

Parkinson's disease Media Backgrounder

What is Parkinson's disease?

Parkinson's disease (PD) is a progressive, degenerative condition of the central nervous system (CNS), caused by the degeneration of dopaminergic neurons in the substantia nigra of the midbrain.

What are the clinical features?

There are 4 cardinal motor features that characterise PD:

- **Resting tremor**

Tremor usually appears first in one limb and as PD progresses, may spread to all four limbs. PD tremor is present when the limb is at rest, disappears on purposeful movement, and may be worsened by tension or anxiety.

- **Muscle rigidity**

Muscle rigidity usually presents as contraction and is experienced as stiffness or resistance of the limb to passive movement when the limb is relaxed.

- **Bradykinesia, or slowness of movement**

Even automatic and unconscious movements such as eye blinking, swallowing, postural adjustment and spontaneous emotional expression can be affected.¹

- **Postural instability**

Postural instability is the least specific sign of PD and occurs at later stages of the disease.

What causes PD symptoms and how does PD progress?

Movement of the body is initiated in an area of the brain called the motor cortex. The main motor pathway consists of the pyramidal system which is modulated by the extrapyramidal circuit and includes the striatum and substantia nigra. Normal movement is dependent on appropriate



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dopamine production by the neurons of the substantia nigra that innervate the striatum.

PD involves a degeneration of these dopamine-producing neurones in the substantia nigra and thus a loss of control of normal movement. PD symptoms start to appear when 50-60% of the dopaminergic neurones have been lost or a reduction in dopamine concentration of approximately 80%.¹

PD progresses slowly in the majority of cases and symptoms intensify steadily over the years. In advanced PD, postural reflexes may be affected, resulting in a stooped shuffling gait, poor balance and frequent falling. People with PD may also experience "freezing episodes", when voluntary movement is impossible.^{1,2,3} Additional features of the disease are loss of volume in speaking, micrographia (small, cramped handwriting), and a lack of facial expression or "mask-like" appearance.^{1,3} Psychiatric symptoms such as depression, sleep disturbances, dementia, and anxiety are relatively common in PD. Additional troublesome symptoms include constipation, urinary and sexual dysfunction and swallowing difficulties.³

"At first I could disguise the symptoms, sit on my shaking hand, fold my arms, but as time marched on, sitting on my hand just made the chair shake ... just walking from A to B became increasingly difficult, then impossible. As my walk got worse, I would sometimes dream that I had found my stride, and wake up, with tears streaming down my face."

Ann, Ireland, 53 years old, diagnosed in 1996

Are there tests available to diagnose PD?

Diagnosis of PD is made by clinical evaluation of the presence of at least two of the four cardinal symptoms.⁴ There are currently no simple, widely available laboratory tests to confirm diagnosis. Fluorodopa positron emission tomography (PET) is a useful index of striatal dopamine function, but is expensive and not widely used. Single photon emission



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computerised tomography (SPECT), using radioisotopes that bind to the dopamine transporter on niagrastriatal neuron terminals, is also emerging as a useful tool. However, these imaging techniques are not be used in routine clinical practice and the decision to perform functional brain imaging should be made after careful evaluation of other diagnostic criteria.

What is the mean age of onset of PD?

The mean age of onset of PD is approximately 60 years. It usually occurs in patients over 50 years of age but can occasionally present in younger adults in their 30s to 50s (and rarely, even younger). Young-onset PD (YOPD) is defined as that which produces symptoms between the ages of 21 and 39 inclusive.

The incidence and prevalence of the disease generally increase with increasing age.

How common is PD?

“Prevalence” and “Incidence” are two terms used to describe the frequency of a disease. Prevalence refers to the total number of people with the disease in a population at a given time. Incidence is the number of new cases of the disease diagnosed in the population during a given time period.

Prevalence rates vary from country to country due to their methods of analysis, however they are all approximately similar. Average prevalence rates for PD have been estimated at between 740 and 920 per 100,000 people worldwide.⁵ Community based studies show the incidence rate (the number of new cases occurring in a specified frame) is around 10 new cases per 100,000 people at age 50, rising to at least 200 per 100,000 people at age 80.⁶

Is PD more common within certain groups, races, ethnicities?

