BMJ Best Practice

# Parkinson's disease

The right clinical information, right where it's needed

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# Summary


- Chronic progressive neurological disorder characterised by motor symptoms of resting tremor, rigidity, bradykinesia, and postural instability.
- Insidious, often asymmetrical, onset.
- Associated with numerous, often disabling, non-motor symptoms.
- Diagnosis is made clinically.
- Treatment is symptomatic and involves multidisciplinary care.

# Definition

Idiopathic Parkinson's disease (PD) is a neurodegenerative disorder. The cardinal features include resting tremor, rigidity, bradykinesia, and postural instability. Patients may demonstrate a combination of these motor symptoms, as well as other non-motor symptoms.

# Epidemiology

With prevalence of disease increasing with age, PD is one of the most common neurodegenerative disorders. Given various age distributions in study populations, reports of incidence and prevalence vary. The overall age-adjusted prevalence of PD is 1% worldwide and 1.6% in Europe.[1] Prevalence rises from 0.6% in the age range 60 to 64 years to 3.5% in the age range 85 to 89 years. The lowest prevalence ratios are in China, Japan, and Africa.[2]

Western countries' average annual incidence ranges from 4.9 in Sardinia, to what is considered a representative average annual incidence in North America: 25.6 per 100,000 person-years in Olmsted County, Minnesota.[3] [4] The overall prevalence in the US is estimated at 329/100,000;[5] estimated prevalence in Germany is 217/100,000.[6]

Approximately 6.1 million people worldwide had PD in 2016, compared with 2.5 million in 1990.[7] Age-standardised prevalence rates increased by 21.7% over the same period, indicating that the rise was not solely due to increased numbers of older people.

The mean age of onset is about 65 years. Cases occurring in people aged 21 to 40 years are considered young-onset PD; those younger than 21 years have juvenile parkinsonism.[8] From ages 0 to 29 years, the average annual incidence rate of parkinsonism is 0.8/100,000 person-years, and rates increase incrementally to 304.8/100,000 person-years in those aged 80 to 99 years.[3]

Some studies show a greater incidence and prevalence of PD among men, but others have not shown a clear sex difference.[3] [9] [10] [11] [12] [13] Differences between sexes relating to clinical presentation of motor and non-motor symptoms have been reported.[14]

Some studies show evidence of reduced risk in people with darker skin, but one review showed no consistent difference.[4] [15] In one meta-analysis, a reduced prevalence was found among people from Asia, although this was significant only for the 70- to 79-year-old age group.[12]

Despite being more common than other neurodegenerative disorders, PD is still generally considered rare. Methodological differences between studies, or poor methodology, complicate efforts to establish reliable estimates of PD incidence and prevalence, and the potential epidemiological role of ancestry and sex.

# Aetiology

The aetiology of PD is unknown, although several factors have been implicated. There is probably a genetic predisposition, with subsequent environmental factors/exposures contributing to the evolution of clinical disease. Within this multifactorial model, age is the only undisputed risk factor.

Generally, this is considered a sporadic disorder, with twin studies not clearly showing a genetic basis in those >50 years.[16] However, some rare autosomal dominant and recessive familial forms have been identified. A growing number of genetic variants have been mapped, and several of the genes involved have

been identified, including SNCA, Parkin, PINK-1, DJ-1, TREM2, MHFTR, and LRRK2.[17] [18] These genes code for proteins including alpha-synuclein, LRRK2 (leucine-rich repeat kinase 2), PINK-1 (a mitochondrial protein kinase), and components of the ubiquitin-protease system. In addition, mutations in the gene encoding glucocerebrosidase, the enzyme that is deficient in Gaucher's disease, have been shown to confer an increased risk of PD.[19] [20] Some gene variants may confer different levels of risk on different populations.[21] [22] Furthermore, certain gene variants may affect cognitive outcomes in people with PD or may predict response to surgical therapies such as deep brain stimulation (DBS).[23] [24]

Environmental factors are likely to be involved in the pathogenesis of PD. Neurotoxic mechanisms have been proposed based on findings that substances such as 1-methyl-4-phenyl-1,2,3,6-tetrahydropyridine (MPTP) cause selective damage to dopaminergic neurons in the nigrostriatal pathway, by means of mitochondrial poisoning of complex I.[25] Heavy metal exposure has also been implicated as a cause.[26] Oxidative stress probably has a role in neuronal loss. The conversion of dopamine into free radicals by numerous mechanisms may contribute to selective substantia nigral damage. Mitochondrial defects, deficiency of neurotrophic factors, programmed cell death (apoptosis), immune system activation, impaired protein clearance, and infection have all also been implicated.

# Pathophysiology

The underlying pathophysiology of PD is unknown. Selective loss of nigrostriatal dopaminergic neurons in the substantia nigra pars compacta (SNc) occurs with findings of intracytoplasmic eosinophilic inclusions (Lewy bodies) and neurites, both of which are composed of the protein synuclein. One theory suggests that misfolded alpha-synuclein can recruit endogenous alpha-synuclein to seed further protein aggregation in new neurons in a prion-like fashion.[27] Loss of striatal dopaminergic output within the circuitry of the basal ganglia accounts for the constellation of motor symptoms. It is believed that decreased activity of the direct pathway and increased activity of the indirect pathway cause increased inhibitory activity from the globus pallidus internus (GPi)/substantia nigra zona reticulata to the thalamus, and therefore reduced output to the cortex.[28]

Bradykinesia, the most characteristic symptom of basal ganglia dysfunction,[29] correlates with dopamine deficiency, as evidenced by reduced striatal fluorodopa uptake measure by positron emission tomography scans.[30] It is the result of excessive stimulation of the subthalamic nucleus (STN) and the GPi.[31] The resulting slowness and delay initiating movement leads to symptoms including loss of dexterity, drooling, monotonous voice, loss of facial expression, and reduced arm swing.

The pathophysiology of rigidity is not well understood, but enhancement of long latency stretch reflexes is a generally accepted hypothesis.[32] Postural instability is due to loss and/or dysfunction of postural righting reflexes.[33]

No definitive cause of the resting tremor (4 to 6 Hz) is known. It is hypothesised that nigrostriatal degeneration leads to disinhibition of either STN or GPi,[34] or possibly disrupts thalamo-cortical-cerebellar circuits,[35] leading to clinical manifestation of thalamic pacemaker cells.[36] Research suggests that synuclein pathology may actually begin in the lower brainstem (dorsal motor nucleus of the vagus in the medulla oblongata) and progress in a predictable caudal to rostral pattern.[37] There is also evidence that pathology may begin distally in the enteric and peripheral autonomic nervous systems.[38] [39]

# Classification

 

## Age of onset

There is no generally applicable classification for idiopathic PD. If described according to age of onset, the following applies:

- Juvenile parkinsonism: under age 21 years
- Young-onset parkinsonism: ages 21 to 40 years.

# Primary prevention

There is no known prevention.

# Screening

Asymptomatic patients are not routinely screened.

In the future, as neuroprotective agents are developed, at-risk populations may be screened. This would include those with family history or other significant risk factors. The use of dopamine transporter imaging with FP-CIT or beta-CIT single photon emission computed tomography (SPECT) and/or 18F-dopa positron emission tomography (PET) may enable identification of pre-clinical PD.

# Case history

## Case history #1

A 69-year-old man presents with a 1-year history of mild slowness and loss of dexterity. His handwriting has become smaller, and his wife feels his face is less expressive and his voice softer. Over the last few months he has developed a subtle tremor in the right hand, noted while watching television. His symptoms developed insidiously but have mildly progressed. He has no other medical history, but he has noted some mild depression and constipation over the last 2 years. His examination demonstrates hypophonia, masked facies, decreased blink rate, micrographia, and mild right-sided bradykinesia and rigidity. An intermittent right upper extremity resting tremor is noted while he is walking. The rest of his examination and a brain magnetic resonance imaging are normal.

## Other presentations

PD can present in myriad ways. The cardinal features of resting tremor, bradykinesia, rigidity, and postural instability can occur in various combinations and sequences during the course of the disease. The signs and symptoms are typically asymmetrical. Bradykinesia and rigidity often present in subtle fashion early in the disease course. For example, reduced arm swing, shuffled gait, softened voice, decreased blink rate, decreased facial expressivity, and reduced spontaneous movement are all signs of parkinsonism. The non-motor symptoms of PD, such as depression, anxiety, fatigue, autonomic dysfunction (constipation, incontinence, dysphagia), and sleep disturbance, may precede the evolution of motor symptoms. Given their non-specificity, however, their relationship to PD is only made after motor symptoms/signs have been identified.



# Step-by-step diagnostic approach

A thorough history and clinical examination enable diagnosis of PD. No specific diagnostic tests are available. The history will contain symptoms suggestive of bradykinesia, rigidity, resting tremor, and/or postural instability. Other non-motor symptoms, such as neuropsychiatric symptoms (i.e., depression, anxiety), autonomic dysfunction, sleep disorders, pain, and constipation, may also be present. History should exclude exposure to drugs (such as neuroleptics or antiemetics) that may induce a secondary parkinsonism.

The 2015 Movement Disorder Society (MDS) diagnostic criteria for PD define 'parkinsonism' as the presence of bradykinesia with at least one of rest tremor or rigidity.[60] [61] Once parkinsonism is diagnosed, supportive criteria for idiopathic PD include a clear response to dopaminergic therapy and/or the presence of levodopa-induced dyskinesias. Exclusion criteria for idiopathic PD include: cerebellar abnormalities; gaze palsy; dementia early in the disease course; parkinsonism restricted to the lower limbs for more than 3 years; treatment with a dopamine-receptor blocking agent (drug-induced parkinsonism); absence of response to high-dose levodopa; cortical sensory loss, apraxia, or aphasia; and normal functional neuroimaging of the pre-synaptic dopaminergic system.[60]

## Examination

A complete neurological examination should provide objective evidence of parkinsonism in the absence of any other neurological abnormalities. Often, simple observation reveals generalised slowness and lack of spontaneous movement.

Neurological examination will support the history:

- Slowness executing movements (bradykinesia), and motor arrests or freezing (akinesia) observed during rapid alternating movements and gait portions of examination.
- The face is masked, with reduced expressivity, reduced blink rate, and a softened, poorly articulated voice.
- Oculomotor examination may reveal abnormalities including impaired saccadic and smooth pursuit, and impaired convergence.
- Rigidity is evaluated by passive movement about a joint and can be accentuated or reinforced by asking the patient to move the opposite limb (i.e., in circular motion or open/close fist).
- Resting tremor is often passively observed, but distraction can elicit subtle findings. A postural tremor and re-emergent resting tremor may be seen with arms outstretched.
- The gait portion of the examination may demonstrate a stooped, shuffling appearance and reduced arm swing. Patients often turn en bloc, requiring numerous steps to complete a 180° turn.
- A pull test (briskly pulling the patient backwards while standing) is performed to assess postural reflexes. Loss of postural reflexes generally occurs in mid- to late-stage disease.

