Parkinson's disease and related conditions

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Abstract
Parkinson's disease (PD) is a common neurodegenerative condition, affecting 2–3% of individuals >65 years of age. It is characterized by a loss of dopaminergic neurons in the midbrain leading to a movement disorder encompassing bradykinesia, rest tremor, rigidity and postural stability. However patients also experience a range of non-motor symptoms, reflecting more widespread pathology in the peripheral and autonomic nervous systems as well as the brainstem and cortex. Some non-motor symptoms emerge years before motor problems. This prodromal stage of PD can represent the optimal time for intervention with future disease-modifying therapies. Other conditions can cause a similar syndrome of motor parkinsonism in combination with a range of non-motor features, leading to a degree of diagnostic uncertainty in early disease. However, they typically differ in their progression rate and response to treatment. Here, we discuss the natural history of PD and provide an update on its genetic and pathological basis before reviewing motor and non-motor symptomatology. We give an overview of related parkinsonian conditions and consider how they differ clinically from PD. We discuss currently available therapies and their complications, before reviewing new therapeutic developments and the need to target these precisely to particular diseases.

Keywords
Genetics; levodopa; Lewy bodies; MRCP; Parkinson's disease; parkinsonism; therapy

Key points
•Parkinson's disease (PD) is a multisystem disorder with prominent non-motor features, some of which occur as a prodrome to the motor symptoms; eliciting these can help an earlier diagnosis
•A number of alternate conditions can mimic PD, causing diagnostic uncertainty, but the long-term prognosis and treatment responses differ
•Levodopa remains the most effective and best tolerated oral therapy for the motor symptoms of PD, despite its long-term complications
•Advanced therapies for patients with motor complications include subcutaneous apomorphine infusion, jejunal levodopa gel infusion and deep brain stimulation; therapies to directly replace striatal dopamine are under investigation including cell-based transplantation and gene therapies
•There are no disease-modifying therapies for PD, but clinical trials are underway of a number of 'repositioned' drugs targeting neuronal dysfunction and immune pathways, as well as vaccine therapies to prevent the spread of α-synuclein aggregates through the brain

Introduction
Parkinson's disease (PD) is defined as a movement disorder caused by a loss of dopamine-producing cells in the substantia nigra. It is, however more complex than this, both clinically and pathologically. As well as motor features of bradykinesia, rigidity, tremor and postural instability, non-motor features including cognitive impairment, depression, hallucinations, autonomic features and sleep problems are a significant burden; they also represent a therapeutic challenge as many of these features do not respond to, or can even be worsened by, typical dopaminergic therapies. These non-motor symptoms are acknowledged in the newly developed Movement Disorder Society (MDS) clinical diagnostic

criteria for PD, with an absence of non-motor features within the first 5 years being a ‘red flag’ against the diagnosis.[1]

A number of other conditions can mimic PD, particularly in its early stages, but differ considerably in their progression and response to therapy. Their early identification is important to allow prognostication and optimal management planning. This article focuses on the clinical features of PD and reviews their pathophysiological basis and treatment. Related conditions and ‘mimics’ are also discussed, and important clinical differences in their presentation and progression are highlighted.

Epidemiology and natural history

PD has an incidence of 13 per 100,000 person–years. It is most prevalent in older people, affecting 2–3% of those >65 years of age, but can begin as early as the third or fourth decade, particularly in inherited cases (see below).

Many symptoms are effectively controlled with dopaminergic medications for the first few years after diagnosis, but non-dopa-responsive symptoms emerge as the disease progresses. These are generally irreversible and have a major impact on quality of life. Two key milestones in the natural history of PD are postural instability and dementia, with average times to onset of approximately 5 and 10 years from diagnosis, respectively, although this is highly variable. Early clinical predictors of an aggressive, rapidly progressive phenotype include early gait and balance problems and deficits on posterior cortically based neuropsychological tests, including pentagon copying and semantic fluency. Some patients have a more benign course, with approximately a quarter surviving without postural instability or dementia 10 years into their illness.[2]

Mortality in PD is often reported as slightly higher than expected for age, but not all studies concur. Pneumonia is the most common cause of death, possibly related to aspiration secondary to swallowing difficulties. In most patients dying with PD, the cause of death is not directly related to PD.[2]

Genetic basis

Around 5–10% of sporadic PD cases are caused by a single genetic variant, with at least 14 variants identified. Mutations in *GBA1* (the glucocerebrosidase gene, which is also linked to Gaucher disease) and *LRRK2* (encoding dardarin, a protein kinase) are the most common genetic causes of PD. These can be indistinguishable from idiopathic PD, but *GBA1*-associated cases are more likely to progress rapidly with early cognitive decline. Monogenic causes are more frequently identified in younger onset cases, with a causative gene found in 40% of patients aged <30 years.

