



## Clinical Updates on Parkinson's Disease

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*For the OPL Scientific Communication Subcommittee.*

April is Parkinson's Awareness Month, so there's no better time than now to refresh your knowledge and raise awareness of Parkinson's illness.

The condition is named after James Parkinson who, in 1817, described the shaking palsy (paralysis agitans).<sup>1</sup>

Interestingly, the symbol for Parkinson's Disease Awareness is a red tulip as chosen at the 9<sup>th</sup> World Parkinson's Disease Day Conference in Luxembourg in 2005 knowing that it had been associated with the disease informally for more than 20 years prior to that.

In 1980, a Dutch horticulturist named J.W.S. Van der Wereld, who was suffering from Parkinson's disease, created a new red and white tulip variety and he named it the Dr James Parkinson tulip in honor of the aforementioned doctor.<sup>2</sup>

### **PATHOPHYSIOLOGY**

Parkinson's disease is a neurodegenerative movement disorder that progresses over time. It's caused by the depletion or dysfunction of dopaminergic neurons in the substantia nigra.

The substantia nigra is the coordination center for movement, motor initiation and structuring, postural regulation, and reflexes within the central nervous system. The extrapyramidal motor system is affected when these cells are depleted, resulting in the debilitating symptoms of Parkinson's disease.<sup>3,4</sup>

### **ETIOLOGY AND DIAGNOSIS**

The etiology of Parkinson's disease is uncertain. Growing old is a major risk factor. The average age at which symptoms of Parkinson's disease appear is around 60 years old. Some people will get Parkinson's disease (PD) before they reach the age of 50.

Family history, environmental or toxin exposure, male gender, and Caucasian race are all risk factors.<sup>5</sup>

Scientists have identified dozens of gene mutations linked to the disease. It is estimated that approximately 10-15% of Parkinson's cases have a genetic cause.<sup>6</sup>

The PD GENERation: Mapping the Future of Parkinson's Disease in the US is an initiative that provides people with Parkinson's disease with free genetic testing for clinically relevant Parkinson's-related genes as well as genetic counseling. The PD GENERation test identifies variants in seven Parkinson's-related genes that include: GBA, LRRK2, PRKN, SNCA, PINK1, PARK7 and VPS35.<sup>7</sup>

There are currently no blood or laboratory tests available to diagnose Parkinson's disease, but there are criteria that can be used to include or exclude PD in a patient.



Some positive PD criteria include unilateral onset, resting tremor, bradykinesia, rigidity, progressive onset, and levodopa (L-DOPA) response. The Hoehn and Yahr scale, as shown in Table 1, can be used to further characterize PD severity.<sup>8-10</sup>

Stage	Hoehn and Yahr Scale
Stage 0	No signs of disease
Stage 1	Unilateral symptoms
Stage 2	Bilateral symptoms without balance impairment
Stage 3	Bilateral symptoms with balance impairment, patient is capable of independent living
Stage 4	Bilateral symptoms with postural instability, patient is able to walk/stand, but requires substantial help
Stage 5	Confinement to bed or wheelchair unless aided, severe fully developed disease

## **SYMPTOMS**

Due to the insidious onset of symptoms, which are frequently attributed to the natural aging process, PD can be difficult to diagnose, leading to misdiagnosis.<sup>3,5</sup> Resting tremor, bradykinesia, muscular rigidity, and impaired posture or gait (typically presenting later on) are the four main clinical manifestations of Parkinson's disease.<sup>5</sup>

Although these are the most noticeable symptoms of Parkinson's disease, they do not include all of the other symptoms that can interfere with a patient's everyday activities, such as depression, anxiety, pain, fatigue, urinary problems, constipation, diminished speaking volume, small handwriting, loss of smell, trouble sleeping, and cognitive impairment.<sup>8</sup>

## **MANAGEMENT OF PD**

### **Pharmacological Management of PD**

Due to the limited therapeutic options and developments over time, guideline-directed pharmacologic management of PD is scarce and rarely updated. The goal of pharmacological management in PD is to manage both motor and non-motor symptoms that interfere with everyday life.<sup>10</sup>

The most effective treatment is levodopa; however, higher doses and long-term use are associated with side effects such as motor fluctuations and dyskinesia. Early treatment of Parkinson's disease with non-levodopa agents such as dopamine agonists and monoamine oxidase type B inhibitors can provide symptomatic relief while delaying the initiation of levodopa therapy.<sup>3</sup>

Table 2 is available to help you understand the various pharmacotherapies for PD, as well as their uses, benefits, and complications.<sup>3,5,10</sup>

There is little evidence to support the use of natural medicines to prevent or slow the progression of Parkinson's disease. Caffeine, coenzyme Q10, creatine, nicotine (although not recommended), and antioxidants such as vitamins C and E are all potential neuroprotective medication possibilities.<sup>10</sup>