Idiopathic PD will demonstrate any combination of the above. Generally, findings occur asymmetrically.

There are features that may suggest atypical parkinsonism. Historical features such as acute onset, rapidly progressive disease, cognitive impairment, prominent postural instability, severe autonomic dysfunction, or significant neuropsychiatric features (e.g., hallucinations, fluctuating levels of arousal) all suggest atypical parkinsonism, not idiopathic PD. In addition, early falls, poor response to levodopa, symmetry of motor findings, lack of tremor, and early autonomic dysfunction are features that distinguish other parkinsonian syndromes from PD.[60]

Abnormalities on neurological examination outside of the extrapyramidal system should alert the physician to a possible alternative diagnosis. Findings such as vertical gaze palsy, aphasia, dementia, weakness, hyperreflexia, cerebellar dysfunction, sensory loss, or marked imbalance are not generally expected in PD.

Non-motor symptoms, such as neuropsychiatric symptoms (e.g., depression, anxiety), dementia, autonomic dysfunction, sleep disorders, pain, and constipation, should be sought. Screening tools exist for depression and dementia; the Beck Depression Inventory (BDI), Geriatric Depression Scale (GDS), and Montreal Cognitive Assessment (MoCA) are commonly used. Validated scales to assess depression in patients with PD are available.[62]

## Investigations

In all younger patients (<40 years), a diagnosis of Wilson's disease should be excluded. Low serum ceruloplasmin, elevated 24-hour urine copper, and the presence of Kayser-Fleischer rings on slit-lamp examination all support this diagnosis. Additionally, younger-onset disease should raise the suspicion of familial PD. If available, genetic testing looking for specific mutations should be provided to younger-onset patients.



 

If findings on examination are consistent with idiopathic PD, no further testing is required. Objective improvement in signs in response to antiparkinsonian (dopaminergic) medications will confirm a diagnosis.[60]

Although not performed routinely, a smell test can be given to substantiate the presumptive diagnosis.[63] [64] Hyposmia or anosmia is a non-specific finding[60] that can be seen in up to 75% to 90% of patients.[65]

If atypical features, such as acute onset, rapidly progressive disease, early cognitive impairment, symmetrical findings, or upper motor neuron signs, are found, magnetic resonance imaging (MRI) of the brain with and without gadolinium contrast is recommended. If cognitive impairment is noted on mental status examination, formal neuropsychometric testing should be performed, in addition to MRI, to assist in determining whether the dementia is consistent with PD with dementia or another neurodegenerative disorder.

If features of a psychogenic aetiology are noted, or a vascular or drug-induced aetiology is suspected, dopamine transporter imaging should be considered when available.[66] Dopamine transporter imaging can also be useful in distinguishing cases of PD with action tremor from cases of essential tremor with parkinsonism.

There is insufficient evidence to support the use of levodopa or apomorphine challenge tests in differentiating between PD and other parkinsonian syndromes.[67]

A strong family history and younger-onset disease may lead one to consider serological genetic testing. However, this is often done as part of a research protocol to determine or investigate a particular lineage, and rarely used as primary means to establish a diagnosis. These tests target specific gene mutations known to be associated with PD and are only carried out through subspecialty clinics.[68]

Basal ganglial sonography and cardiac sympathetic innervation studies are emerging diagnostic tests that may be available, usually as part of a research protocol.

Definitive diagnosis can be made postmortem with pathological examination of the brain.



# Risk factors

## Strong

### increasing age

- Single most important risk factor. From age 0 to 29 years, the average annual incidence rate of parkinsonism is 0.8/100,000 person-years, and rates increase incrementally to 304.8/100,000 person-years in those aged 80 to 99 years.[3]

### history of familial PD in younger-onset disease

- In younger-onset disease, autosomal dominant and autosomal recessive mutations have been identified in familial PD cohorts.[40] [41] [42]

### mutation in gene encoding glucocerebrosidase

- Mutations in the gene encoding glucocerebrosidase (GBA), the enzyme that is deficient in Gaucher's disease, have been shown to confer a fivefold increased risk of PD.[19] [20]

### 1-methyl-4-phenyl-1,2,3,6-tetrahydropyridine (MPTP) exposure

- In the early 1980s this neurotoxin produced acute onset parkinsonism in a group of people exposed inadvertently.[43] It is rarely found outside laboratory models, and therefore poses minimal risk to populations at large. However, exposure would have a high association with parkinsonism.

## Weak

### chronic exposure to metals (manganese, iron)

- Generally, chronic exposure to metals (i.e., mining or welding),[44] or a specific metabolic disorder (e.g., haemochromatosis), may cause a parkinsonism syndrome, rather than idiopathic PD.[45]

### male sex

- Some studies have shown greater incidence among males.[3] [11]

### additional genetic risk factors

- Evidence of slightly increased risk if first-degree relative affected. Cumulative incidence of 2% up to age 75 years in first-degree relatives with PD, versus 1% incidence among first-degree relatives of controls.[46]

### head trauma

- History of significant traumatic brain injury may increase risk.[47] [48] [49] [50]

### geographic influence

- May be a contributing risk factor among numerous other multifactorial influences. Variations in the prevalence of the disease in individual racial groups in different geographic areas have suggested an increased risk associated with rural living.[51]

### toxin exposure

- Exposure to toxins such as carbon disulfide and solvents[52] such as trichloroethylene, perchloroethylene, and carbon tetrachloride may contribute to PD, along with many other factors. Occupational exposures to insecticides and herbicides have been identified as risk factors.[53] Some cases of parkinsonism occurred after acute exposure to paraquat or glyphosate.[54] [55] [56]

### occupation as a teacher, healthcare provider, construction worker, carpenter, or cleaner

- Higher frequencies of disease have been reported in teachers, healthcare providers,[57] construction workers,[58] carpenters, and cleaners,[59] as well as those involved in farming, the steel industry, and welding.

# History & examination factors

## Key diagnostic factors

### presence of risk factors (common)

- Key risk factors include increasing age, familial PD, and 1-methyl-4-phenyl-1,2,3,6-tetrahydropyridine (MPTP) exposure.[3] [40] [41] [42] [43] Aetiology is most likely to be multifactorial.[69]



 

### bradykinesia (common)

- Slowness of movements, progressive reduction in amplitude of repeated movements, delay in initiating movements, and freezing of gait are eventually seen in all patients. Required sign for many diagnostic criteria.[60] [70]

### resting tremor (common)

- A 4 to 6 Hz tremor is noted at rest and dissipates with use of the limbs. Generally the onset is asymmetrical. A chin tremor may occur as well. This tremor may re-emerge when the arms are outstretched.[71]

### rigidity (common)

- Hypertonicity is defined as unvarying increased resistance within the range of passive movement about a joint.[72] Often cogwheeling will be noted, especially (although not only) if tremor is also present.

### postural instability (common)

- Imbalance or falling noted with pull test or spontaneously; retropulsion; common in mid- to late-stage disease.

## Other diagnostic factors

### masked facies (common)

- Loss of spontaneous facial movement and expressivity, often noted only by partner.

### hypophonia (common)

- Reduced volume of voice.

### hypokinetic dysarthria (common)

- Related to bradykinesia and rigidity of orobuccolingual and laryngeal musculature.

### micrographia (common)

- Decrease in amplitude of handwriting/printing.

### stooped posture (common)

- Related to rigidity.

### shuffling gait (common)

- Related to rigidity and bradykinesia.

### conjugate gaze disorders (common)

- Saccadic (jerky) pursuit and hypometric saccades (falling short of intended target).

### fatigue (common)

- Disabling symptom reported commonly.

### constipation (common)

- Reflection of autonomic dysfunction.

### depression (common)

- Common neuropsychiatric complaint. Should be sought in patients.

### anxiety (common)

- Often unrecognised but common. Should be sought in patients.

### dementia (common)

- Non-motor symptom that should be screened for at consultations; common in mid- to late-stage disease.

### exposure to neuroleptics or antiemetics (uncommon)

- Dopamine blocking agents may induce a secondary parkinsonism. Additionally, they may unmask incipient PD.

### features of atypical parkinsonism (uncommon)

- These include acute onset, rapidly progressive disease, cognitive impairment, prominent postural instability, severe autonomic dysfunction, and significant neuropsychiatric features (i.e., hallucinations, fluctuating levels of arousal).

## Diagnostic tests

### 1st test to order

| Test | Result |
|---|---|
| **dopaminergic agent trial**<br>• The diagnosis of PD is made clinically, and in cases without atypical features no additional diagnostic testing is indicated. If diagnostic testing is warranted due to atypical features or unclear clinical diagnosis, tests may include dopaminergic agent trial.<br>• Performed if diagnosis is in question; ultimately performed in all patients as treatment is instituted.<br>• Useful to confirm diagnosis.<br>• However, in some instances, as in cases of tremor-predominant disease, doses as high as 1200 mg of levodopa may need to be reached before concluding lack of efficacy. | **improvement in symptoms** |



 

## Other tests to consider

| Test | Result |
|---|---|
| **MRI brain**<br>• The diagnosis of PD is made clinically, and in cases without atypical features no additional diagnostic testing is indicated.<br>• MRI should be ordered if atypical features (atypical course, early dementia, significant imbalance in early disease, autonomic dysfunction, gaze abnormalities, or atypical abnormalities on neurological examination) are present.<br>• Absence of dorsolateral nigral hyperintensity on 3.0 Tesla susceptibility-weighted scan (a normal finding, the 'swallow-tail-sign') has been used to distinguish healthy controls from patients with neurodegenerative parkinsonism with high reliability.[73] Assessment of dorsolateral nigral hyperintensity on iron-sensitive MRI may also be a marker of nigral pathology.[74] | **normal image in most patients with idiopathic PD; age-related changes such as mild small vessel disease acceptable; similarly acceptable if patient has appropriate history to explain other abnormalities (i.e., stroke, trauma); in advanced disease with dementia, may see cortical atrophy; dorsolateral nigral hyperintensity (the 'swallow-tail-sign') may be absent** |
| **functional neuroimaging (dopamine transporter imaging such as FP-CIT or beta-CIT SPECT, or fluorodopa PET)**<br>• The diagnosis of PD is made clinically, and in cases without atypical features no additional diagnostic testing is indicated. If diagnostic testing is warranted due to atypical features or unclear clinical diagnosis, tests may include functional neuroimaging.<br>• Functional neuroimaging may be helpful in distinguishing a neurodegenerative parkinsonian disorder from vascular,[75] drug-induced, or psychogenic parkinsonism, or essential tremor,[66] and also may serve as a pre-clinical marker for future application of neuroprotective agents.[76] | **decreased basal ganglia (putaminal) pre-synaptic dopamine uptake** |
| **olfactory testing**<br>• The diagnosis of PD is made clinically, and in cases without atypical features no additional diagnostic testing is indicated. If diagnostic testing is warranted due to atypical features or unclear clinical diagnosis, tests may include olfactory testing.<br>• Smell tests to support clinical diagnosis include the University of Pennsylvania Smell Identification Test (UPSIT) and the Sniffin' Sticks test.[63] [64] [77]<br>• Impairment in odour identification, threshold for detection, and odour recognition memory present early in disease.[78] | **hyposmia or anosmia** |
| **genetic testing**<br>• The diagnosis of PD is made clinically, and in cases without atypical features no additional diagnostic testing is indicated. If diagnostic testing is warranted due to atypical features or unclear clinical diagnosis, tests may include genetic testing.<br>• Should be performed if young onset or significant family history exists, with assistance of a movement disorders specialist and genetic counsellor. Often done as part of a research protocol to determine or investigate a particular lineage, and rarely used as primary means to establish a diagnosis. | **specific mutation would be identified** |
| **neuropsychometric testing**<br>• The diagnosis of PD is made clinically, and in cases without atypical features no additional diagnostic testing is indicated. If diagnostic | **executive dysfunction can occur in PD with dementia** |