Studies conducted in the US have generally found a lower prevalence of PD among African-Americans. Even in Africa, the prevalence has been found to be lower in blacks than in whites or Indians. However, further



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studies are needed to substantiate the belief that PD is more common in Caucasians.⁷

Is there a difference between men and women?

According to epidemiological studies carried out in Western countries, there are marginally more men with PD than women, although the reasons for this are unclear. A meta-analysis of several population-based incidence studies of PD found that the incidence was 1.5 times greater in men than women.⁸

How I felt when I was diagnosed

“As I left, the consultant was practising his golf swing for the benefit of two young receptionists. My life had changed, but his hadn’t ... I was 44, but I had never felt so old.”

Ann, Ireland, 53 years old, diagnosed in 1996

How is PD measured?

Measurement scales for PD assess different aspects of the disease:

- **Disability**

The Unified Parkinson’s Disease Rating Scale (UPDRS) is used most commonly in clinical trials. It measures disability in four distinct areas: mental activity, behaviour and mood; activities of daily living; motor function; and complications of therapy. UPDRS provides a score between 0 and 200, where 0 represents no disability and 199 represents total disability.⁹

- **Severity**

The Hoehn and Yahr (H&Y) scale is used to classify the severity of the disease, but lacks sensitivity to functional condition. The H&Y scale produces a rating from stage 1 (the mildest stage of disease) to stage 5 (the most advanced).¹⁰

- **Activities of Daily Living**

The Schwab & England Activities of Daily Living Scale provides a score based on the independent ability to complete activities of daily living.



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The scoring range is from 100% (normal functioning) to 0% (vegetative function only).¹¹

- **Quality of Life**

The Parkinson's Disease Questionnaire (PDQ-39)¹² and Parkinson's Disease Quality of Life Scale (PDQUALIF) assess the impact of PD on 7 dimensions of quality of life including physical function, communication or social role and function. The PDQUALIF also includes one item of global health related quality of life (HRQoL), i.e. rating of QoL associated with your general health level).¹³

What are the protective factors for PD?

Some protective factors identified in research include:

- **Coffee:** Caffeine consumption is also associated with a reduced incidence of PD. A recent prospective longitudinal study involving 8,004 subjects over 30 years of follow-up found those who did not drink coffee had a 5-fold greater risk when compared with those who drank 840ml or more coffee a day.¹⁴
- **Smoking:** The single factor that has been most consistently associated with a reduced risk of PD is cigarette smoking, which has been demonstrated in numerous studies. It is not known whether smoking confers a genuine protective effect, or whether individuals who are prone to develop PD for other reasons are also prone to avoid smoking. A study has shown that smokers have a lower mean parkinsonian sign score than non-smokers.¹⁵

What are the goals of PD treatment?

The goals of PD treatment are to alleviate the symptoms of disease and to try to preserve the function of dopamine production.^{16, 17, 18, 19} As the disease progresses, response to treatment can become unpredictable and therapeutic goals also include reducing "OFF" time (periods of time when the effects of medication wears off and symptoms return), and controlling the side effects of long-term medication.^{17, 18, 19}



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The ideal PD treatment should have a safe side-effect profile, a simple dosing schedule, the ability to provide symptomatic relief and the potential to alter disease progression.²⁰

What are the treatment options for PD?

Pharmacological treatment of PD focuses on replacing dopamine, or augmenting its effects in the central nervous system.

There are three main dopaminergic therapies for the treatment of PD:

1. Levodopa therapies that provide a supply of exogenous dopamine, thereby restoring the full spectrum of regulatory effects that dopamine exerts in the normal basal ganglia.
2. MAO-B inhibitors that prolong the availability of endogenous dopamine (when used as monotherapy) and exogenous dopamine (when used as adjunct therapy).
3. Dopamine agonists that exert their antiparkinsonian effects by acting directly on striatal dopamine receptors.

