



INFORMATION SHEET

Parkinson's Disease

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KEY SUMMARY

1. Parkinson's disease (PD) is an age-related, progressive neurodegenerative disease characterised by motor and non-motor symptoms. The symptoms can vary from patient to patient, but worsen over time.¹
2. Rest tremor is often the first motor symptom of PD.¹
3. Whilst PD is most commonly associated with motor symptoms, it is the often overlooked non-motor symptoms of the disease, such as depressive symptoms, that negatively impact PD patients' quality of life. It is estimated that approximately 40% of people with PD suffer from some form of depressive symptom.^{2,3}
4. Parkinson's disease is the second most common chronic neurological disorder following Alzheimer's disease, and its worldwide prevalence is estimated to be approximately 1 to 2% of those over 65 years, but can also manifest earlier in life.⁴⁻⁸

What is Parkinson's disease?

- Parkinson's disease (PD) is an age-related, progressive neurodegenerative disease of the brain that affects nerve cells involved with movement. It is characterised by three main motor symptoms, all of which worsen over time:
 - bradykinesia/akinesia (a slowness or absence of movement respectively) often resulting in shuffling gait.
 - rigidity (stiffness) leading to loss of facial expression.
 - tremor (shaking of arms, legs or head). This symptom is particularly debilitating in terms of its impact on patients' quality of life.
- In addition, PD is frequently complicated by psychiatric syndromes and cognitive impairment. Up to 90% of PD patients with idiopathic PD experience psychiatric complications including depressive symptoms such as mood disorders, adjustment disorders, anxiety syndromes, psychosis or delirium.⁹ A central question is whether psychiatric problems in PD are a reaction to the motor disability and impaired quality of life or are intrinsic to the pathophysiology of PD.⁹ In this regard, there is considerable evidence that depressive symptoms can precede development of motor symptoms.⁹ Research suggests that depressive symptoms in people with PD are not merely a reaction to chronic disability, but a

combination of both psychosocial and biochemical factors associated with the degenerative process¹⁰⁻¹⁷ and therefore may require a different treatment approach.

How common is Parkinson's disease?

- Parkinson's disease is the second most common chronic neurological disorder of the central nervous system in older adults following Alzheimer's disease. Its worldwide prevalence is estimated to be approximately 1 to 2% of those over 65 years.⁴⁻⁸ However, the disease can also manifest earlier in life, before 40 to 50 years, referred to as early onset PD.

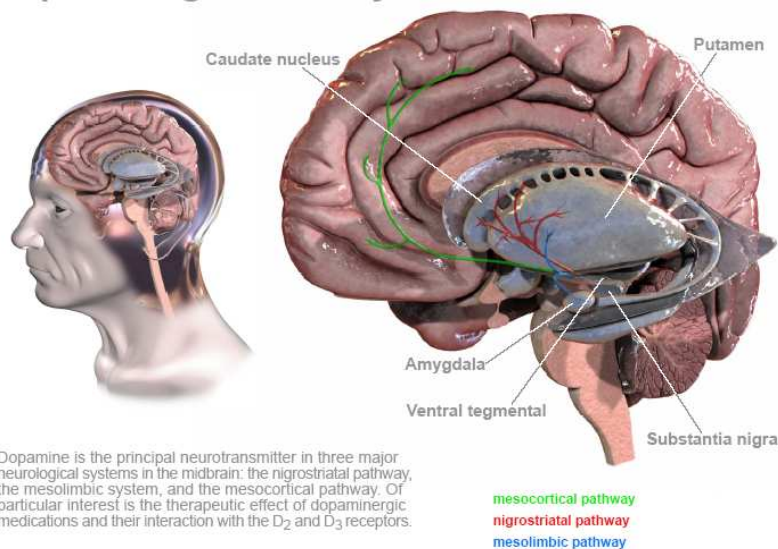
What impact does Parkinson's disease have?