| Test | Result |
|---|---|
| testing is warranted due to atypical features or unclear clinical diagnosis, tests may include neuropsychometric testing.<br>• Performed if cognitive deficits are reported in history or demonstrated in bedside screening. | |
| **serum ceruloplasmin**<br>• The diagnosis of PD is made clinically, and in cases without atypical features no additional diagnostic testing is indicated. If diagnostic testing is warranted due to atypical features or unclear clinical diagnosis, tests may include serum ceruloplasmin.<br>• In all younger patients (<40 years), a diagnosis of Wilson's disease should be excluded. The presence of Kayser-Fleischer rings on slit-lamp examination supports this diagnosis. | **low in Wilson's disease** |
| **24-hour urine copper**<br>• The diagnosis of PD is made clinically, and in cases without atypical features no additional diagnostic testing is indicated. If diagnostic testing is warranted due to atypical features or unclear clinical diagnosis, tests may include 24-hour urine copper.<br>• In all younger patients (<40 years), a diagnosis of Wilson's disease should be excluded. The presence of Kayser-Fleischer rings on slit-lamp examination supports this diagnosis. | **elevated in Wilson's disease** |
| **brain pathology (postmortem)**<br>• Impractical to perform on patient antemortem (except in extraordinary circumstances).<br>• Gross examination may reveal frontal atrophy and loss of pigmented cells of substantia nigra; microscopic observation of presence of Lewy bodies and positive reactivity to synuclein with immunohistochemical staining. | **nigrostriatal degeneration and Lewy bodies** |

## Emerging tests

| Test | Result |
|---|---|
| **sonography, basal ganglia**<br>• Used in clinical research.[79] | **hyperechogenicity of substantia nigra** |
| **cardiac sympathetic innervation using iodine-123 meta-iodobenzylguanidine (MIBG)**<br>• Impractical to perform routinely. | **decreased heart to mediastinum average count ratio** |



 

# Differential diagnosis

| Condition | Differentiating signs / symptoms | Differentiating tests |
|---|---|---|
| **Progressive supranuclear palsy (PSP)** | • Gaze palsies and early falls within 1 year of diagnosis.[80] [81]<br>• Neurological examination: vertical gaze palsy and significant postural instability. | • Evidence of midbrain atrophy on MRI brain can be supportive of PSP diagnosis, but is not definitive. |
| **Multiple system atrophy (MSA; MSA-A, formerly Shy-Drager syndrome; MSA-P, striatonigral degeneration; MSA-C, olivopontocerebellar atrophy)** | • Poor response to levodopa.<br>• Autonomic dysfunction (symptomatic hypotension, constipation, urinary urge incontinence, faecal incontinence, urinary retention, persistent erectile dysfunction).<br>• Speech or bulbar dysfunction.[82]<br>• Pyramidal or cerebellar dysfunction. Neurological examination reveals deficits outside of the extrapyramidal system (i.e., pyramidal, cerebellar, or autonomic deficits). | • Evidence of pontine and cerebellar atrophy on MRI brain can be supportive of MSA-C diagnosis, but is not definitive.<br>• Electromyography (EMG) may demonstrate denervation and reinnervation of rectal sphincter muscle.<br>• Iodine-131-meta-iodobenzylguanidine (MIBG) scan may be normal, whereas in idiopathic PD abnormal result expected (available only for research purposes). |
| **Lewy body dementia** | • Dementia, hallucinations, fluctuating mental status.[83] History is often sufficient for diagnosis. | • Neuropsychometric testing may distinguish domains of cognitive deficits. |
| **Corticobasal degeneration** | • Apraxia, alien limb phenomenon, cortical sensory loss on neurological examination. | • None. |
| **Alzheimer's disease with parkinsonism** | • Dementia, aphasia. | • Neuropsychometric testing. |
| **Drug-induced parkinsonism** | • History of neuroleptic, metoclopramide, reserpine, tetrabenazine, lithium, or calcium-channel blocker usage.<br>• Symmetrical symptoms. History is sufficient to make diagnosis. | • Functional neuroimaging of striatal dopamine transporter uptake, using FP-CIT SPECT, beta-CIT SPECT, or fluorodopa PET, can be helpful in differentiating from neurodegenerative parkinsonism (i.e., scan would be normal in drug-induced parkinsonism). |
| **Metabolic abnormalities** | • History of hypoxia, hepatocerebral degeneration, hypoglycaemia. | • Electrolyte testing (laboratory) will demonstrate |

| Condition | Differentiating signs / symptoms | Differentiating tests |
|---|---|---|
| | • Symmetrical symptoms. | abnormalities (i.e., liver dysfunction, hypoglycaemia). |
| **Normal pressure hydrocephalus** | • Dementia, incontinence, prominent gait abnormalities.<br>• Rapid or subacute onset. | • CT head or MRI brain will demonstrate ventricular enlargement incongruous with degree of atrophy. MRI flow study may also demonstrate increased cerebrospinal fluid (CSF) flow velocity.<br>• Large-volume CSF tap may lead to temporary improvement of symptoms. |
| **Structural abnormalities** | • History of tumour, hydrocephalus, subdural haematoma, or trauma. | • MRI brain shows abnormalities consistent with specific aetiology (i.e., tumour = mass; stroke = area of encephalomalacia; subdural haematoma = collection of blood). |
| **Vascular parkinsonism** | • Lower extremity prominence of symptoms.<br>• Symmetrical symptoms.<br>• Stepwise progression.<br>• Less responsive to levodopa. | • MRI brain shows significant small vessel disease or basal ganglia lacunar infarct(s). |
| **Toxin exposure** | • History of carbon monoxide, manganese, or 1-methyl-4-phenyl-1,2,3,6-tetrahydropyridine (MPTP) exposure.<br>• Acute onset. | • MRI brain: abnormalities (T2 changes) in basal ganglia noted. |
| **Infections** | • History of AIDS, subacute sclerosing panencephalitis, or postencephalitic or prion disease.<br>• Acute or subacute onset. | • Abnormalities on MRI brain (any changes); serologies (HIV); cerebrospinal fluid (any abnormalities). |
| **Hereditary disorders** | • History of Huntington's disease, spinocerebellar ataxias, Wilson's disease, neurodegeneration with brain iron accumulation (formerly Hallervorden-Spatz disease), parkinsonism-dementia-amyotrophic lateral sclerosis, and mitochondrial cytopathies.<br>• Juvenile PD or young-onset PD. | • Serological genetic testing will identify mutation.<br>• Low serum ceruloplasmin and elevated 24-hour urine copper support a diagnosis of Wilson's disease. |

| Condition | Differentiating signs / symptoms | Differentiating tests |
|---|---|---|
| | • Associated chorea, myoclonus, cerebellar dysfunction, and dementia.<br>• Kayser-Fleischer rings on slit-lamp examination support a diagnosis of Wilson's disease. | |

# Diagnostic criteria

## UK PD Society Brain Bank criteria (UKPDSBB) for diagnosis of probable Parkinson's Disease[84]

Inclusion criteria.

1. Bradykinesia (slowness of initiation of voluntary movement with progressive reduction in speed and amplitude of repetitive actions); and at least one of the following:

- Muscular rigidity
- 4 to 6 Hz rest tremor
- Postural instability not caused by visual, vestibular, cerebellar, or proprioceptive dysfunction.

2. Exclude other causes of parkinsonism.

3. At least three of the following supportive (prospective) criteria:

- Unilateral onset
- Rest tremor present
- Progressive disorder
- Persistent asymmetry affecting side of onset most
- Excellent response (70%-100%) to levodopa
- Severe levodopa-induced chorea
- Levodopa response for 5 years or more
- Clinical course of 10 years or more.

## Movement Disorder Society clinical diagnostic criteria for Parkinson disease[60] [61]

The 2015 Movement Disorder Society (MDS) diagnostic criteria for PD define 'parkinsonism' as the presence of bradykinesia with at least one of rest tremor or rigidity. Once parkinsonism is diagnosed, supportive criteria for idiopathic PD include a clear response to dopaminergic therapy and/or the presence of levodopa-induced dyskinesias. Exclusion criteria for idiopathic PD include: cerebellar abnormalities; gaze palsy; dementia early in the disease course; parkinsonism restricted to the lower limbs for more than 3 years; treatment with a dopamine-receptor blocking agent (drug-induced parkinsonism); absence of response to high-dose levodopa; cortical sensory loss, apraxia, or aphasia; and normal functional neuroimaging of the pre-synaptic dopaminergic system.

## Revised Unified Parkinson's Disease Rating Scale (MDS-UPDRS)[85]

Four-part multi-modular rating scale system revised to capture more non-motor features of PD and shift scale from mild/moderate/severe/marked to slight/mild/moderate/severe (to allow more clinically relevant distinctions in earlier disease).

- Part I = non-motor experiences of daily living (13 items)
- Part II = motor experiences of daily living (13 items)
- Part III = motor examination (33 scores based on 18 items, several with right, left, etc.)
- Part IV = motor complications (6 items).

# Step-by-step treatment approach

Treatment is symptomatic as no curative or disease-modifying agents are available. Treatment is designed to supplement depleted dopamine stores in the substantia nigra, thus minimising or eliminating symptoms and improving quality of life.[86] Initiation of treatment is based on severity of symptoms. Pharmacological therapy should be accompanied by physical and occupational therapy for gait and balance training, stretching, and strength exercises. Patients with mild disease may elect to postpone treatment until disability occurs.[87]

Response to pharmacological therapy manifests as an improvement or resolution of symptoms is, by convention, referred to as 'on-time'. Conversely, 'off-time' refers to time spent with maximal symptoms.