Although most PD cases are not inherited in a Mendelian fashion, multiple common genetic variants have been identified that each make a small contribution to disease risk, and overall PD has a heritability (i.e. proportion of risk due to genetic variation) of approximately 35%. Genetic factors implicate mitochondrial and autophagy/lysosomal dysfunction, alpha synuclein aggregation, dopamine metabolism and the immune system as important mechanistic pathways in the disease process.[3]

Pathology

Pathologically, PD is defined as a loss of dopaminergic cells in the substantia nigra with the deposition of intraneuronal aggregates of α-synuclein in so-called Lewy neurites and Lewy bodies. Lewy pathology in PD involves not only dopaminergic cells, but also cholinergic, noradrenergic, serotonergic, histaminergic and glutaminergic cells, accounting for its wide clinical spectrum.

It has been proposed that Lewy pathology develops along a stereotyped trajectory through the brain, beginning in the olfactory bulb and dorsal motor nucleus of the vagus, and spreading rostrocaudally through the brainstem into the midbrain tegmental nuclei, then to forebrain structures before reaching the anteromedial temporal cortex, and finally to more widespread regions of the neocortex. This ‘Braak hypothesis’ of spreading pathology has, however, been challenged, as the neuropathology does not always follow this pattern.

The mechanisms driving the spread of pathology in PD and why this occurs at different rates are still unclear. The initiating events are also not fully determined. Observations of early pathology in the gastrointestinal tract as well as the olfactory bulb in prodromal PD cases suggest that an environmental pathogen might trigger the first conformational change in α-synuclein in these regions. Immune activation and inflammation may play an early role in worsening neuronal damage.

Clinical features

Prodromal PD

The nigrostriatal degeneration that underlies the typical motor features of PD can be preceded for many years by changes in the olfactory bulb, brainstem and peripheral enteric nervous system. Predictably, therefore, some patients have prodromal symptoms for years before the onset of typical parkinsonian motor features. These include loss of sense of smell, constipation, rapid eye movement (REM) sleep behaviour disorder and mood changes, and their presence may support a clinical diagnosis of PD.

New research criteria for 'prodromal PD' from the MDS allow an estimation of the probability of conversion to PD based on these clinical features, with dopamine transporter single-photon emission computed tomography (DAT SPECT) scanning contributing additional predictive value. More reliable identification of prodromal cases allows the possibility of initiating future disease-modifying therapies at a time when they might have most benefit.

Motor presentation

The diagnosis of PD depends on the presence of bradykinesia (defined as slowness of movement and decrement of amplitude or speed) in combination with either rest tremor or rigidity. Almost all patients exhibit rigidity but around a third do not have a tremor. The motor features are usually asymmetrical at onset,[1] but can become more symmetrical over time. A good response to levodopa strongly supports the diagnosis of PD. Postural instability and falls typically occur in PD at least 3 years after the first motor symptoms; early falls raise the possibility of an alternate diagnosis (see Other causes of parkinsonism, below).

Cognitive deficits

The earliest cognitive deficits in PD involve dysfunction of the nigrostriatal dopaminergic system and its cortical projections, with executive problems, such as of planning, working memory and shifting attention; these are sometimes detectable at the time of diagnosis. Dopaminergic medication can worsen some of these problems because of an 'overload' effect. Neuropsychological deficits involving the temporal and posterior cortex, such as poor semantic fluency and difficulty with figure copying tasks, probably reflect the cortical spread of Lewy pathology and represent the earliest features of the dementing process in PD.