- Parkinson's disease has a significant impact on quality of life. As the disease progresses, movement and everyday tasks such as dressing and writing become more difficult. Speech may also be affected. A person may develop an expressionless or mask-like face. After several years, sufferers may develop a shuffling walk without arm movement. Initiating activity may be difficult but once started, patients move too fast and can end up almost running.¹
- However, the traditional motor features of PD are not necessarily the features that lead to the most profound disability. It is estimated that approximately 40% of people with PD suffer from some form of depressive symptom.^{2,3}
- Depressive symptoms have also been found to have a significant impact on caregivers' quality of life.¹⁸

Pathophysiology and natural history

- The primary cause of PD is a progressive degeneration of dopaminergic neurons in a part of the brain called the substantia nigra leading to a decrease in the dopamine levels in the brain. A deficit of dopamine is directly linked to the appearance of the characteristic motor symptoms. However, despite intensive research the cause of the degeneration remains unknown.¹

Dopaminergic Pathways



Dopamine is the principal neurotransmitter in three major neurological systems in the midbrain: the nigrostriatal pathway, the mesolimbic system, and the mesocortical pathway. Of particular interest is the therapeutic effect of dopaminergic medications and their interaction with the D₂ and D₃ receptors.

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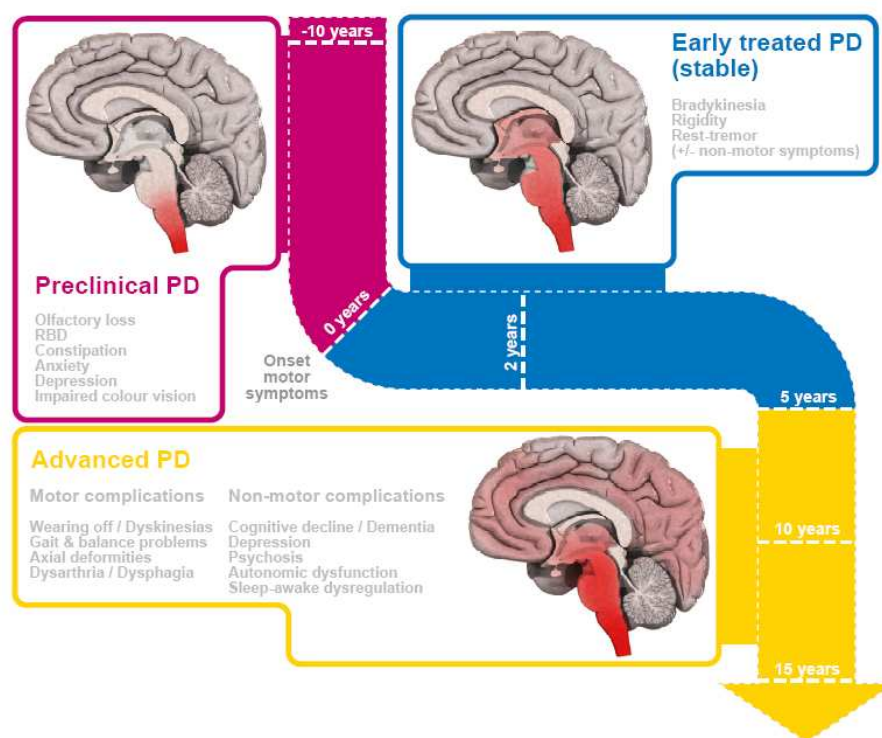
- As PD progresses, the loss of dopaminergic neurons continues and motor function declines. To date there is no cure. A major problem is that by the time the patient's symptoms have been sufficiently apparent to seek treatment, about 50 to 80% of their dopaminergic neurons may have died.¹⁹⁻²⁵
- There is increasing evidence of a genetic component to PD. A number of population studies found a doubling of risk of PD in first-degree relatives compared with controls. The life-time risk in first-degree relatives is estimated to be 17%.²⁶

Clinical presentation and diagnosis

- The clinical onset of PD is typically around the age of 60 years although juvenile or young adult onset of the disease occurs.^{1,25}
- It is difficult to diagnose PD in the early stages and there is no single reliable diagnostic test.
- The motor symptoms, rest tremor or bradykinesia, are often the first symptoms recognised by a patient.¹
- Non-motor symptoms such as cognitive impairment, depressive PD-related symptoms and autonomic dysfunction can contribute to an accurate diagnosis of PD.²⁷⁻³⁰
- At least two of the motor symptoms, including tremor at rest or bradykinesia, need to be identified in order for a clinical diagnosis of Parkinson's disease to be made.^{1,31}

The evolution of PD

This figure shows how PD progresses from the earliest symptoms (often non-motor symptoms) to diagnosis and start of treatment through to the early and advanced stages of the condition.