Research is underway to develop agents that slow disease progression, reverse neuronal loss, and even prevent neuronal loss by identifying at-risk patient groups and administering neuroprotective agents.[88] [89] However, no treatment has been shown to be definitively neuroprotective.[90] [91]

## Symptomatic parkinsonism (symptoms requiring treatment)

Early in the disease, dopaminergic supplementation is often sufficient to markedly reduce, and even eliminate, symptoms. However, as the disease progresses, complications develop. Adjunctive medication regimens are moderately effective in managing these complications. However, in most patients medications will become less effective and complications will make treatment challenging. The moderate stage of parkinsonism is arbitrarily defined by increased severity in symptoms, as well as evolution of complications of disease treatment.

Non-motor symptoms, such as depression, anxiety, fatigue, cognitive impairment, autonomic dysfunction, constipation, and sleep disturbance, can develop at any time during the disease course, even before diagnosis or evolution of the widely recognised motor symptoms. These symptoms are numerous, and treatment is specific to each symptom.[92] It is important that clinicians screen for these non-motor symptoms, as they cause significant psychological and physical disability.[93] [94] Depression and anxiety are under-recognised and likely undertreated; the former may affect up to 25% to 35% of patients with PD, the latter 6% to 55%.[95] [96] [97]

Given the constellation and diverse list of symptoms associated with PD, optimal treatment strategies involve a multidisciplinary team approach aimed at improving quality of life.

Exercise should always be encouraged; it has been shown to improve functional performance on motor tasks at any stage of disease, and may have beneficial effects on cognition.[98] [99] [100] Progressive resistance exercise, in particular, reduces motor symptoms and improves functional status.[98] [101] Activities such as Tai Chi and dance have also been shown to be safe and beneficial in PD, and may improve quality of life and reduce falls.[102] [103] [104] [105] [106] [107] [108]

Physiotherapy,[109] occupational therapy,[110] and speech therapy are important to treat specific symptoms, such as hypophonia and dysphagia. Individually tailored and standard cognitive training may improve memory, executive function, and attention in people with PD.[111]

Despite pre-clinical data indicating that nutritional antioxidants may be neuroprotective in PD, there is no clinical evidence that any vitamin, food additive, or supplement can improve motor function or delay disease progression.[102]

## Mild parkinsonism

When symptoms begin to interfere with the patient's quality of life or activities of daily living, treatment is initiated with a dopaminergic agent. An attempt is made to improve symptoms without causing unwanted adverse effects. Adverse effects are typically dose-dependent and differ slightly between agents. However, overall, these medications are well tolerated and safe.

Levodopa is considered the definitive treatment, and does not appear to accelerate disease progression.[112] However, levodopa does not protect against disease progression in patients with early disease and, due to the increased risk of developing dyskinesias, other dopaminergic medications should be considered when initiating treatment, particularly in younger patients.[89] [112]

First-line treatment for mild symptoms in any age group can vary,[86] but a trial of a monoamine oxidase-B (MAO-B) inhibitor (e.g., rasagiline, selegiline) is reasonable. These agents have modest symptomatic benefit, and appear to be well tolerated.[89] [113] [114] Early treatment with rasagiline does not confer long-term benefits.[91]

Dopamine agonists (e.g., pramipexole, ropinirole, rotigotine) or carbidopa/levodopa are effective first-line options, or can be instituted if MAO-B inhibitors are ineffective.[89] [115] [116] Adverse effects are monitored and can limit usage, particularly in older people. Patients who do not respond to dopaminergic agents are unlikely to have idiopathic PD.[86] However, in some instances, for example tremor-predominant disease, doses as high as 1200 mg of levodopa may need to be reached before concluding lack of efficacy. Possible gene markers of levodopa response (adverse effects) have been investigated.[117]

Anticholinergic agents (e.g., trihexyphenidyl) and amantadine may effectively treat mild symptoms, especially tremor, but adverse effects often limit their use in older patients.[86]

## Moderate parkinsonism

Management is similar to that of mild parkinsonism. However, this stage is characterised by the evolution of complications in treatment. Foremost, symptoms may become more severe, and higher doses of medication are needed. Using carbidopa/levodopa and dopamine agonists together is more common.

Wearing off (motor fluctuations)

- Of the complications of disease, wearing off with motor fluctuations is the most common. This is defined as fluctuations in the response and duration of response to medications. Patients begin to experience an 'up and down' of symptoms based on the timing of their medications: that is, fluctuation of symptoms.
- Treatment strategy is aimed at minimising off-time by prolonging the duration of response to dopaminergic supplementation.
- Taking medications more frequently (up to 4 times daily) may improve symptoms in patients who experience wearing off (motor fluctuations) while taking a dopamine agonist. Instituting carbidopa/levodopa is appropriate if it is not possible to increase dose frequency.
- When carbidopa/levodopa is used, the addition of a catechol-o-methyltransferase (COMT) inhibitor (e.g., entacapone, tolcapone, opicapone) may extend therapeutic benefit.[118] [119] Entacapone is typically taken with each dose of levodopa.[120] Due to the risk of serious hepatotoxicity, tolcapone is not a first-line adjunct therapy to carbidopa/levodopa. Opicapone is a new selective COMT-inhibitor that has been shown to be non-inferior to entacapone for reducing off-time, with an



 

average of slightly more than 1-hour reduction of off-time without troublesome dyskinesias per day.[121]

- MAO-B inhibitors and dopamine agonists can be added to carbidopa/levodopa to reduce off-time, with or without reducing requisite levodopa dose.[118] [119] Safinamide, a selective reversible MAO-B inhibitor, improved daily on-time without troublesome dyskinesia by 1 to 2 hours in a phase 3 randomised placebo-controlled trial of levodopa-treated patients with motor fluctuations.[122]
- The pharmacokinetics of currently available extended-release formulation are often unpredictable. An extended-release capsule formulation of carbidopa/levodopa that combines immediate- and sustained-release pellets has been shown to reduce daily off-time compared with immediate-release formulations and the combination of carbidopa/levodopa and entacapone.[123] [124] [125]

Refractory tremor

- If patients have tremor that is insufficiently treated with dopaminergic agents, adding an anticholinergic agent (e.g., trihexyphenidyl) or amantadine may be considered.[86] However, anticholinergic agents can cause or worsen cognitive impairment, and patients should be educated about and monitored for this potential adverse effect. Anticholinergics should be used with caution in patients with any cognitive impairment.
- Second-line options include medications used to treat essential tremor, such as propranolol and primidone.
- Deep brain stimulation may also be considered in some patients with tremor that is refractory to medication.[126]

Dyskinesias

- A common complication of moderate disease. If mild and not bothersome, dyskinesias can be observed. However, dyskinesias often lead to discomfort and, in some cases, undesired weight loss.
- Excessive movements reflect overstimulation of dopamine receptors. Therefore, the first approach should be to consider reduction in dopaminergic supplementation, without loss of therapeutic efficacy. If this cannot be achieved, amantadine can be used.[89]
- An extended-release amantadine formulation has been approved by the Food and Drug Administration (FDA) in the US for the treatment of dyskinesias in people with PD receiving levodopa-based therapy, with or without concomitant dopaminergic medications.

## Advanced parkinsonism

This stage of disease is often complicated by sudden and unpredictable periods of wearing off, motor fluctuations, freezing, and dysphagia. These can be managed with an injectable form of dopamine, apomorphine.[127] This subcutaneous formulation is often helpful for patients who have dysphagia in the off-state, or first thing in the morning, when symptoms are severe. Similarly, if swallowing becomes an issue, dissolvable carbidopa/levodopa and/or selegiline can be used. These are considered rescue treatment approaches.

Deep brain stimulation (DBS) is effective for refractory complications such as motor fluctuations and dyskinesias.[89] [128] [129] [130] Use and benefit of DBS is also being evaluated in earlier stages of PD.[131] [132] The two primary targets for DBS for PD are the globus pallidus interna (GPi) and the subthalamic nucleus (STN).[133] Guidelines provide advice on target selection when using DBS to improve motor symptoms or levodopa-induced dyskinesias under various circumstances.[128] The DBS device is typically left on, but patients can turn it off when desired.

Continuous intrajejunal infusion of levodopa/carbidopa enteral suspension reduces plasma concentration variability. One double-blind randomised controlled trial demonstrated reduction in off-time and improvement in on-time, without troublesome dyskinesias, compared with placebo.[134] [135] [136]

Ultimately, in many patients, exogenous dopaminergic agents are ineffective in treatment of disease. The severity of neuronal loss prevents improvement in symptoms. Treatment becomes supportive and ultimately palliative.

# Treatment details overview

Please note that formulations/routes and doses may differ between drug names and brands, drug formularies, or locations. Treatment recommendations are specific to patient groups: see disclaimer



 

## Ongoing ( summary )

| | | |
|---|---|---|
| **mild parkinsonism** | | |
| | 1st | MAO-B inhibitor, dopaminergic agent, amantadine, or trihexyphenidyl |
| | plus | physical activity |
| with nausea and/or vomiting on carbidopa/levodopa | plus | additional carbidopa or domperidone |
| with nausea and/or vomiting on dopamine agonist | plus | domperidone |
| **moderate parkinsonism** | | |
| | 1st | MAO-B inhibitor, dopaminergic agent, amantadine, or trihexyphenidyl |
| | plus | physical activity |
| with refractory tremor | plus | pharmacotherapy or deep brain stimulation |
| with wearing off (motor fluctuations) on dopamine agonists, not taking carbidopa/levodopa | plus | carbidopa/levodopa |
| with wearing off (motor fluctuations), taking carbidopa/levodopa | plus | COMT inhibitor, dopamine agonist, MAO-B inhibitor, or switch to extended-release carbidopa/levodopa |
| with dyskinesias | plus | reduce dopaminergic medications (if tolerated) or add amantadine |
| with nausea and/or vomiting on carbidopa/levodopa | plus | additional carbidopa or domperidone |
| with nausea and/or vomiting on dopamine agonist | plus | domperidone |
| **advanced parkinsonism** | | |
| | 1st | MAO-B inhibitor, dopaminergic agent, amantadine, or trihexyphenidyl |
| | plus | physical activity |
| with refractory tremor | plus | pharmacotherapy or deep brain stimulation |
| with unpredictable off-times, motor fluctuations, or freezing | plus | apomorphine or as-needed doses of carbidopa/levodopa |

