

## Parkinson's Disease

Welcome to **Neuroscience Pearls**: A publication from the **UW Medicine Neurosciences Institute**. Our goal is to provide useful information pertinent to your practice. Here we bring you key points related to **Parkinson's Disease and management**.

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**Parkinson's Disease (PD)** is the second most common neurodegenerative disorder, after Alzheimer's disease. It is the most common cause of Parkinsonism, a syndrome of rigidity, tremor and bradykinesia. Medical and surgical therapies can ameliorate the symptoms of PD, improving both quality of life, and life expectancy; however, PD continues to result in progressive disability and increased mortality, affecting more than 1 million Americans.

**DEFINING PARKINSON'S DISEASE AND PARKINSONISM:** Parkinsonism describes a syndrome characterized by tremor, rigidity and bradykinesia. Parkinson's disease is the main cause. Definite diagnosis of this entity requires autopsy; pathological findings in PD include a diminished number of nigral dopamine neurons with the presence of Lewy bodies in surviving neurons. Clinical diagnosis of PD is based on history and physical examination (**Table 1**). There are no laboratory tests or imaging studies that unequivocally confirm the diagnosis. Advanced neuroimaging of the nigrostriatal dopamine pathway with Single-Photon Emission Computed Tomography (SPECT) may be a useful diagnostic tool, but should be viewed as complementary to clinical acumen in the evaluation of PD.

The causes of Parkinsonism include genetic factors, environmental toxins, infections, structural lesions in the brain, metabolic disorders, or other neurologic disorders. The clinician routinely needs to consider several main alternative diagnoses: drug-induced Parkinsonism, vascular Parkinsonism (due to heavy burden of cerebrovascular disease), and "Parkinsonism-plus" syndromes such as Lewy-body dementia, multiple system atrophy, progressive supranuclear palsy, and corticobasal degeneration.

**EPIDEMIOLOGY AND ETIOLOGY:** PD affects about 1% of the population over 60 years of age. Men are slightly more prone to the disease. All ethnic groups can be affected. The mean age of onset is in the early 60s. Young-onset PD presents before the age of 50 and affects about 5-10% of patients. Most cases of PD are idiopathic. True familial PD associated with gene mutations is rare. Aging, genetic susceptibility, and environmental exposure likely contribute to the development of PD. The underlying pathology is injury to dopaminergic projections from the substantia nigra pars compacta (SNpc) to the striatum. Intraneural Lewy bodies in these areas are the pathological hallmarks of this disease; however, they can be seen also in the cortex, brainstem, and peripheral autonomic system.

**CLINICAL FEATURES:** Rest tremor, rigidity and bradykinesia are the cardinal features of PD. Autonomic dysfunction, cognitive and psychiatric changes, sensory changes, impaired sense of smell, and sleep disturbance are also typical. The classic "pill-rolling" resting tremor (3-5 Hz) is the initial presenting symptom in 70% of patients. This is often asymmetric, worsening with contralateral motor activity, and anxiety. Rigidity is raised resistance during passive movement, and commonly presents as a clumsy, weak, stiff or uncomfortable limb. Bradykinesia is usually manifested by difficulty in fine motor tasks, micrographia and reduced arm swing while walking. Gait disturbances manifest as asymmetric slowness, shuffling and reduced arm swing. Postural instability can be tested by pulling the patient backwards to check for balance recovery (retropulsion test). Autonomic dysfunction is evidenced by constipation, urinary frequency, and occasionally orthostatic hypotension. Depression is seen in more than half of Parkinson's patients. These two manifestations of PD contribute to sleep disturbances seen in many patients, which are compounded by restless leg syndrome and REM sleep behavior disorder, which are also common. Cognitive impairment even in early PD is common and the risk of dementia is several-fold higher in PD patients compared to the age-matched population.

**Table 1: Diagnostic Criteria for PD**

<b>Clinically Possible</b>	<b>One of:</b> Asymmetric Resting Tremor, Asymmetric Rigidity, Asymmetric Bradykinesia
<b>Clinically Probable</b>	<b>Any two of:</b> Asymmetric Resting Tremor, Asymmetric Rigidity, Asymmetric Bradykinesia
<b>Clinically Definite</b>	Criteria for clinically probable, definitive response to anti-Parkinson drugs
<b>Exclusion Criteria</b>	Exposure to drugs that can cause Parkinsonism such as neuroleptics, some antiemetic drugs, Tetrabenazine, and Reserpine, Flunarizine, and Cinnarizine.  Cerebellar signs, corticospinal tract signs, eye movement abnormalities other than slight limitation of upward gaze, severe dysautonomia, early moderate to severe gait disturbance or dementia, history of encephalitis, recurrent head injury (such as seen in boxers), or family history of Parkinson's disease in two or more family members, evidence of severe subcortical white-matter disease, hydrocephalus, or other structural lesions on MRI that may account for Parkinsonism.