1. Levodopa (L-dopa)

The only therapy directly to replace dopamine is L-dopa, a substance that is converted to dopamine once it enters the brain. L-dopa is highly effective in treating PD symptoms, and is considered to be the gold standard in PD treatment. However, complications often develop with long-term use, including episodes of "OFF" time and the appearance of involuntary movements (dyskinesias).²¹ Because of these complications, L-dopa is usually used to treat PD patients with more moderate to advanced PD symptoms.

Current treatment strategies focus on providing the maximum clinical benefit to the PD patient in the long term by initiating treatment early, and on delaying the need for L-dopa treatment, thus minimizing the risk for motor complications.^{16,17,18,19} As long-term L-dopa therapy can cause motor complications, studies are currently being conducted to show whether combined drug treatments could delay the initiation of L-dopa.²² In addition there is an on-going need for new treatments



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that can provide additional therapeutic benefits in patients with advanced PD already treated with L-dopa, without increasing the burden of side effects.

L-dopa is always combined with an enzyme inhibitor called carbidopa or benserazide, to prevent its breakdown in the bloodstream before it enters the brain. L-dopa has a short half-life in the body, and needs to be dosed several times a day.²¹ The initial dose is 50-100mg/day taken at 3 time intervals.

2. **Monoamine oxidase-B inhibitors (MAO-B inhibitors)**

MAO-B inhibitors work by inhibiting monoamine oxidase-B, an enzyme that normally metabolises dopamine in the central nervous system. Inhibition of this enzyme increases the availability of the PD patient's own (endogenous) dopamine to the neurones of the substantia nigra.

MAO-B inhibitors used in the treatment of PD include the first generation MAO-B inhibitor, Deprenyl (selegiline), which was developed in the late 1970s and is still sometimes used in the treatment of early PD.²³ Selegiline is associated with a number of side effects, mostly related to the amphetamine metabolites produced from its break down. These interfere with neuronal re-uptake and enhance the release of several neurotransmitters (e.g. noradrenaline, dopamine, serotonin), and are in fact assumed to provoke and induce parkinsonism.¹

By contrast the newer, second-generation MAO-B inhibitor, Azilect[®] (rasagiline) is free from these metabolites and thereby provides advantages over selegiline. Azilect[®] can be used as monotherapy in early PD patients, where it has proven efficacy in controlling PD symptoms; and as adjunct therapy in the more severe stages of the disease by reducing the amount of "OFF" time and alleviating these more severe PD symptoms.

3. **Dopamine agonists (DAs)**

Dopamine agonists (DAs) mimic the actions of dopamine in the central nervous system by stimulating dopamine receptors directly. This



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category of drugs includes the more recent non-ergot derived agents (pramipexole, ropinirole and rotigotine) and the earlier ergots DAs (cabergoline, pergolide).¹⁸

Unlike Azilect[®], dopamine agonists are usually given several times daily and require lengthy titration periods (from several weeks to months) until the effective therapeutic dose is reached. This is because DAs show limited tolerability owing to predominant nausea and dizziness in the initiation period. Vasopressors may also be added to combat the onset of orthostatic syndrome.

Loss of appetite, sleepiness (sudden onset) and/or oedema may also occur and reduce compliance with DAs. However, the availability of differing DAs means it is possible to switch from one to another to test tolerability and response.

Long-term use of ergot-derived DAs has been associated with pulmonary (or pleuropulmonary), pericardial, retroperitoneal, and cardiac valvular fibrosis.²⁴

Hypersexuality and pathological gambling have also reported as side effects.