A diagnosis of dementia in PD depends on impairment in at least two neuropsychological domains sufficient to impair day-to-day functioning. This develops in 50% of individuals within 10 years of diagnosis, three times more commonly than in an age-matched population.[2] It has a major impact on the individual's and carer's quality of life, is a frequent reason for institutional care, and is associated with higher mortality.

Psychiatric features

The most common psychiatric problem in PD is mood disturbance, with depression and/or anxiety affecting approximately a third of patients, often in the early stages. Causes include psychosocial factors and disability, disturbances of noradrenergic, serotonergic and dopaminergic function, and Lewy pathology in the limbic regions. It is easily missed as symptomatic clues such as fatigue, poor concentration, lack of motivation and sleep disturbance can be attributed directly to the PD. Affective problems should be monitored in this population to ensure prompt treatment.

Later in the disease, other neuropsychiatric features can develop, including visual hallucinations. Initially, these tend to involve misperceptions, particularly in dim light, and are relatively benign. Over time, they can become animate objects or figures that can be unpleasant and occur with loss of insight. These distressing symptoms can lead to paranoia and behavioural problems. Visual hallucinations are aggravated by intercurrent illness (infection) and dopaminergic medication (particularly agonists); they can be improved by treatment of medical factors and reducing medication doses. They tend to recur and are usually an indicator of incipient PD dementia.

Other non-motor features

As PD progresses, speech becomes slow and quiet. Swallowing can deteriorate in advanced cases, prompting consideration of gastrostomy feeding. Early speech and swallowing difficulties are unusual in typical PD and more suggestive of progressive supranuclear palsy (PSP). Constipation is a common prodromal or early feature, possibly caused by early α-synuclein pathology in the gut. Other autonomic problems occur with advancing disease, including postural hypotension (worsened by dopaminergic medication) which contributes to falls risk, bladder irritability and excessive sweating.

Prominent early autonomic features are atypical and suggest an alternate diagnosis of multiple system atrophy (MSA).

Sleep problems are frequent. REM sleep behaviour disorder can occur (often in the prodromal phase) and manifests with patients acting out their dreams, sometimes in a violent fashion, leading to injury to themselves or their bed partner. Sleep disturbance can also be caused by nocturnal restless leg syndrome or 'off' rigidity and akinesia. Excessive daytime sleepiness is common, tends to be worsened by dopamine agonist drugs, and can have implications for driving safety. Other non-motor symptoms include pain, cramps and sensory disturbance.

Other causes of parkinsonism

Parkinsonism can be described as a syndrome of bradykinesia with variable additional features including rigidity, rest tremor and postural instability. It is most commonly caused by PD but there are a number of other possible causes. These can be divided broadly into secondary and neurodegenerative causes (Table 1).[4]

Secondary causes result from disruption to basal ganglia signalling pathways rather than loss of midbrain dopaminergic neurones, and typically do not respond to levodopa therapy. *Vascular parkinsonism* can arise from silent infarcts in the basal ganglia, or from hypertensive vascular changes and cerebrovascular small vessel disease causing disruption to the thalamocortical circuits. Patients tend to present with symmetrical lower body parkinsonism and an unsteady gait but without tremor; although it can be difficult to distinguish from PD clinically.

Drug-induced parkinsonism (DIP) is caused by the prolonged use of dopamine-blocking drugs, particularly those with a higher affinity for D_2 receptors. Commonly involved drugs include antipsychotics (e.g. haloperidol, risperidone, olanzapine), antiemetics (e.g. metoclopramide, prochlorperazine) and dopamine-depleting drugs (e.g. tetrabenazine, reserpine). Motor parkinsonism is usually symmetrical in DIP. Removal of the causative drug is recommended but does not always lead to compete resolution of the symptoms.

Repeated head injury in individuals who have been involved in contact sports (particularly boxing) can lead to a *chronic traumatic encephalopathy* presenting with parkinsonism and dementia. *Normal-pressure hydrocephalus* typically leads to a triad of ataxia, urinary incontinence and dementia, but parkinsonism is sometimes a presenting feature. *Structural lesions* of the basal ganglia or supratentorial tumours (e.g. meningioma at the sphenoid ridge) are very rare causes of parkinsonism.