**TREATMENT:** Diagnosis of PD is not necessarily a cause to begin treatment. Drug therapy is initiated when symptoms become bothersome or the disease is producing disability. Initial therapy is usually with a monoamine oxidase-B (MAO-B) inhibitor, a dopamine agonist, or carbidopa/levodopa. The last is the most effective anti-Parkinson agent. The efficacy of all anti-Parkinson medications diminishes with disease progression but even after three or four decades of having PD, many patients still respond to these drugs to some degree. Long-term treatment with carbidopa/levodopa is associated with development of motor fluctuations and dyskinesia. The former can progress from predictable "wearing-off" of effects, to unpredictable, sudden switches between mobility and immobility, termed "on-off" phenomena. Dyskinesia can take several forms, but is most commonly seen as "peak-dose" chorea.

Dopamine agonists are less effective than carbidopa/levodopa; however, their use is associated with a lower risk of dyskinesia and motor fluctuations in the first few years of treatment. Common side effects include somnolence (and sudden sleep attacks), impulse control disorder (gambling, hyper-sexuality, excessive shopping or eating, etc.), hallucinations and paranoia, nausea, hypotension, and lower extremity edema. These can limit use in older, frailer patients. MAO-B inhibitors are the least potent of anti-Parkinson medications. More than half of patients started on an MAO-B inhibitor or a dopamine agonist will require carbidopa/levodopa within 5 years.

**Table 2: Inclusion Criteria for DBS in PD**

1. Clinically definite Parkinson's disease
2. Hoehn & Yahr stage 2-4 (moderate to severe bilateral disease, but still ambulatory when on)
3. L-dopa responsive with clearly defined off and on periods
4. Persistent disabling motor fluctuations despite best drug treatment with some combination of:
  - At least 3 h of off period daily
  - Unpredictable off periods
  - Disabling dyskinesia
5. Intact cognition as measured by neuropsychological testing and no active psychiatric disturbances.
6. Strong social support system and commitment from patient and family members to keep follow-up appointments

**Table 3: University of Florida Mnemonic Device for Patients with PD Considering DBS: "DBS IN PD"**

<b>D</b>	Does not cure.
<b>B</b>	Bilateral DBS is often required to improve gait.
<b>S</b>	Smooths out on/off fluctuations.
<b>I</b>	Improves tremor, bradykinesia (slowness) stiffness (rigidity) and dyskinesia in most cases, but may not completely eliminate them.
<b>N</b>	Never improves symptoms that are unresponsive to your best "on".
<b>P</b>	Programming visits are likely to occur many times. There will be multiple adjustments in the stimulator and in the medications.
<b>D</b>	Decreases medications in many, but not all patients.

Surgical treatment for PD can be destructive or neuromodulatory. Unilateral pallidotomy can improve contralateral tremor and dyskinesia. Unilateral thalamotomy can also be used to improve contralateral tremor. Bilateral ablative procedures are unsafe. Deep Brain Stimulation (DBS) involves implantation of electrodes through which high frequency stimulation of deep brain targets produces treatment effect. DBS can be implanted bilaterally without the morbidity of ablative procedures.

DBS plus best medical management has been shown to be superior to best medical management alone in patients who have had PD for more than 5 years and exhibit motor symptoms or dyskinesia that limit their ability to perform activities of daily living. Improvements in symptoms and quality of life are significant and maintained in the long term. Severe complications of DBS surgery can include infarct, seizures, and intraparenchymal hemorrhage. These are very uncommon, with reported rates generally between 1-3%. The most common complications of DBS surgery are wound infection and hardware failure, which can necessitate further surgery.

Patient selection and management of patient expectations are critical for successful outcomes. Patients with Parkinson-plus syndromes, vascular Parkinsonism, or drug-induced Parkinsonism should be excluded. Neuropsychology evaluation should be performed to exclude dementia or untreated psychiatric disease. A patient's commitment or ability to return for postoperative care needs to be considered. Even with careful patient selection (**Table 2**), unrealistic expectations for DBS therapy can result in disappointment despite significant and meaningful improvements in PD symptoms. Active intervention and education can help ensure that outcome meets or exceeds expectation. (**Table 3**).

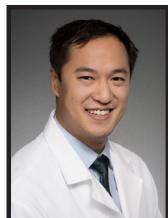
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**KEY REFERENCES:**

- 1) Deuschl, G., Schade-Brittinger, C., Krack, P., Volkmann, J., Schäfer, H., Bötzel, K.,...Voges, J. (2006). A Randomized Trial of Deep-Brain Stimulation for Parkinson's Disease. **New England Journal of Medicine**, 355(9), 896-908. doi:10.1056/NEJMoa060281.
- 2) Nutt, J. G., & Wooten, G. F. (2005). Diagnosis and Initial Management of Parkinson's Disease. **New England Journal of Medicine**, 353(10), 1021-1027. doi:10.1056/NEJMcp043908.
- 3) Samii, A., Nutt, J. G., & Ransom, B. R. (2004). Parkinson's disease. **The Lancet**, 363(9423), 1783-1793. doi:10.1016/S0140-6736(04)16305-8.
- 4) Weaver, F. M., Follett, K. A., Stern, M., Luo, P., Harris, C. L., Hur, K.,... Moy, C. (2012). Randomized trial of deep brain stimulation for Parkinson disease Thirty-six-month outcomes. **Neurology**, 79(1), 55-65.



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