Transdermal DA delivery has also been shown to improve motor symptoms and motor complications. Rotigotine (Neupro[®]) is the first patch to be approved for treating PD. It is a transdermal delivery system that provides rotigotine continuously over a 24-hour period. In monotherapy studies, rotigotine was found to be significantly inferior to the comparator drug ropinirole. In adjunct therapy, rotigotine was compared to pramipexole and was found to have similar efficacy. Besides the usual side effects of DAs, local allergic skin reactions, which may appear immediately or after several months, are the most common side effect.²⁵



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Other PD treatment options

- **COMT inhibitors**

Catechol-o-methyltransferase (COMT) is an enzyme that is also present in the periphery (bloodstream) where it breaks down L-dopa. COMT inhibitors such as entacapone and tolcapone work by inhibiting the catechol-o-methyltransferase (COMT) enzyme, thereby facilitating an increase in the concentrations of L-dopa and dopamine. Tolcapone is not widely used due to its requirement for continuous monitoring of liver function. Entacapone requires no liver function monitoring, but must always be given with L-dopa and is used in more advanced PD patients to control motor symptoms. Common side effects are hypotension, sedation, headache and dyskinesias.²⁶

COMT inhibitors are administered several times daily together with each L-dopa dose.

- **Anticholinergic drugs**

Anticholinergic drugs work by decreasing the activity of the neurotransmitter acetylcholine, and help reduce tremors and muscle stiffness that result from having more acetylcholine than dopamine in the centres of the brain controlling movement. They are usually taken alone or in combination with L-dopa,²⁷ but their efficacy is limited as patients usually only respond for a brief period. Their side-effect profile, which includes cognitive problems or confusion, means they are rarely used in elderly patients.²⁸

- **Amantadine**

Amantadine was originally developed as an antiviral medication, but has been found to reduce PD symptoms including tremor, bradykinesia and fatigue in people with early PD. For people with more advanced PD, amantadine may reduce motor fluctuations, in particular, dyskinesias. Its efficacy may wear off after several months, but may return after a brief withdrawal from the drug.¹⁸



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How is PD treated?

- **Treatment of early PD**

At the time of diagnosis, patients can have significant impairment of quality of life with symptoms for which they have sought medical advice.²⁹ It is likely that patients may still be working when first diagnosed and their need for symptomatic therapy will depend on their performance both at home and at work.³⁰ The average life expectancy for a PD patient at diagnosis is 17 years, so a long-term treatment strategy is required.³⁰

Recent studies have shown the importance of treating PD early, rather than waiting for the symptoms of the disease to increase to an uncomfortable level. PD patients in these studies were associated with less PD symptom progression over a long period of time.^{31, 32}

Although L-dopa provides the most effective symptom relief at all stages of PD, its high risk of inducing motor complications means that other drugs are often preferred, especially at treatment initiation:³⁰

- In patients with mild motor disability and no cognitive impairment, MAO-B inhibitors are often used as the first choice treatment.³⁰ Azilect® provides an efficacious, simple and convenient option providing symptomatic benefit in early PD.¹⁸
- Dopamine agonists can also be considered as a first choice treatment in patients with mild/moderate motor disability and no cognitive impairment.³⁰
- In patients with more severe symptoms and in patients over 70 years of age, L-dopa may be the first choice treatment, especially if there is moderate/severe disability or significant co-morbidity such as cognitive impairment.³⁰ Elderly patients can also be considered for treatment with a dopamine agonist or an MAO-B inhibitor if they are cognitively intact,³⁰ but this group is more prone to the side effects associated with dopamine agonists - such as hallucinations,



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orthostatic hypertension, somnolence (sleepiness) and oedema – than younger patients.^{33,34}

- **Treatment of moderate to advanced PD**

As PD progresses, effective symptom control becomes more challenging and additional drugs may need to be added.³⁰

- For patients who are starting treatment with an MAO-B inhibitor, a dopamine agonist will often be considered as the first adjunct therapy. This can be titrated to maximum response or tolerance before adding L-dopa.³⁰
- Similarly, for those who started treatment with a dopamine agonist, this will generally be titrated to the level of maximum response or tolerance before adding an MAO-B inhibitor. L-dopa will often be reserved until the level of disability required additional therapy.³⁰
- For patients already receiving L-dopa who require improved symptom control, the total daily dose can be raised by increasing the individual dose and/or the dosing frequency. However, this may lead to a greater risk of dyskinesias. Instead, a MAO-B inhibitor or a COMT inhibitor can be added to decrease the 'wearing off' of the benefits of L-dopa.³⁰

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