**Table 2: Pharmacological Options for the Management of PD**

Medication	Early PD 1 <sup>st</sup> Choice Therapy	Adjunct 1 <sup>st</sup> Choice Therapy	Symptom Control	Motor Complications	Ideal Patient	Notes
Carbidopa/Levodopa <sup>a</sup>	X		+++	Worsen	Severe motor symptoms Age >65	Most patients will eventually require L-Dopa
Non-ergot derived dopamine agonists <sup>b</sup> (pramipexole, ropinirole, rotigotine)	X	X	++	Improve	Want to delay initiating L-Dopa therapy Age <65	Rotigotine is a transdermal patch
Catechol-O-Methyl Transferase (COMT) Inhibitors <sup>c</sup> (entacapone, tolcapone)		X	++	Improve	Want to potentiate L-Dopa therapy	Not used as monotherapy
Monoamine Oxidase B (MAO-B) Inhibitors <sup>d</sup> (rasagiline, selegiline)	X	X	+	Improve	Mild-Moderate PD or adjunctive therapy	May be used prior to L-Dopa
Anticholinergics <sup>e</sup> (benztropine, trihexyphenidyl)			LE	LE	Predominant resting tremor	Avoid in age >65
Amantadine <sup>f</sup>			LE	Improve	L-Dopa-induced dyskinesia	Less effective with tremor
Apomorphine <sup>g</sup>			+	Improve	Acute "Off" and "Freezing" episodes	Administered SQ as a rescue agent

+++ Good degree of symptom control ++ Moderate degree of symptom control + Limited degree of symptom control LE: Limited evidence SQ: Subcutaneously  
Mechanisms of Action:

- a: increases levels of levodopa (a dopamine precursor) crossing the blood-brain barrier by blocking peripheral degradation with a dopa decarboxylase inhibitor
- b: directly stimulates dopamine receptors, requiring no metabolic conversion
- c: prevents the degradation of dopamine and L-Dopa, while potentiating the effects of L-Dopa therapy
- d: prevents the degradation of dopamine
- e: blocks the cholinergic overactivity caused by dopaminergic depletion
- f: mechanism of action in PD is unclear, but it is believed to be a dopamine receptor agonist or an NMDA receptor antagonist
- g: potent mixed dopamine receptor agonist



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### **Motor Complications**

Multiple motor complications can arise as a result of the disease progression or the treatment options utilized. Almost all patients on long-term L-DOPA treatment lose motor control, which presents as "early wearing off" or "on-off" state fluctuations.<sup>5</sup>

To further delay dyskinesia manifestations, L-DOPA should be started at the lowest effective dose. The addition of MAO-B inhibitors or dopamine agonists is often used to treat another motor problem known as start hesitation or "freezing."<sup>5,10</sup>

### **NON-PHARMACOLOGICAL MANAGEMENT OF PD**

Both functional and motor benefits have been linked to physical activity. Balance therapy, tai chi, resistance training, boxing, walking, and physical therapy are examples of exercise strategies. Treatment of motor symptoms may include the following for patients whose symptoms are refractory to pharmacological therapy or limited by drug side effects:<sup>11</sup>

- Deep Brain Stimulation (DBS) is a surgical procedure that helps people with movement related symptoms<sup>4</sup>
- Low-frequency repetitive transcranial magnetic stimulation (rTMS)<sup>11</sup>
- Magnetic resonance imaging (MRI)-guided focused ultrasound thalamotomy<sup>11</sup>

### **CLINICAL RESEARCH**

Despite the fact that there have been few novel pharmaceutical alternatives for patients with PD in the past few past years, clinical research is ongoing to improve the therapeutic management and etiology understanding.

According to a study published in 2019, it demonstrated that Ibogaine, an atypical psychedelic alkaloid, altered the expression of glial cell-derived neurotrophic factor (GDNF), brain-derived neurotrophic factor, and nerve growth factor transcripts in areas of rat brains relative to dopamine neurotransmission.

Because of the involvement of the nigrostriatal pathway in neurodegenerative diseases, this could be a potential area of interest for research in PD. It would be possible to evaluate Ibogaine's ability to attenuate cell loss in the substantia nigra, as well as its biochemical changes in the striatum, if it could be studied using an experimental model of PD.<sup>12</sup>

Forest Hills Lab announced its plans to file for phase 2 of a clinical trial evaluating the tolerability and efficacy of FHL-301 in Parkinson's disease patients on March 26, 2021. FHL-301 is a peroxisome proliferator-activated receptor alpha (PPAR-) agonist that binds to peroxisome proliferator response elements in the promoter region of GDNF, according to reports.

This would result in an upregulation in GDNF gene transcription, which could help to restore damaged nerve cells, particularly those that produce dopamine. However, the significance of GDNF in PD therapy is still misunderstood.<sup>13,14</sup>



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