## Ongoing ( summary )

| | | |
|---|---|---|
| ■ with refractory motor fluctuations | plus | deep brain stimulation |
| | adjunct | intrajejunal infusion of levodopa/ carbidopa |
| ■ with refractory dyskinesias | plus | reduce dopaminergic medications (if tolerated) or add amantadine |
| | plus | deep brain stimulation |
| ■ with dysphagia | plus | dissolvable selegiline or carbidopa/ levodopa or transdermal rotigotine |
| ■ with nausea and/or vomiting on carbidopa/ levodopa | plus | additional carbidopa or domperidone |
| ■ with nausea and/or vomiting on dopamine agonist | plus | domperidone |

# Treatment options

Please note that formulations/routes and doses may differ between drug names and brands, drug formularies, or locations. Treatment recommendations are specific to patient groups: see disclaimer

# Ongoing

## mild parkinsonism

**1st** **MAO-B inhibitor, dopaminergic agent, amantadine, or trihexyphenidyl**

### Primary options

» rasagiline: 1 mg orally once daily

**OR**

» pramipexole: 0.125 mg orally (immediate-release) three times daily initially, increase by 0.125 mg/dose increments every 5-7 days according to response, maximum 4.5 mg/day; 0.375 mg orally (extended-release) once daily initially, increase by 0.75 mg/day increments every 5-7 days according to response, maximum 4.5 mg/day

**OR**

» ropinirole: 0.25 mg orally (immediate-release) three times daily initially for 1 week, increase by 0.25 mg/dose increments every week for 3 weeks according to response, then increase by 0.5 mg/dose increments at weekly intervals up to 9 mg/day total dose, then increase by 1 mg/dose increments at weekly intervals thereafter, maximum 24 mg/day; 2 mg orally (extended-release) once daily initially for 1-2 weeks, increase by 2 mg/day increments every week according to response, maximum 24 mg/day

**OR**

» carbidopa/levodopa: 50 mg orally (immediate-release) three times daily initially, increase by 50-100 mg/day increments every 5-7 days according to response
Dose expressed as levodopa component. Tablet strengths of 10/100 mg (carbidopa/levodopa), 25/100 mg, or 25/250 mg may be used depending on whether a higher amount of carbidopa or levodopa is required. A ratio of 25:100 is likely to be optimal for reducing peripheral side effects of levodopa such as nausea.

**OR**

» rotigotine transdermal: apply 2 mg/24 hour patch initially, increase by 2 mg/24 hour increments at weekly intervals according to response, maximum 8 mg/24 hours

# Ongoing

### Secondary options

» selegiline: 5 mg orally twice daily at breakfast and lunchtime

**OR**

» trihexyphenidyl: 1 mg orally (immediate release) once daily initially, increase by 2 mg/day increments every 3-5 days according to response, maximum 10 mg/day given in 3-4 divided doses

**OR**

» amantadine: 100 mg orally once daily initially for 1 week, increase to 100 mg twice daily, maximum 400 mg/day
Doses are often given in the morning and at noon to reduce the risk of insomnia.

» When symptoms begin to interfere with the patient's quality of life or activities of daily living, treatment is initiated with a dopaminergic agent. An attempt is made to improve symptoms without causing unwanted adverse effects. Adverse effects are typically dose-dependent and differ slightly between agents. However, overall, these medications are well tolerated and safe.[89]

» For very mild, early symptoms, a monoamine oxidase-B (MAO-B) inhibitor (e.g., rasagiline, selegiline) may be used. These agents have modest but significant symptomatic benefit, and appear to be well tolerated.[113] [114] Rasagiline is approved for monotherapy or use in combination with other agents.[137] [138] Early treatment with rasagiline does not confer long-term benefits.[91] Selegiline is only approved for adjunctive use. This treatment may have some benefit to disease course.

» Dopamine agonists (e.g., pramipexole, ropinirole, transdermal rotigotine) or carbidopa/levodopa are effective first-line options, or can be instituted if MAO-B inhibitors are ineffective.[89] [115] [116] Adverse effects are monitored and can limit usage, particularly in older people.

» Given the higher risk of dyskinesias in young patients with carbidopa/levodopa, and the higher risk of orthostasis and hallucinations in older patients with dopamine agonists, dopamine agonists are often the initial treatment of choice

## Ongoing

in younger patients (<70 years), while carbidopa/levodopa may be the initial treatment in older patients (>70 years).

» Anticholinergic agents (e.g., trihexyphenidyl) and amantadine may effectively treat mild symptoms, especially tremor, but adverse effects often limit their use in older patients.[86]

» Choice of initial therapy is a decision that is based on the individual patient's needs and risk for adverse effects.[89]

**plus** **physical activity**

Treatment recommended for ALL patients in selected patient group

» Exercise should always be encouraged; it has been shown to improve functional performance on motor tasks at any stage of disease, and may have beneficial effects on cognition.[98] [99] [100] Progressive resistance exercise, in particular, reduces motor symptoms and improves functional status.[98] [101] Activities such as Tai Chi and dance have also been shown to be safe and beneficial in PD, and may improve quality of life and reduce falls.[102] [103] [104] [105] [106] [107] [108]

» Physiotherapy,[109] occupational therapy,[110] and speech therapy are important to treat specific symptoms, such as hypophonia and dysphagia. Individually tailored and standard cognitive training may improve memory, executive function, and attention in people with PD.[111]

**with nausea and/or vomiting on carbidopa/levodopa**

**plus** **additional carbidopa or domperidone**

Treatment recommended for ALL patients in selected patient group

### Primary options

» carbidopa: 25 mg orally with each dose of carbidopa/levodopa

### Secondary options

» domperidone: 10 mg orally three times daily for a maximum of 7 days, maximum 30 mg/day

» For patients taking carbidopa/levodopa, nausea and vomiting can be treated with additional doses of carbidopa or with domperidone.

» Following a European review, the Medicines and Healthcare products Regulatory Agency



 

## Ongoing

and European Medicines Agency have issued recommendations concerning the use of domperidone. The review found the drug was associated with a small increased risk of potentially life-threatening cardiac effects. As a consequence, it should be used at the lowest effective dose for the shortest possible duration and the maximum treatment duration should not usually exceed 1 week. The new maximum dose recommended in adults is 30 mg/day. Domperidone is contraindicated in patients with severe hepatic impairment or underlying cardiac disease. It should not be administered with other drugs that prolong the QT interval or inhibit CYP3A4.[139]

**with nausea and/or vomiting on dopamine agonist**

**plus**

**domperidone**

Treatment recommended for ALL patients in selected patient group

**Primary options**

» domperidone: 10 mg orally three times daily for a maximum of 7 days, maximum 30 mg/day

» For patients being treated with a dopamine agonist, nausea and vomiting can be treated with domperidone.

» Following a European review, the Medicines and Healthcare products Regulatory Agency and European Medicines Agency have issued recommendations concerning the use of domperidone. The review found the drug was associated with a small increased risk of potentially life-threatening cardiac effects. As a consequence, it should be used at the lowest effective dose for the shortest possible duration and the maximum treatment duration should not usually exceed 1 week. The new maximum dose recommended in adults is 30 mg/day. Domperidone is contraindicated in patients with severe hepatic impairment or underlying cardiac disease. It should not be administered with other drugs that prolong the QT interval or inhibit CYP3A4.[139]

**moderate parkinsonism**

**1st**

**MAO-B inhibitor, dopaminergic agent, amantadine, or trihexyphenidyl**

**Primary options**

» rasagiline: 1 mg orally once daily

**OR**

## Ongoing

» pramipexole: 0.125 mg orally (immediate-release) three times daily initially, increase by 0.125 mg/dose increments every 5-7 days according to response, maximum 4.5 mg/day; 0.375 mg orally (extended-release) once daily initially, increase by 0.75 mg/day increments every 5-7 days according to response, maximum 4.5 mg/day

**OR**

» ropinirole: 0.25 mg orally (immediate-release) three times daily initially for 1 week, increase by 0.25 mg/dose increments every week for 3 weeks according to response, then increase by 0.5 mg/dose increments at weekly intervals up to 9 mg/day total dose, then increase by 1 mg/dose increments at weekly intervals thereafter, maximum 24 mg/day; 2 mg orally (extended-release) once daily initially for 1-2 weeks, increase by 2 mg/day increments every week according to response, maximum 24 mg/day

**OR**

» carbidopa/levodopa: 50 mg orally (immediate-release) three times daily initially, increase by 50-100 mg/day increments every 5-7 days according to response; dose of extended-release capsule depends on previous dose of carbidopa/levodopa
Dose expressed as levodopa component. Tablet strengths of 10/100 mg (carbidopa/levodopa), 25/100 mg, or 25/250 mg may be used depending on whether a higher amount of carbidopa or levodopa is required. A ratio of 25:100 is likely to be optimal for reducing peripheral side effects of levodopa such as nausea.

**OR**

» rotigotine transdermal: apply 2 mg/24 hour patch initially, increase by 2 mg/24 hour increments at weekly intervals according to response, maximum 8 mg/24 hours

### Secondary options

» selegiline: 5 mg orally twice daily at breakfast and lunchtime

**OR**

## Ongoing

» trihexyphenidyl: 1 mg orally (immediate release) once daily initially, increase by 2 mg/day increments every 3-5 days according to response, maximum 10 mg/day given in 3-4 divided doses

**OR**

» amantadine: 100 mg orally once daily initially for 1 week, increase to 100 mg twice daily, maximum 400 mg/day
Doses are often given in the morning and at noon to reduce the risk of insomnia.

» Management is similar to that of mild parkinsonism. However, this stage is characterised by the evolution of complications in treatment. Symptoms may become more severe and higher doses of medication are needed. Using carbidopa/levodopa and a dopamine agonist (e.g., pramipexole, ropinirole, rotigotine) together is more common.

» An extended-release capsule formulation of carbidopa/levodopa that combines immediate- and sustained-release pellets has been shown to reduce daily off-time compared with immediate-release formulations and the combination of carbidopa/levodopa and entacapone.[123] [124] [125]

**plus** **physical activity**

Treatment recommended for ALL patients in selected patient group

» Exercise should always be encouraged; it has been shown to improve functional performance on motor tasks at any stage of disease, and may have beneficial effects on cognition.[98] [99] [100] Progressive resistance exercise, in particular, reduces motor symptoms and improves functional status.[98] [101] Activities such as Tai Chi and dance have also been shown to be safe and beneficial in PD, and may improve quality of life and reduce falls.[102] [103] [104] [105] [106] [107] [108]

» Physiotherapy,[109] occupational therapy,[110] and speech therapy are important to treat specific symptoms, such as hypophonia and dysphagia. Individually tailored and standard cognitive training may improve memory, executive function, and attention in people with PD.[111]

**with refractory tremor** **plus** **pharmacotherapy or deep brain stimulation**

## Ongoing

Treatment recommended for ALL patients in selected patient group

### Primary options

» trihexyphenidyl: 1 mg orally (immediate release) once daily initially, increase by 2 mg/day increments every 3-5 days according to response, maximum 10 mg/day given in 3-4 divided doses

**OR**

» amantadine: 100 mg orally once daily initially for 1 week, increase to 100 mg twice daily, maximum 400 mg/day
Doses are often given in the morning and at noon to reduce the risk of insomnia.

