can be used to address delay or difficulty in absorption of oral dopaminergic medications.

Collective evidence has revealed that nonmotor symptoms and nonmotor fluctuations can be as disabling and affect quality of life as much as PD motor symptoms. The most recent Movement Disorders Society evidence-based recommendations suggested that it is likely efficacious to treat depression, dementia, psychosis, constipation, and

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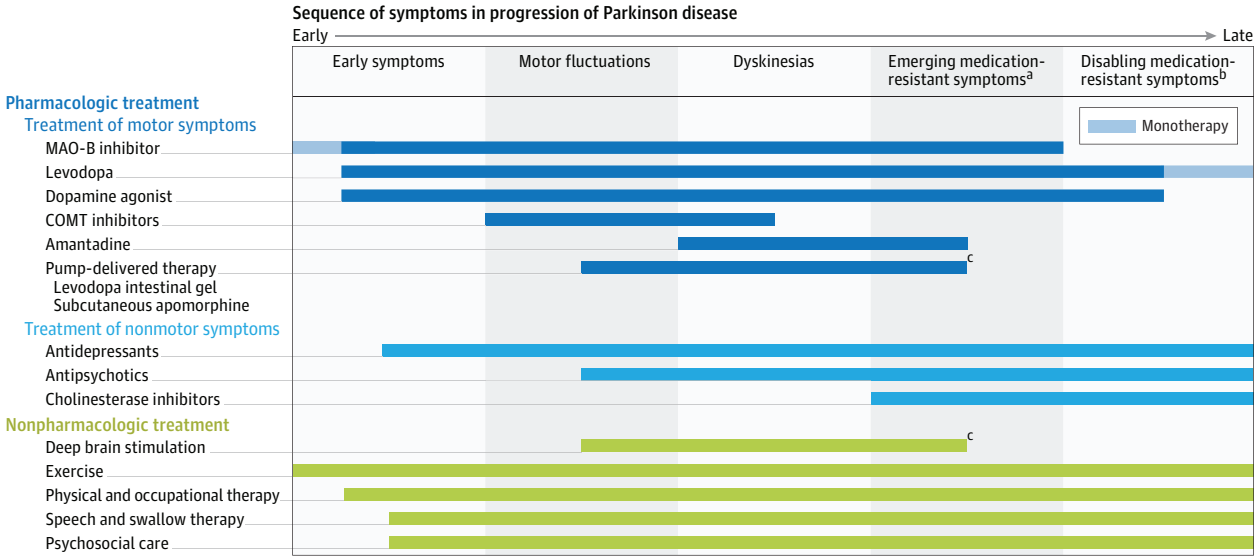
Figure. Symptom Progression and Proposed Treatment of Parkinson Disease



Bars indicate approximate periods of initiation and duration of each treatment except where noted. COMT indicates catechol-O-methyl transferase.

For the treatment of motor symptoms, drugs are usually added sequentially. Monoamine oxidase type B (MAO-B) inhibitor monotherapy may be started in the early symptom period followed by the addition of levodopa or a dopamine agonist. As symptoms progress, other drugs may be added and then discontinued as medication-resistant symptoms and adverse effects emerge. Levodopa may be continued through late stages of the disease as monotherapy.

Medication-resistant symptoms refer to symptoms resistant to medications for the treatment of motor symptoms.

[a] Gait dysfunction, soft speech (hypophonia), and memory and cognitive problems.

[b] Dysphagia, falls, and memory and cognitive problems.

[c] Beyond this point, pump-delivered therapy and deep brain stimulation should not be initiated but may be continued if already prescribed.

sialorrhea. Although there is less current evidence for treatments of orthostatic hypotension, sexual symptoms, urinary symptoms, and apathy, these are also important. Clozapine, quetiapine, and pimavanserin can be used to address psychosis without worsening motor PD features.

Deep Brain Stimulation and Infusion Therapy

The introduction of deep brain stimulation (DBS) for severe motor symptoms is an another advance in the treatment of PD. Clinical trials have demonstrated that DBS is useful for addressing tremor, dyskinesia, motor fluctuations, and off-dopaminergic time. Subthalamic nucleus and globus pallidus internus DBS are both FDA approved, and a randomized trial involving 251 patients revealed potential benefits to applying DBS earlier and in younger patients, especially those with motor fluctuations.[7] In 2015, the FDA approved use of a gel formulation of carbidopa/levodopa enteral suspension that can be infused directly into the small intestine using an externally worn medication pump, providing another option for patients with severe medication-resistant motor fluctuations.

Personalizing Therapy

The 2017 approach to the treatment of patients with PD requires personalization of therapy and attention to the varied and changing symptoms. Clinicians must be adept at diagnosing clusters of motor and nonmotor symptoms and mapping a comprehensive symptom-specific strategy that may necessitate involvement of a multidisciplinary team, including neurology, neuropsychology, psychiatry, neurosurgery, and rehabilitative services. Clinicians must also be aware that PD is dynamic and treatment strategies may need to shift abruptly as the disease progresses and the symptom clusters shift. The combination of medical therapy with exercise and in some cases surgical interventions can improve quality of life for most patients with PD and can transform a potentially debilitating disease into a livable condition.

ARTICLE INFORMATION

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