

For the Primer, visit [doi:10.1038/nrdp.2017.13](https://doi.org/10.1038/nrdp.2017.13)

➔ Parkinson disease is a neurodegenerative disorder associated with dopamine depletion in the basal ganglia. Although best known as a movement disorder, non-motor symptoms, such as depression and cognitive impairment, are also frequent.

**DIAGNOSIS**

! Parkinson disease is defined by the presence of motor symptoms, including bradykinesia (a slowness of movement) and one or more additional cardinal motor feature (rigidity or rest tremor).

Although sporadic (also known as idiopathic) Parkinson disease is the most common type (>90% of patients), heritable forms have also been described. Genetic abnormalities identified in the latter have greatly contributed to understanding the processes involved in Parkinson disease.

In addition to the motor symptoms, patients show persistent and new non-motor symptoms, such as cognitive impairment, disorders of mood and autonomic dysfunction (for example, hypotension).

**EPIDEMIOLOGY**

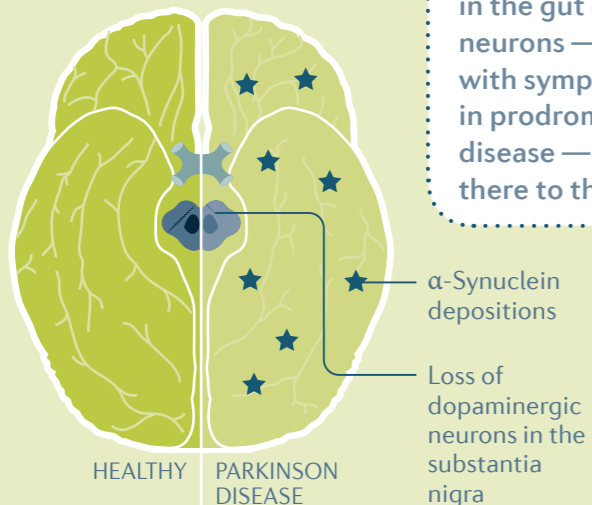
Parkinson disease is the second-most common neurodegenerative disorder. The incidence of the disease sharply increases with age. Indeed, the global prevalence across all age groups is estimated at 0.3%, whereas levels increase to 2–3% in the population ≥65 years of age. Parkinson disease is more common in men than in women. The incidence varies depending on ethnicity, environmental factors (such as exposure to organic pollutants), lifestyle factors (for example, smoking and caffeine intake) and genetic factors.

**MECHANISMS**

The motor symptoms associated with Parkinson disease result from loss of dopaminergic neurons in the substantia nigra, which ultimately inhibits neuronal output from the basal ganglia to the thalamus. Damage to dopaminergic neurons is caused by a complex interplay between toxic  $\alpha$ -synuclein aggregates (owing to impaired protein degradation), mitochondrial dysfunction, oxidative stress, impaired intracellular calcium homeostasis and neuroinflammation.



A prion-like propagation of  $\alpha$ -synuclein has been proposed, in which aggregated  $\alpha$ -synuclein can be transported within a neuron to different brain regions, be released by the affected neuron and 'infect' neighbouring neurons. This hypothesis implies that initial insults might develop in the gut or olfactory neurons — in accordance with symptom development in prodromal Parkinson disease — and spread from there to the brain.



PRODROMAL

EARLY-STAGE

MID-STAGE

LATE-STAGE

Several non-motor symptoms (including REM sleep behaviour disorder, constipation and loss of smell) antedate motor symptoms by years.

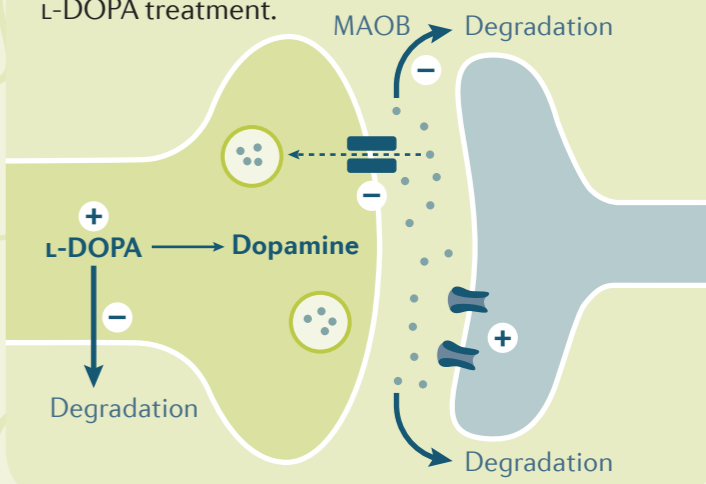


Motor symptoms  
Diagnosis



**MANAGEMENT** Rx

Systemic administration of the dopamine precursor L-DOPA is the gold-standard treatment, although chronic use can result in adverse effects, such as motor fluctuations or L-DOPA-induced dyskinesia (involuntary movement). Inhibitors of dopamine metabolism can complement L-DOPA therapy, whereas L-DOPA-degrading enzymes or dopamine receptors provide alternative targets. Non-dopaminergic pharmacological treatments can improve motor and non-motor symptoms. Deep brain stimulation of the subthalamic nucleus is a valid option for patients with advanced Parkinson disease who experience adverse effects to L-DOPA treatment.



200 years after James Parkinson's seminal essay on 'the shaking palsy', Parkinson disease can now effectively be managed with sustained symptom control and improvement of quality of life for many years.

In addition to clinical evaluation, diagnostic tests are mainly based on imaging, for example, of striatal dopamine levels.

**OUTLOOK**

The identification of markers for prodromal disease and the development and optimization of curative treatments remain considerable challenges. New

treatments might involve gene therapy, fetal cell transplantation, stem cell treatment or new disease-modifying drugs.

! Combined loss of specific neurons and widespread, intracellular  $\alpha$ -synuclein aggregations are the pathophysiological hallmarks of Parkinson disease.