### Secondary options

» propranolol: 40 mg (immediate-release) orally twice daily, increase gradually according to response, maximum 160 mg/day given in 2-3 divided doses

**OR**

» primidone: 25 mg orally once daily initially, increase gradually according to response, maximum 750 mg/day given in 3 divided doses

**OR**

» deep brain stimulation

» If the patient has a tremor that is insufficiently treated with dopaminergic agents, adding an anticholinergic agent (e.g., trihexyphenidyl) or amantadine, if the patient isn't already on this, may be considered. However, anticholinergic agents can cause or worsen cognitive impairment, and patients should be educated about and monitored for this potential adverse effect. These agents should be used with caution in patients with any cognitive impairment.

» Second-line options include medications used to treat essential tremor, such as propranolol and primidone.

» If a patient has disabling tremor that is refractory to all medical therapy, deep brain stimulation (DBS) of the subthalamic nucleus or the ventral intermediate nucleus of the thalamus should be considered. In general, the goal of

## Ongoing

surgery in PD is to provide a constant 'best medicine' state, and no additional improvement beyond what is achieved with dopaminergic agents is expected. However, tremor is an exception, as drug-refractory tremor often does respond to DBS.[126]

**with wearing off (motor fluctuations) on dopamine agonists, not taking carbidopa/levodopa** **plus** **carbidopa/levodopa**

Treatment recommended for ALL patients in selected patient group

### Primary options

» carbidopa/levodopa: 50 mg orally (immediate-release) three times daily initially, increase by 50-100 mg/day increments every 5-7 days according to response; dose of extended-release capsule depends on previous dose of carbidopa/levodopa
Dose expressed as levodopa component. Tablet strengths of 10/100 mg (carbidopa/levodopa), 25/100 mg, or 25/250 mg may be used depending on whether a higher amount of carbidopa or levodopa is required. A ratio of 25:100 is likely to be optimal for reducing peripheral side effects of levodopa such as nausea.

» Taking medications more frequently (up to 4 times daily) may improve symptoms in patients who experience wearing off (motor fluctuations) while taking a dopamine agonist.

» Instituting carbidopa/levodopa is appropriate if it is not possible to increase dose frequency.

» An extended-release capsule formulation of carbidopa/levodopa that combines immediate- and sustained-release pellets has been shown to reduce daily off-time compared with immediate-release formulations and the combination of carbidopa/levodopa and entacapone.[123] [124] [125]

**with wearing off (motor fluctuations), taking carbidopa/levodopa** **plus** **COMT inhibitor, dopamine agonist, MAO-B inhibitor, or switch to extended-release carbidopa/levodopa**

Treatment recommended for ALL patients in selected patient group

### Primary options

» entacapone: 200 mg orally with each dose of carbidopa/levodopa, maximum 1600 mg/day

**OR**

## Ongoing

» opicapone: 50 mg orally once daily

### Secondary options

» ropinirole: 0.25 mg orally (immediate-release) three times daily initially for 1 week, increase by 0.25 mg/dose increments every week for 3 weeks according to response, then increase by 0.5 mg/dose increments at weekly intervals up to 9 mg/day total dose, then increase by 1 mg/dose increments at weekly intervals thereafter, maximum 24 mg/day; 2 mg orally (extended-release) once daily initially for 1-2 weeks, increase by 2 mg/day increments every week according to response, maximum 24 mg/day

**OR**

» pramipexole: 0.125 mg orally (immediate-release) three times daily initially, increase by 0.125 mg/dose increments every 5-7 days according to response, maximum 4.5 mg/day; 0.375 mg orally (extended-release) once daily initially, increase by 0.75 mg/day increments every 5-7 days according to response, maximum 4.5 mg/day

**OR**

» rotigotine transdermal: apply 2 mg/24 hour patch initially, increase by 2 mg/24 hour increments at weekly intervals according to response, maximum 8 mg/24 hours

**OR**

» selegiline: 5 mg orally twice daily at breakfast and lunchtime

**OR**

» rasagiline: 1 mg orally once daily

**OR**

» safinamide: 50-100 mg orally once daily

**OR**

» carbidopa/levodopa: dose of extended-release tablet or capsule depends on previous dose of carbidopa/levodopa

### Tertiary options

## Ongoing

» tolcapone: 100 mg orally three times daily, with the first dose of the day given with the first daily dose of carbidopa/levodopa

» When levodopa is used initially, adding a catechol-O-methyltransferase (COMT) inhibitor (e.g., entacapone, tolcapone, opicapone) may extend therapeutic benefit.[120] [140]

» Entacapone is available as a proprietary formulation with carbidopa/levodopa to ease administration and improve patient compliance.

» Opicapone is a new selective COMT-inhibitor that has been shown to be non-inferior to entacapone for reducing off-time, with an average of slightly more than 1-hour reduction of off-time without troublesome dyskinesias per day.[121]

» Due to the risk of serious hepatotoxicity, tolcapone use is restricted to when other adjunctive therapy is ineffective or contraindicated.

» If after adding a COMT inhibitor patients still experience motor fluctuations, a dopamine agonist or monoamine oxidase-B (MAO-B) inhibitor can also be added to reduce off-time.

» Safinamide, a selective reversible MAO-B inhibitor, improved daily on-time without troublesome dyskinesias by 1 to 2 hours per day in a phase 3 randomised placebo-controlled trial of levodopa-treated patients with motor fluctuations.[122]

**with dyskinesias** **plus** **reduce dopaminergic medications (if tolerated) or add amantadine**

Treatment recommended for ALL patients in selected patient group

### Primary options

» amantadine: 137 mg orally (extended-release) once daily at bedtime initially, increase to 274 mg once daily at bedtime after 1 week; 100 mg orally (immediate-release) once daily initially for 1 week, increase to 100 mg twice daily, maximum 400 mg/day
Doses of the immediate-release formulation are often given in the morning and at noon to reduce the risk of insomnia.

» Dyskinesias are an adverse effect of carbidopa/levodopa therapy, characterised by excessive movements, that can develop as disease progresses.

## Ongoing

» If mild and not bothersome, dyskinesias can be observed. However, they often lead to discomfort and, in some cases, undesired weight loss.

» It is important to ensure this is not an adverse effect of excessive dopaminergic medications. However, often a reduction in medications results in worsening of symptoms.

» Therefore, amantadine is usually added (if patient is not already on this drug) to reduce these symptoms. An extended-release formulation of amantadine is available for the treatment of dyskinesias in people with PD receiving levodopa-based therapy, with or without concomitant dopaminergic medications. The immediate-release formulation is also commonly used off-label for treating dyskinesias in people with PD.

**with nausea and/or vomiting on carbidopa/levodopa** **plus** **additional carbidopa or domperidone**

Treatment recommended for ALL patients in selected patient group

### Primary options

» carbidopa: 25 mg orally with each dose of carbidopa/levodopa

### Secondary options

» domperidone: 10 mg orally three times daily for a maximum of 7 days, maximum 30 mg/day

» For patients taking carbidopa/levodopa, nausea and vomiting can be treated with additional doses of carbidopa or with domperidone.

» Following a European review, the Medicines and Healthcare products Regulatory Agency and European Medicines Agency have issued recommendations concerning the use of domperidone. The review found the drug was associated with a small increased risk of potentially life-threatening cardiac effects. As a consequence, it should be used at the lowest effective dose for the shortest possible duration and the maximum treatment duration should not usually exceed 1 week. The new maximum dose recommended in adults is 30 mg/day. Domperidone is contraindicated in patients with severe hepatic impairment or underlying cardiac disease. It should not be administered with other drugs that prolong the QT interval or inhibit CYP3A4.[139]



 

## Ongoing

**with nausea and/or vomiting on dopamine agonist**

**plus**

**domperidone**

Treatment recommended for ALL patients in selected patient group

**Primary options**

» domperidone: 10 mg orally three times daily for a maximum of 7 days, maximum 30 mg/day

» For patients taking a dopamine agonist, nausea and vomiting can be treated with domperidone.

» Following a European review, the Medicines and Healthcare products Regulatory Agency and European Medicines Agency have issued recommendations concerning the use of domperidone. The review found the drug was associated with a small increased risk of potentially life-threatening cardiac effects. As a consequence, it should be used at the lowest effective dose for the shortest possible duration and the maximum treatment duration should not usually exceed 1 week. The new maximum dose recommended in adults is 30 mg/day. Domperidone is contraindicated in patients with severe hepatic impairment or underlying cardiac disease. It should not be administered with other drugs that prolong the QT interval or inhibit CYP3A4.[139]

**advanced parkinsonism**

**1st**

**MAO-B inhibitor, dopaminergic agent, amantadine, or trihexyphenidyl**

**Primary options**

» rasagiline: 1 mg orally once daily

**OR**

» pramipexole: 0.125 mg orally (immediate-release) three times daily initially, increase by 0.125 mg/dose increments every 5-7 days according to response, maximum 4.5 mg/day; 0.375 mg orally (extended-release) once daily initially, increase by 0.75 mg/day increments every 5-7 days according to response, maximum 4.5 mg/day

**OR**

» ropinirole: 0.25 mg orally (immediate-release) three times daily initially for 1 week, increase by 0.25 mg/dose increments every

## Ongoing

week for 3 weeks according to response, then increase by 0.5 mg/dose increments at weekly intervals up to 9 mg/day total dose, then increase by 1 mg/dose increments at weekly intervals thereafter, maximum 24 mg/day; 2 mg orally (extended-release) once daily initially for 1-2 weeks, increase by 2 mg/day increments every week according to response, maximum 24 mg/day

**OR**

» carbidopa/levodopa: 50 mg orally (immediate-release) three times daily initially, increase by 50-100 mg/day increments every 5-7 days according to response; dose of extended-release capsule depends on previous dose of carbidopa/levodopa
Dose expressed as levodopa component. Tablet strengths of 10/100 mg (carbidopa/levodopa), 25/100 mg, or 25/250 mg may be used depending on whether a higher amount of carbidopa or levodopa is required. A ratio of 25:100 is likely to be optimal for reducing peripheral side effects of levodopa such as nausea.

**OR**

» rotigotine transdermal: apply 2 mg/24 hour patch initially, increase by 2 mg/24 hour increments at weekly intervals according to response, maximum 8 mg/24 hours

### Secondary options

» selegiline: 5 mg orally twice daily at breakfast and lunchtime

**OR**

» trihexyphenidyl: 1 mg orally (immediate release) once daily initially, increase by 2 mg/day increments every 3-5 days according to response, maximum 10 mg/day given in 3-4 divided doses

**OR**

» amantadine: 100 mg orally once daily initially for 1 week, increase to 100 mg twice daily, maximum 400 mg/day
Doses are often given in the morning and at noon to reduce the risk of insomnia.