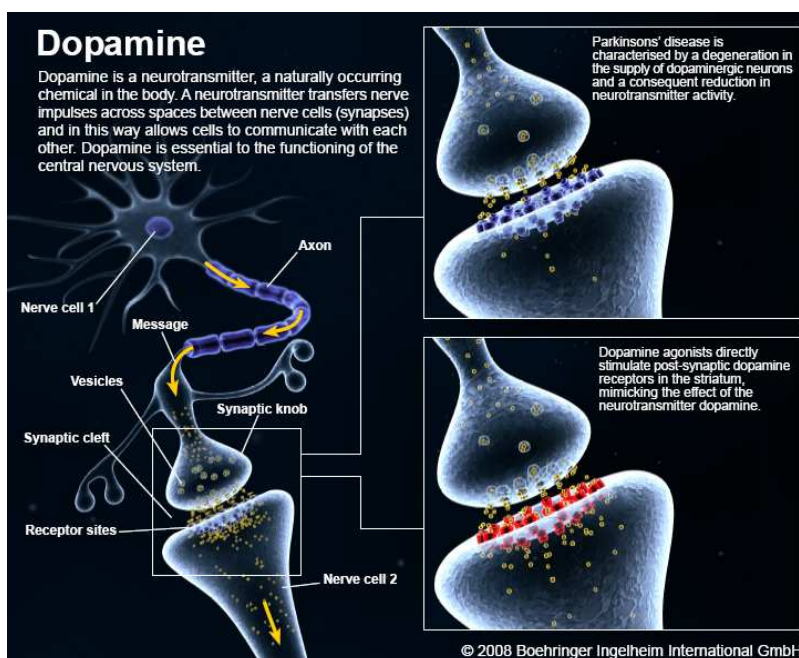
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- Increasing attention is being paid to the need to also treat the non-motor symptoms of PD, particularly motivation and depressive symptoms, which may even precede the occurrence of the motor symptoms of the disease.^{9,32-34} In addition, research suggests that depression in PD populations is not merely a reaction to chronic disability, but a combination of both psychosocial and biochemical factors associated with the degenerative process¹⁰⁻¹⁷ and therefore may require a different treatment approach.
- Results from the PRODEST* study showed that up to 40% of the studied PD patients continued to experience depressive symptoms in spite of receiving an antidepressant treatment.² This implies that the depressive symptoms in PD may be distinct from what is known as a depressive syndrome, suggesting the need for a different approach in treating depressive symptoms in PD.^{2,35}

***PRO**file of **DE**pressive **Symp**Toms in Parkinson's Disease: The largest pan-European, prospective observational study of depressive symptoms in PD

Parkinson's disease and dopamine

- Research from the 1950s by Professor Arvid Carlsson, co-recipient of the Nobel Prize in Physiology or Medicine in 2000, led to the realisation that PD is caused by a lack of dopamine in certain parts of the brain. The observation that the symptoms of PD can be relieved by modifying dopamine activity has been critical in understanding this disease. This understanding helped advance a new generation of symptomatic treatments, such as initially levodopa and, more recently, dopamine agonists.
- Levodopa (L-dopa) has traditionally been regarded as the gold standard in the initial treatment of PD. It is a dopamine precursor, which is converted to dopamine once it has crossed the blood brain barrier (dopamine does not cross the blood brain barrier). It must be administered in combination with a peripheral decarboxylase inhibitor such as carbidopa to prevent conversion to levodopa in the peripheral circulation. Levodopa is effective in controlling PD motor symptoms. However, after an initial period of relevant benefit, several limitations become apparent: over time the beneficial motor effects of levodopa wane necessitating the use of increasingly higher dosages of levodopa ever more frequently to prevent 'on-off' fluctuations in motor control and most patients also develop abnormal involuntary jerking movements – dyskinesia – that can be very disabling.³⁶
- As a result of these established limitations of levodopa, guidelines for the management of PD recommend the initiation of early PD treatment with a dopamine agonist.^{37,38} Dopamine agonists mimic the effect of natural dopamine in the body and produce dopamine-like effects. They are categorised into ergot and non-ergot subclasses
- Non-ergot dopamine agonists (such as pramipexole) differ from ergot dopamine agonists (such as pergolide and cabergoline) by virtue of their chemical structure and receptor affinities, specificities and selectivities. Whereas studies have suggested that ergot-derived dopamine agonists can cause fibrotic reactions at the heart valve, no increased risk with the non-ergot dopamine agonists such as pramipexole has been seen.³⁹



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