Neurodegenerative causes include *PSP*, *MSA*, *corticobasal degeneration* (CBD) and *dementia with Lewy bodies* (DLB). Like PD, these conditions are associated with an accumulation of toxic protein aggregates and midbrain dopaminergic deficit, but they are distinct in terms of their neuropathological and clinical features, particularly over time. They generally respond poorly to levodopa and have a more aggressive course with higher mortality.

PSP is characterized pathologically by tau inclusions in the brainstem and basal ganglia. Typical clinical features include symmetrical parkinsonism without tremor, a supranuclear vertical gaze palsy (corrected by passive head movement), axial rigidity, an upright posture (in contrast to the stooped posture of PD), early falls, prominent apathy and executive-type cognitive impairment.

CBD is also a tauopathy but the pathology is more widespread, affecting cortical as well as brainstem regions. The clinical presentation can be highly variable but the classic syndrome encompasses ideomotor apraxia, dystonia and myoclonus, and in some cases an 'alien limb' (with involuntary movement), in addition to asymmetrical rigidity and bradykinesia. Cognitive impairment is common.

MSA is an α-synucleinopathy, but aggregates are found within glia as well as neurones throughout the nervous system. It is characterized clinically by early autonomic dysfunction along with parkinsonism and cerebellar dysfunction. REM Sleep Behaviour Disorder is a common feature. Tremor tends to be more postural than in PD. Cognitive function is usually well preserved.

DLB cannot be distinguished pathologically from PD at post mortem, but differs in its clinical and pathological evolution: cognitive symptoms (including memory and visuospatial deficits, fluctuating confusion and visual hallucinations) resulting from limbic and cortical Lewy body pathology are an early feature, with a concurrent or later emergence of motor parkinsonism. Diagnostic criteria use an arbitrary cut-off of <1 year between the onset of motor and cognitive symptoms to support a diagnosis of DLB rather than PD.

In cases of diagnostic uncertainty, DAT SPECT scanning can be helpful to demonstrate evidence of a presynaptic dopaminergic deficit in the striatum: this excludes some secondary causes such as DIP and makes vascular parkinsonism unlikely (unless there is a basal ganglia infarct). It does not, however, distinguish PD from other neurodegenerative causes of parkinsonism (Table 1). Although the alternative neurodegenerative causes can be difficult to distinguish from PD at disease

onset, their clinical features become more clearly distinguishable over time; this underlines the importance of revisiting the diagnosis in patients with a poor response to levodopa, atypical features or rapid disease progression.

Various other rare inherited neurodegenerative conditions can exhibit parkinsonism but in the context of other distinct neurological syndromes; therefore they are not typically considered in the differential diagnosis of PD. These include Huntington disease, spinocerebellar ataxia, neurodegeneration with brain iron accumulation, Wilson disease and dopa-responsive dystonia.

PD treatment and its complications

The UK National Institute for Health and Care Excellence (NICE) guidelines for the diagnosis and treatment of PD were updated in 2017 and provide useful evidence for each type of pharmacological therapy.

Currently available pharmacological therapies for PD are shown in Table 2. Early motor symptoms are usually well controlled on dopamine agonists or levodopa. The choice of agent is guided by the adverse effect profile in the context of the person's age. Levodopa-based therapies are usually the most effective option, but patients on levodopa can develop 'wearing-off' phenomena after a few years, and dyskinesias during the 'on' phase. Dopamine agonists can cause excessive daytime sleepiness (which can affect driving), ankle swelling and impulse control disorders such as gambling, excessive internet shopping or hypersexual behaviours, particularly in patients with early-onset disease and a personal or family history of addictive behaviours.

Some clinicians opt to use dopamine agonists as first-line drugs in younger patients to delay the introduction of levodopa and subsequent problems with dyskinesias and motor fluctuations; however, the development of these motor complications is probably related more to disease duration than duration of levodopa therapy. Results from the PD MED study, which randomized newly diagnosed patients to either levodopa, dopamine agonists or monoamine oxidase-B (MAO-B) inhibitors, indicate that individuals started on levodopa have better outcomes in terms of quality of life at 3 years. In addition, levodopa is better tolerated than the alternatives, with only 2% of patients stopping the drug over 3 years versus approximately a quarter of those on agonists or MAO-B inhibitors.[5]

These factors, coupled with concerns about the higher risk of impulse control disorders on dopamine agonists, which can have devastating financial and social consequences, provide a rationale for levodopa-based therapies as first-line treatment even in younger patients. The choice of therapy must be made individually, based on patient preference, symptom profile and co-morbidities.

