# Parkinson's disease

*Lorraine V Kalia, Anthony E Lang*

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**Morton and Gloria Shulman Movement Disorders Clinic and the Edmond J Safra Program in Parkinson's Disease, Toronto Western Hospital, Division of Neurology, Department of Medicine, University of Toronto, Toronto, ON, Canada** (L V Kalia MD, A E Lang MD)

Correspondence to:
Dr Anthony Lang, Movement Disorders Centre, Toronto Western Hospital, Toronto, ON, M5T 2S8, Canada
**lang@uhnres.utoronto.ca**

**Parkinson's disease is a neurological disorder with evolving layers of complexity. It has long been characterised by the classical motor features of parkinsonism associated with Lewy bodies and loss of dopaminergic neurons in the substantia nigra. However, the symptomatology of Parkinson's disease is now recognised as heterogeneous, with clinically significant non-motor features. Similarly, its pathology involves extensive regions of the nervous system, various neurotransmitters, and protein aggregates other than just Lewy bodies. The cause of Parkinson's disease remains unknown, but risk of developing Parkinson's disease is no longer viewed as primarily due to environmental factors. Instead, Parkinson's disease seems to result from a complicated interplay of genetic and environmental factors affecting numerous fundamental cellular processes. The complexity of Parkinson's disease is accompanied by clinical challenges, including an inability to make a definitive diagnosis at the earliest stages of the disease and difficulties in the management of symptoms at later stages. Furthermore, there are no treatments that slow the neurodegenerative process. In this Seminar, we review these complexities and challenges of Parkinson's disease.**

## Introduction

Parkinson's disease is a common and complex neurological disorder. The first detailed description of Parkinson's disease was made almost two centuries ago, but the conceptualisation of the disease continues to evolve. At its core, Parkinson's disease is a neurodegenerative disease with early prominent death of dopaminergic neurons in the substantia nigra pars compacta (SNpc). The resultant dopamine deficiency within the basal ganglia leads to a movement disorder characterised by classical parkinsonian motor symptoms. Parkinson's disease is also associated with numerous non-motor symptoms, some of which precede the motor dysfunction by more than a decade. The mainstay of Parkinson's disease management is symptomatic treatment with drugs that increase dopamine concentrations or directly stimulate dopamine receptors. However, Parkinson's disease involves neurotransmitters other than dopamine and regions of the nervous system outside the basal ganglia. Previously, Parkinson's disease was thought to be caused primarily by environmental factors, but research is revealing that the disease develops from a complicated interplay of genetics and environment. Thus, Parkinson's disease is now viewed as a slowly progressive neurodegenerative disorder that begins years before diagnosis can be made, implicates multiple neuroanatomical areas, results from a combination of genetic and environmental factors, and manifests with a broad range of symptoms. These complexities of Parkinson's disease are accompanied by clinical challenges. In particular, diagnostic tests which allow for definitive diagnosis at early stages of the disease do not exist. The gold standard for diagnosis of Parkinson's disease has been the presence of SNpc degeneration and Lewy pathology at post-mortem pathological examination. Lewy pathology consists of abnormal aggregates of α-synuclein protein, called Lewy bodies and Lewy neurites. The association between Lewy pathology and pathogenesis of the disease is poorly understood. Management strategies for many of the disabling features that occur in late stages of the disease are poor. These features include motor symptoms that do not respond to dopaminergic therapies or develop as complications of long-term dopaminergic drug use, as well as an array of non-motor symptoms. Disease-modifying treatments that reduce the rate of neurodegeneration or stop the disease process have remained elusive and are the greatest unmet therapeutic need in Parkinson's disease. However, the understanding of the pathogenesis of Parkinson's disease is expanding and thereby helping to identify potential targets for disease modification.

### Search strategy and selection criteria

The authors searched personal files and PubMed for peer-reviewed articles published in English from Jan 1, 2000, to Feb 28, 2015. The search terms "parkinson", "motor features", "non-motor features", "prevalence", "incidence", "risk factors", "pathology", "genetics", "pathogenesis", "treatment", and "deep brain stimulation" were used. The search term "parkinson" with the "clinical trials" filter was also used. Additional articles were identified by searching the reference lists of identified reviews that provided insightful or comprehensive overviews on relevant aspects of Parkinson's disease.