## Ongoing

» An extended-release capsule formulation of carbidopa/levodopa that combines immediate- and sustained-release pellets has been shown to reduce daily off-time compared with immediate-release formulations and the combination of carbidopa/levodopa and entacapone.[123] [124] [125]

» Advanced PD is often complicated by sudden and unpredictable periods of wearing-off, motor fluctuations, freezing, and dysphagia. These can be managed by the addition of rescue treatment approaches.[89]

**plus** **physical activity**

Treatment recommended for ALL patients in selected patient group

» Exercise should always be encouraged; it has been shown to improve functional performance on motor tasks at any stage of disease, and may have beneficial effects on cognition.[98] [99] [100] Progressive resistance exercise, in particular, reduces motor symptoms and improves functional status.[98] [101] Activities such as Tai Chi and dance have also been shown to be safe and beneficial in PD, and may improve quality of life and reduce falls.[102] [103] [104] [105] [106] [107] [108]

» Physiotherapy,[109] occupational therapy,[110] and speech therapy are important to treat specific symptoms, such as hypophonia and dysphagia. Individually tailored and standard cognitive training may improve memory, executive function, and attention in people with PD.[111]

» This patient group should exercise with supervision and fall precautions in place.

**with refractory tremor** **plus** **pharmacotherapy or deep brain stimulation**

Treatment recommended for ALL patients in selected patient group

### Primary options

» trihexyphenidyl: 1 mg orally (immediate release) once daily initially, increase by 2 mg/day increments every 3-5 days according to response, maximum 10 mg/day given in 3-4 divided doses

**OR**

TREATMENT

## Ongoing

» amantadine: 100 mg orally once daily initially for 1 week, increase to 100 mg twice daily, maximum 400 mg/day
Doses are often given in the morning and at noon to reduce the risk of insomnia.

### Secondary options

» propranolol: 40 mg (immediate-release) orally twice daily, increase gradually according to response, maximum 160 mg/day given in 2-3 divided doses

**OR**

» primidone: 25 mg orally once daily initially, increase gradually according to response, maximum 750 mg/day given in 3 divided doses

**OR**

» deep brain stimulation

» If the patient has a tremor that is insufficiently treated with dopaminergic agents, adding an anticholinergic agent (e.g., trihexyphenidyl) or amantadine, if the patient isn't already on this, may be considered. However, anticholinergic agents can cause or worsen cognitive impairment, and patients should be educated about and monitored for this potential adverse effect. These agents should be used with caution in patients with any cognitive impairment.

» Second-line options include medications used to treat essential tremor, such as propranolol and primidone.

» If a patient has disabling tremor that is refractory to all medical therapy, deep brain stimulation (DBS) of the subthalamic nucleus or the ventral intermediate nucleus of the thalamus should be considered. In general, the goal of surgery in PD is to provide a constant 'best medicine' state, and no additional improvement beyond what is achieved with dopaminergic agents is expected. However, tremor is an exception, as drug-refractory tremor often does respond to DBS.[126]

**with unpredictable off-times, motor fluctuations, or freezing** **plus** **apomorphine or as-needed doses of carbidopa/levodopa**

Treatment recommended for ALL patients in selected patient group

### Primary options

 

## Ongoing

» apomorphine: consult specialist for guidance on dose

**OR**

» carbidopa/levodopa: 50 mg orally as needed for sudden unpredictable off periods; increase by 50 mg/dose according to response
Dose expressed as levodopa component. Tablet strengths of 10/100 mg (carbidopa/levodopa), 25/100 mg, or 25/250 mg may be used depending on whether a higher amount of carbidopa or levodopa is required. A ratio of 25:100 is likely to be optimal for reducing peripheral side effects of levodopa such as nausea.

» This later stage of disease is often complicated by sudden and unpredictable periods of wearing off.

» Apomorphine (an injectable form of dopamine) can be used as rescue therapy for sudden wearing off, under specialist guidance.

» Similarly, as-needed doses of carbidopa/levodopa can be used as rescue therapy.

**with refractory motor fluctuations** — **plus** — **deep brain stimulation**

Treatment recommended for ALL patients in selected patient group

» Deep brain stimulation (DBS) is only used in patients who are refractory to medication.

» In patients with motor fluctuations, deep brain stimulation can be beneficial to reduce off-time. In general, the goal of surgery is to provide a constant 'best medicine' state, and no additional improvement beyond what is achieved with dopaminergic agents is expected.

» The globus pallidus interna (GPi) and the subthalamic nucleus (STN) are two possible primary targets in DBS; one or other may be preferred depending on circumstances.[128]

**adjunct** — **intrajejunal infusion of levodopa/carbidopa**

Treatment recommended for SOME patients in selected patient group

### Primary options

» carbidopa/levodopa: consult specialist for guidance on dose of enteral suspension

## Ongoing

» Continuous intrajejunal infusion of levodopa/carbidopa enteral suspension reduces plasma concentration variability. One double-blind randomised controlled trial demonstrated reduction in off-time and improvement in on-time without troublesome dyskinesias compared with placebo.[134] [135] [136]

» It is approved for use in some countries, including the US.

» As use requires several hours of titration/programming to determine the appropriate dose, it should be used only by a specialist.

**with refractory dyskinesias**

**plus**

**reduce dopaminergic medications (if tolerated) or add amantadine**

Treatment recommended for ALL patients in selected patient group

### Primary options

» amantadine: 137 mg orally (extended-release) once daily at bedtime initially, increase to 274 mg once daily at bedtime after 1 week; 100 mg orally (immediate-release) once daily initially for 1 week, increase to 100 mg twice daily, maximum 400 mg/day
Doses of the immediate-release formulation are often given in the morning and at noon to reduce the risk of insomnia.

» Dyskinesias are an adverse effect of carbidopa/levodopa therapy, characterised by excessive movements, that can develop as disease progresses.

» If mild and not bothersome, dyskinesias can be observed. However, they often lead to discomfort and, in some cases, undesired weight loss.

» It is important to ensure this is not an adverse effect of excessive dopaminergic medications. However, often a reduction in medications results in worsening of symptoms.

» Therefore, amantadine is usually added (if patient is not already on this drug) to reduce these symptoms. An extended-release formulation of amantadine is available for the treatment of dyskinesias in people with PD receiving levodopa-based therapy, with or without concomitant dopaminergic medications. The immediate-release formulation is also commonly used off-label for treating dyskinesias in people with PD.

**plus**

**deep brain stimulation**

## Ongoing

Treatment recommended for ALL patients in selected patient group

» Deep brain stimulation is used for patients who previously responded well to medication, but have developed intolerable side effects or no longer receive benefit from medication.

» In general, the goal of surgery is to provide a constant 'best medicine' state, and no additional improvement beyond what is achieved with dopaminergic agents is expected.

» The globus pallidus interna (GPi) and the subthalamic nucleus (STN) are the two primary targets. The Congress of Neurological Surgeons recommends targeting the GPi if reduction of medication is not anticipated and a goal is to reduce the severity of 'on' medication dyskinesias.[128]

**with dysphagia** **plus** **dissolvable selegiline or carbidopa/levodopa or transdermal rotigotine**

Treatment recommended for ALL patients in selected patient group

### Primary options

» selegiline: 1.25 mg orally (disintegrating tablet) once daily initially for at least 6 weeks, may increase to 2.5 mg once daily thereafter

**OR**

» carbidopa/levodopa: 50 mg orally (disintegrating tablet) three times daily initially, increase by 50-100 mg/day increments every 5-7 days according to response

**OR**

» rotigotine transdermal: apply 2 mg/24 hour patch initially, increase by 2 mg/24 hour increments at weekly intervals according to response, maximum 8 mg/24 hours

» If a patient who is taking selegiline or carbidopa/levodopa develops dysphagia, a dissolvable formulation of each of these medications is available.

» Rotigotine, a dopamine agonist that is administered via a transdermal patch, is also an option.

## Ongoing

**with nausea and/or vomiting on carbidopa/levodopa** **plus** **additional carbidopa or domperidone**

Treatment recommended for ALL patients in selected patient group

### Primary options

» carbidopa: 25 mg orally with each dose of carbidopa/levodopa

### Secondary options

» domperidone: 10 mg orally three times daily for a maximum of 7 days, maximum 30 mg/day

» For patients taking carbidopa/levodopa, nausea and vomiting can be treated with additional doses of carbidopa or with domperidone.

» Following a European review, the Medicines and Healthcare products Regulatory Agency and European Medicines Agency have issued recommendations concerning the use of domperidone. The review found the drug was associated with a small increased risk of potentially life-threatening cardiac effects. As a consequence, it should be used at the lowest effective dose for the shortest possible duration and the maximum treatment duration should not usually exceed 1 week. The new maximum dose recommended in adults is 30 mg/day. Domperidone is contraindicated in patients with severe hepatic impairment or underlying cardiac disease. It should not be administered with other drugs that prolong the QT interval or inhibit CYP3A4.[139]

**with nausea and/or vomiting on dopamine agonist** **plus** **domperidone**

Treatment recommended for ALL patients in selected patient group

### Primary options

» domperidone: 10 mg orally three times daily for a maximum of 7 days, maximum 30 mg/day

» For patients taking a dopamine agonist, nausea and vomiting can be treated with domperidone.

» Following a European review, the Medicines and Healthcare products Regulatory Agency and European Medicines Agency have issued recommendations concerning the use of domperidone. The review found the drug was associated with a small increased risk of



 

## Ongoing

potentially life-threatening cardiac effects. As a consequence, it should be used at the lowest effective dose for the shortest possible duration and the maximum treatment duration should not usually exceed 1 week. The new maximum dose recommended in adults is 30 mg/day. Domperidone is contraindicated in patients with severe hepatic impairment or underlying cardiac disease. It should not be administered with other drugs that prolong the QT interval or inhibit CYP3A4.[139]

# Emerging

## Nilotinib

A tyrosine kinase inhibitor with some proposed neuroprotective effects. Nilotinib is being evaluated in a phase 2a randomised, double-blind, placebo-controlled trial to determine safety, tolerability, and activity in patients with PD. [ClinicalTrials.gov Identifier: NCT03205488]

## Stem cell therapy

TRANSEURO, a multicentre collaborative study for the treatment of PD, has three principal objectives: to demonstrate that dopaminergic cell replacement can be improved by careful attention to tissue preparation and delivery, patient selection, and immunosuppressive treatment; to show that dopaminergic cell replacement can be clinically efficacious; to develop a protocol that can serve as a template for all future clinical trials in the cell therapy field, including of stem cell-based therapies. [TRANSEURO] [141] A small investigational cell transplantation therapy study using human neural stem cells is underway. [ClinicalTrials.gov Identifier: NCT02452723] ISC-hpNSC, a cellular therapeutic consisting of human parthenogenetic neural stem cells (hpNSC), will be injected intracerebrally to the striatum and substantia nigra of patients with PD. The main study objective is to evaluate the safety of the cell transplantation.