Motor fluctuations can initially be managed by adding long-acting dopamine agonists, or using MAO-B inhibitors or catechol-*O*-methyl transferase (COMT) inhibitors to slow dopamine metabolism. Opicapone, a third-generation once-daily COMT inhibitor, can be useful in some patients who do not tolerate entacapone (most commonly owing to diarrhoea). Over time, 'on–off' variations become more marked and less predictable, and L-dopa-induced dyskinesias more prominent. Fractionating levodopa into smaller, more frequent doses can be helpful, as can introducing amantadine for dyskinesias. Safinamide, a drug with a novel mode of action combining MAO-B inhibitory activity with possible anti-dyskinetic activity, can be useful in patients suffering both wearing off and dyskinesias.

Other management options for late disease with motor complications include continuous dopaminergic therapies: the dopamine agonist apomorphine via a subcutaneous pump, or levodopa gel administered continuously via a jejunal tube (Duodopa). Deep brain stimulation (usually targeting the subthalamic nucleus) is an option for dopa-responsive patients without significant cognitive problems. This allows a significant reduction in the dose of L-dopa, minimizing dyskinesias and fluctuations, but can aggravate speech problems.

Many non-motor problems improve with symptomatic therapies. Depression responds to standard pharmacological options including selective serotonin reuptake inhibitors, venlafaxine and mirtazapine, and the dopamine agonist pramipexole has some efficacy for mood disturbance in PD. Non-pharmacological options such as cognitive behavioural therapy can be effective, particularly for patients with prominent anxiety. Cholinesterase inhibitors have modest efficacy for dementia in PD. Removing anticholinergics, amantadine and dopamine agonists, which contribute to confusion and hallucinations, and prompt management of infections are also important in the management of PD dementia. NICE recommends midodrine as a first line for orthostatic hypotension in PD, with fludrocortisone as an alternative (unlicensed indication).

New therapeutic developments

Given the problems with existing dopaminergic therapies, owing to their peripheral administration route and pulsatile delivery, new strategies to replace dopamine directly and

continuously into the striatum are being tested. An open-label trial of a cell-based therapy, using fetal midbrain tissue transplanted into the striatum, has recently been completed (TRANSEURO (NCT01898390)), and trials of embryonic stem-cell-derived dopaminergic grafts for PD are now underway (e.g. STEM-PD (NCT05635409)).

Gene therapy to replace striatal dopamine, using key enzymes for dopamine synthesis delivered directly to the striatum via viral vectors, has been tested in several early-phase trials. Encouraging safety and tolerability data are emerging and efficacy trials are ongoing. These gene- and cell-replacement therapies are not disease modifying and improve only dopaminergic motor symptoms, so the selection of appropriate patients is critical. Individuals with pathology restricted to the nigrostriatal tract, i.e. without clinical and genetic markers to suggest they are at high risk of dementia or rapid disease progression, are the ideal candidates for these therapies.

'High-risk' patients with more rapidly progressing disease may be better candidates for trials of novel therapies aimed at preventing the spread of protein aggregates, such as antibody or vaccine therapies targeting α-synuclein. Multiple preclinical studies and clinical trials of α-synuclein immunotherapies are currently underway. Other disease-modifying strategies include repositioning the diabetes drug exenatide (a glucagon-like peptide 1 analogue), which is now being tested in a Phase III trial (ISRCTN14552789), and repositioning of drugs targeting mitochondrial dysfunction, lysosomal dysfunction, immune activation and neuroinflammation is being tested in Phase II trials.