## Clinical features

The classical motor symptoms of Parkinson's disease have been recognised as prominent components of the disease since James Parkinson's initial description in the 19th century, later refined by Jean-Martin Charcot.[1] These parkinsonian symptoms include bradykinesia, muscular rigidity, rest tremor, and postural and gait impairment (panel 1).[2] Motor features in patients with Parkinson's disease are heterogeneous, which has prompted attempts to classify subtypes of the disease.[3] A consensus on the classification of Parkinson's disease subtypes has not yet been established, but empirical clinical observations suggest two major subtypes: tremor-dominant Parkinson's disease (with a relative absence of other motor symptoms)

and non-tremor-dominant Parkinson's disease (which includes phenotypes described as akinetic-rigid syndrome and postural instability gait disorder). An additional subgroup of patients with Parkinson's disease has a mixed or indeterminate phenotype with several motor symptoms of comparable severity. Course and prognosis of disease differ between the subtypes; tremor-dominant Parkinson's disease is often associated with a slower rate of progression and less functional disability than non-tremor-dominant Parkinson's disease.[4] Furthermore, the various Parkinson's disease subtypes are hypothesised to have distinct aetiologies and pathogenesis.[3]

Non-motor features include olfactory dysfunction, cognitive impairment, psychiatric symptoms, sleep disorders, autonomic dysfunction, pain, and fatigue (figure 1). These symptoms are common in early Parkinson's disease[5] and are associated with reduced health-related quality of life.[6,7] Non-motor features are also frequently present in Parkinson's disease before the onset of the classical motor symptoms (figure 1).[8] This premotor or prodromal phase of the disease can be characterised by impaired olfaction, constipation, depression, excessive daytime sleepiness, and rapid eye movement sleep behaviour disorder (RBD; panel 2). In fact, mood disorders and constipation have both been shown to nearly double an individual's risk of subsequently developing Parkinson's disease.[14] The premotor phase can be prolonged; for example, the average latency between onset of RBD and occurrence of parkinsonian motor symptoms is 12–14 years.[8] The pathogenic process that causes Parkinson's disease is presumed to be underway during the premotor phase, involving regions of the peripheral and central nervous system in addition to the dopaminergic neurons of the SNpc. Thus, this prodromal period provides a potential temporal window during which disease-modifying therapy, once it becomes available, could be administered to prevent or delay the development and progression of disease.[15]

Progression of Parkinson's disease is characterised by worsening of motor features, which initially can be managed with symptomatic therapies. However, as the disease advances, there is an emergence of complications related to long-term symptomatic treatment, including motor and non-motor fluctuations, dyskinesia, and psychosis (panel 3).[16] These treatment-related complications are substantial challenges in the clinical management of the advanced stage of Parkinson's disease. In late-stage Parkinson's disease, treatment-resistant motor and non-motor features are prominent and include axial motor symptoms such as postural instability, freezing of gait, falls, dysphagia, and speech dysfunction. After about 17 years of disease, up to 80% of patients with Parkinson's disease have freezing of gait and falls, and up to 50% of patients report choking.[16] Autonomic symptoms, such as urinary incontinence, constipation with the need for daily laxatives, and symptomatic postural hypotension, are common non-motor features in these late stages of Parkinson's disease.[16,17] Dementia is particularly prevalent, occurring in 83% of patients with Parkinson's disease who have had 20 years disease duration.[17] These

***Panel 1:*** **UK Parkinson's Disease Society Brain Bank clinical diagnostic criteria[2]**

**Step 1: diagnosis of parkinsonian syndrome**

Bradykinesia (ie, slowness of initiation of voluntary movement with progressive reduction in speed and amplitude of repetitive actions) plus one or more of the following features:

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

**Step 2: exclusion criteria for Parkinson's disease**

One or more of the following features suggest an alternate diagnosis:

- History of repeated strokes with stepwise progression of parkinsonian features
- History of repeated head injury
- History of definite encephalitis
- Neuroleptic treatment at onset of symptoms
- 1-methyl-4-phenyl-1,2,3,6-tetrahydropyridine (MPTP) exposure
- Negative response to large doses of levodopa (if malabsorption excluded)
- More than one affected relative*
- Sustained remission
- Strictly unilateral features after 3 years
- Early severe autonomic involvement
- Early severe dementia with disturbances of memory, language, and praxis
- Oculogyric crises
- Supranuclear gaze palsy
- Babinski sign
- Cerebellar signs
- Presence of a cerebral tumour or communicating hydrocephalus on CT scan or MRI

**Step 3: supportive prospective positive criteria for Parkinson's disease**

Three or more of the following features are required for diagnosis of definite Parkinson's disease:

- Unilateral onset
- Rest tremor present
- Progressive disorder
- Persistent asymmetry affecting the 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

*This criterion is generally no longer applied.