## Gene therapy

Long-term follow-up (5 years) of lentiviral vector-based gene therapy (ProSavin) aimed at restoring local and continuous dopamine production in patients with advanced PD suggests that it is well tolerated and gives rise to moderate improvements in motor behaviour.[142] [143] Long-term safety analyses of patients with advanced PD who received surgically administered recombinant adeno-associated virus serotype-2 (rAAV2)-neurturin (NRTN) are ongoing.[144]

## Immunotherapy: alpha-synuclein vaccine

Accumulation of toxic forms of alpha-synuclein are implicated in neuronal death in PD. Targeting this protein with immunisation-based therapy via a vaccine is of interest, although there are no published data. Issues related to specificity of targeting toxic forms of alpha-synuclein must be addressed.

## Other pharmacological trials

Istradefylline, an adenosine 2A receptor antagonist, may reduce daily off-time in patients with PD, but study results are inconsistent.[145] [146] [147] Dipraglurant, a glutamate receptor modulator, has received orphan drug designation from the US Food and Drug Administration (FDA) for the management of levodopa-induced dyskinesia in PD.[148] One phase 3 trial is evaluating the potential role of isradipine, a dihydropyridine calcium channel antagonist, as a disease-modifying agent in patients with PD.[149] [150] Another potential neuroprotective agent being studied is inosine, a precursor to urate.[151]

## Alternative drug delivery systems

In 2018, the FDA approved levodopa inhalation powder for intermittent treatment during off-time for people with PD who are already taking oral carbidopa/levodopa.[152] Apomorphine can be given by continuous infusion in some countries; intranasal delivery of apomorphine is also being researched.

## Emerging treatments for non-motor symptoms

Droxidopa, an oral noradrenaline (norepinephrine) precursor, improved symptomatic neurogenic orthostatic hypotension in a phase 3 clinical trial of patients with PD or multiple system atrophy (MSA).[153] Droxidopa is the first drug for orthostatic hypotension to be specifically approved for use in this population. Midodrine and fludrocortisone are likely effective in treating orthostatic hypotension, although they have not been evaluated in patients with PD and are often associated with supine hypertension.

FOLLOW UP

# Recommendations

## Monitoring

Monitoring by a movement disorder specialist is recommended every 4 months. History and neurological examination are sufficient to detect and manage changes and/or complications. If cognitive deficits evolve, brain magnetic resonance imaging, full blood count, electrolyte panel, thyroid-stimulating hormone, B12, and folate may be helpful in further evaluation.

## Patient instructions

Advise patients to take medications as instructed, at regular intervals on a regimented schedule. For example, levodopa should be taken 1 hour before or 2 hours after eating food containing protein to maximise efficacy.

Explain to patients and their carers that:

- If postural instability exists, activities requiring good balance should be avoided
- Patients should consider not driving if symptoms are severe or any cognitive deficits exist
- Regular exercise is beneficial (this can include progressive resistance exercise such as weightlifting, endurance exercise, or activities such as Tai Chi and dance)
- A symptom diary may assist in treating complications
- Joining a local support group may be of benefit.

Useful websites include the following:

- Parkinson’s UK [Parkinson's UK]
- National Institute of Neurological Disorders and Stroke (NINDS) [National Institute of Neurological Disorders and Stroke]
- American Academy of Neurology [American Academy of Neurology]
- American Parkinson Disease Association [American Parkinson Disease Association]
- Parkinson's Foundation [Parkinson's Foundation]
- Michael J. Fox Foundation for Parkinson's Research [Michael J. Fox Foundation for Parkinson's Research]
- International Parkinson and Movement Disorder Society (MDS) [The International Parkinson and Movement Disorder Society (MDS)]

# Complications

| Complications | Timeframe | Likelihood |
|---|---|---|
| **levodopa-induced dyskinesias** | **long term** | **high** |
| Develop as a result of advanced disease and the inability of the dopaminergic cells in the substantia nigra to buffer exogenous levodopa. The excess dopamine results in excessive movements. Management involves lowering dopaminergic medication dosages and/or lengthening dosing intervals. If this results in decreased efficacy, amantadine can be used in lieu of reducing dopaminergic medications. Lastly, disabling refractory dyskinesias can be treated with deep brain stimulation to the subthalamic nucleus or globus pallidus interna. | | |
| **motor fluctuations** | **long term** | **high** |
| Advancing disease and inability to buffer exogenous dopamine explains this complication. Institution of a catechol-O-methyltransferase (COMT) inhibitor as an adjunct to carbidopa/levodopa is the first-line treatment. Long-acting carbidopa/levodopa can be effective in extending response time. Unexpected wearing off can be treated with injectable apomorphine. Finally, deep brain stimulation to the subthalamic nucleus or globus pallidus interna is effective in treating this complication. | | |
| **dementia** | **long term** | **high** |
| It is important to routinely screen for this non-motor neuropsychiatric complication. If it is identified, cholinesterase inhibitors, such as rivastigmine or donepezil, can be effective.[158] [159] [160] | | |
| **constipation** | **long term** | **high** |
| Constipation is a common pre-motor symptom of PD that many patients have well before they are diagnosed.[168] Prevalence tends to increase with disease progression, and PD medication may make it worse. Recognising and treating constipation are important to prevent complications (e.g., intestinal occlusion) and to ensure an optimal response to levodopa.[169] | | |
| **psychosis** | **long term** | **low** |
| Clozapine has been shown to be effective for treating psychosis,[158] [161] [162] but risk of agranulocytosis and need for frequent WBC monitoring can limit its use. Quetiapine may improve symptoms, although evidence is lacking.[161] One meta-analysis has suggested that atypical antipsychotics may worsen motor function in people with PD.[163] Pimavanserin, a selective serotonin 5-HT2A inverse agonist, appears to benefit patients with PD psychosis.[158] [162] [164] [165] It has been shown to decrease frequency and/or severity of hallucinations and delusions as measured by the Parkinson's disease-adapted scale for assessment of positive symptoms (SAPS-PD). | | |
| **depression** | **variable** | **medium** |
| Non-motor neuropsychiatric complications can occur at any point in people with PD and are evidence that areas outside the basal ganglia are affected. Management is specific to the symptom.<br><br>Depression is often managed with selective serotonin reuptake inhibitors (SSRIs) and/or referral to a psychiatrist. Although there is evidence for tricyclic antidepressants, adverse effects limit use.[158] | | |
| **anxiety** | **variable** | **medium** |

 

FOLLOW UP

| Complications | Timeframe | Likelihood |
|---|---|---|
| The prevalence of anxiety disorders in patients with PD ranges from 6% to 55%.[97] It should be sought and treated. | | |
| **impulse control disorder** | **variable** | **low** |
| Screening tools are being developed to assist in identifying this complication. If it is present, dopamine agonist should be reduced or discontinued. Appropriate psychological and social support should be provided.[166] [167] | | |

# Prognosis

Treatment of PD is symptomatic as no curative or disease-modifying agents are available. Therefore, the course is progressive. Unilateral symptoms ultimately become bilateral. Rates of progression vary between patients, but the typical course is as follows:

- A period of 2 to 3 years when treatment with dopaminergic agents results in resolution of symptoms.
- After 5 years of levodopa treatment, motor complications develop.
- Eventually, after a number of years, the emergence of symptoms such as freezing, falling, and dementia, which do not respond to levodopa, cause significant disability.

Cognitive dysfunction was shown to be highly prevalent in the longest followed PD cohort from the Sydney multicentre study.[154]

The disease course varies between patients, with many living a normal life span. Certain features can predict a slower progression, such as tremor predominance.[155]

Factors to predict more rapid rate of progression are:[155] [156]

- Older age at symptom onset
- Rigidity/hypokinesia as presenting symptoms (versus rest tremor)
- Associated comorbidities
- Decreased response to dopaminergic medications.

Cognitive dysfunction and non-dopaminergic symptoms at the time of diagnosis are the main determinants of increased disability in the first 5 years of disease.[157]

# Diagnostic guidelines

## Europe

### Parkinson's disease in adults

**Published by:** National Institute for Health and Care Excellence **Last published:** 2017

## International

### MDS clinical diagnostic criteria for Parkinson's disease

**Published by:** International Parkinson and Movement Disorder Society (MDS) **Last published:** 2015

# Treatment guidelines

## Europe

### Parkinson's disease in adults

**Published by:** National Institute for Health and Care Excellence **Last published:** 2017

### Joint EFNS/MDS-ES guidelines on early (uncomplicated) Parkinson's disease

**Published by:** European Academy of Neurology (European Federation of Neurological Societies); Movement Disorder Society-European Section **Last published:** 2011

### Joint EFNS/MDS-ES guidelines on late (complicated) Parkinson's disease

**Published by:** European Academy of Neurology (European Federation of Neurological Societies); Movement Disorder Society-European Section **Last published:** 2011

## International

### Update on treatments for nonmotor symptoms of Parkinson’s disease

**Published by:** International Parkinson and Movement Disorder Society **Last published:** 2019

### Update on treatments for the motor symptoms of Parkinson's disease

**Published by:** International Parkinson and Movement Disorder Society **Last published:** 2018

## North America

### Systematic review and evidence-based guideline on subthalamic nucleus and globus pallidus internus deep brain stimulation for the treatment of patients with Parkinson's disease

**Published by:** Congress of Neurological Surgeons **Last published:** 2018

### Deep brain stimulation for Parkinson disease: an expert consensus and review of key issues

**Published by:** Expert Group on Deep Brain Stimulation for Parkinson Disease **Last published:** 2011

### Initiation of treatment for Parkinson's disease

**Published by:** American Academy of Neurology **Last published:** 2002 (reaffirmed 2005)

# Online resources

1. ClinicalTrials.gov Identifier: NCT03205488 *(external link)*
2. TRANSEURO *(external link)*
3. ClinicalTrials.gov Identifier: NCT02452723 *(external link)*
4. Parkinson's UK *(external link)*
5. National Institute of Neurological Disorders and Stroke *(external link)*
6. American Academy of Neurology *(external link)*
7. American Parkinson Disease Association *(external link)*
8. Parkinson's Foundation *(external link)*
9. Michael J. Fox Foundation for Parkinson's Research *(external link)*
10. The International Parkinson and Movement Disorder Society (MDS) *(external link)*

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