Causes of parkinsonism

Cause	Clinical features	Levodopa responsiveness	DAT SPECT binding
Neurodegenerative			
PD	Asymmetrical parkinsonism; variable non-motor symptoms including hyposmia, REM sleep behaviour disorder	++	Asymmetrically reduced
Progressive supranuclear palsy	Axial rigidity, falls, symmetrical parkinsonism, supranuclear gaze palsy, apathy, executive deficits	+/–	Reduced
Multiple system atrophy	Autonomic dysfunction, parkinsonism, cerebellar signs, REM sleep behaviour disorder	+/–	Reduced
Corticobasal degeneration	Asymmetrical parkinsonism, apraxia, dystonia myoclonus, alien limb, cognitive impairment	+/–	Asymmetrically reduced
Dementia with Lewy bodies	Cognitive impairment, fluctuating confusion, hallucinations, REM sleep behaviour disorder, concurrent with or preceding motor parkinsonism	+	Reduced
Secondary			
Vascular parkinsonism	Symmetrical lower body parkinsonism without tremor	–	Normal; or well-demarcated lesion if basal ganglia infarct
Drug-induced parkinsonism	Symmetrical parkinsonism, suggestive drug history	–	Normal
Chronic traumatic encephalopathy	Cognitive impairment, behavioural and mood disturbance, parkinsonism	–	Normal
Normal - pressure hydrocephalus	Ataxia, urinary incontinence, dementia ± parkinsonism	–	Normal or slightly reduced
Structural lesions	Dependent on anatomical location	–	Normal (unless lesion in caudate/putamen)

Table 1

Overview of pharmacological therapies for PD

Drug class	Administration route	Drug name	Key benefits/uses	Common/important adverse effects
Levodopa (+ peripheral DDC inhibitor)	Oral	Madopar Sinemet	Good efficacy for motor symptoms Well tolerated Formulations include standard, slow release and dispersible	Early – nausea, dizziness Late – motor fluctuations, dyskinesias, hallucinations, orthostatic hypotension
	Enteral	Duodopa	Continuous administration via a pump for managing advanced disease with motor fluctuations	As for oral levodopa Jejunal tube occlusion or dislocation
Dopamine agonists	Oral	Ropinirole Pramipexole	'Levodopa sparing' in early disease Modified-release formulations available for once-daily dosing Some anxiolytic effects	Nausea Orthostatic hypotension Excessive daytime sleepiness Impulse control disorders Confusion Ankle oedema
	Transdermal	Rotigotine	Slow release over 24 hours Useful alternative to oral therapy for postoperative/nil-by-mouth patients	As for oral dopamine agonists Local skin reactions
	Subcutaneous	Apomorphine	Injections provide rapid-onset 'rescue therapy' for severe 'off' periods Continuous infusion via pump for management of advanced disease with motor fluctuations	As for oral dopamine agonists but nausea and vomiting more problematic Infusion site skin reactions
MAO-B inhibitors	Oral	Rasagiline Selegiline	Well tolerated Once-daily dosing Some evidence to suggest small disease-modifying effect Monotherapy or add-on therapy to improve motor fluctuations	Headache Depression Agitation Dry mouth Orthostatic hypotension
COMT inhibitors	Oral	Entacapone (Stalevo = entacapone +	Improves levodopa-	Gastrointestinal disturbance (entacapone)

Drug class	Administration route	Drug name	Key benefits/uses	Common/important adverse effects
		levodopa + carbidopa) Opicapone Tolcapone	associated motor fluctuations Enables reduction of levodopa dose to help manage dyskinesias (Tolcapone second line only, requires monitoring of liver function)	Orthostatic hypotension Dyskinesias Hallucinations Orange discoloration of urine (entacapone) Hepatic impairment (tolcapone)
Combined MAO-B inhibition and anti-glutamatergic release	Oral	Safinamide	Once-daily adjunct to levodopa Potentially useful for patients with both wearing off and dyskinesias	Dyskinesia Nausea Orthostatic hypotension Dizziness Headache Insomnia
Anticholinergics	Oral	Trihexyphenidyl Orphenadrine	Can be useful to manage tremor (Avoid in the elderly due to high risk of side effects)	Confusion Hallucinations Dry mouth Constipation Urinary retention
(Uncertain mode of action; weak NMDA receptor antagonist)	Oral	Amantadine	Can improve dyskinesias	Confusion Hallucinations Peripheral oedema Livedo reticularis

DDC, dopa decarboxylase; NMDA, *N*-methyl-D-aspartate receptor.

Table 2.

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