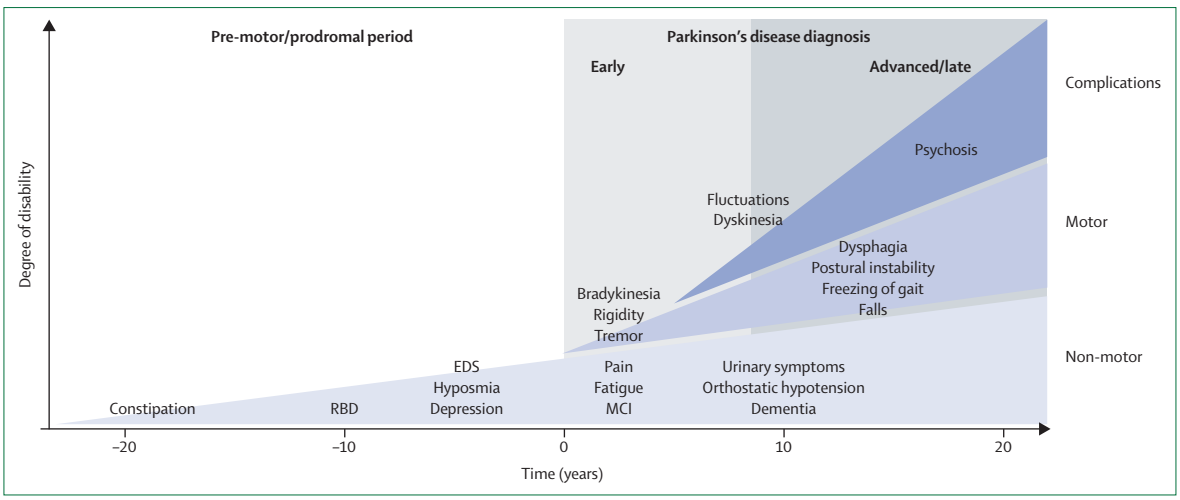


***Figure 1:*** **Clinical symptoms and time course of Parkinson's disease progression**
Diagnosis of Parkinson's disease occurs with the onset of motor symptoms (time 0 years) but can be preceded by a premotor or prodromal phase of 20 years or more. This prodromal phase is characterised by specific non-motor symptoms. Additional non-motor features develop following diagnosis and with disease progression, causing clinically significant disability. Axial motor symptoms, such as postural instability with frequent falls and freezing of gait, tend to occur in advanced disease. Long-term complications of dopaminergic therapy, including fluctuations, dyskinesia, and psychosis, also contribute to disability. EDS=excessive daytime sleepiness. MCI=mild cognitive impairment. RBD=REM sleep behaviour disorder.

levodopa-resistant symptoms of late-stage Parkinson's disease contribute substantially to disability and are strong predictors of a need for admission to an institution and mortality.[18]

## Risk factors

Parkinson's disease is recognised as the most common neurodegenerative disorder after Alzheimer's disease.[19,20] Prevalence of Parkinson's disease seems higher in Europe, North America, and South America (estimated crude prevalence for all ages: 66–1500 per 100 000,[21] 111–329 per 100 000,[22] and 31–470 per 100 000,[23] respectively) compared with African, Asian, and Arabic countries (estimated crude prevalence for all ages: 10–43 per 100 000,[24] 15–119 per 100 000,[25] and 27–43 per 100 000,[26] respectively). The incidence of Parkinson's disease ranges from 10–18 per 100 000 person-years.[27] Gender is an established risk factor, with the male-to-female ratio being approximately 3:2.[28] Ethnicity is also a risk factor for the disease. In the USA, incidence is highest in people of Hispanic ethnic origin, followed by non-Hispanic Whites, Asians, and Blacks.[27] Age is the greatest risk factor for the development of Parkinson's disease. The prevalence and incidence increase nearly exponentially with age and peak after 80 years of age.[29,30] This trend has important public health implications; with an aging population and rising life expectancy worldwide, the number of people with Parkinson's disease is expected to increase by more than 50% by 2030.[19]

Other risk factors for Parkinson's disease include environmental exposures (figure 2). Results of a meta-analysis[14] examining 30 different potential risk factors identified 11 environmental factors that significantly altered the risk of Parkinson's disease. The factors that

### *Panel 2:* Rapid eye movement sleep behaviour disorder and Parkinson's disease

**Definition**
Rapid eye movement sleep behaviour disorder (RBD) is a parasomnia characterised by abnormal or disruptive behaviours (eg, talking, laughing, shouting, gesturing, grabbing, punching, kicking, sitting up in bed), which occur during rapid eye movement sleep and are often related to dream enactment

**Diagnosis**
The International Classification of Sleep Disorders (ICSD-2) diagnostic criteria for RBD[9] requires overnight polysomnogram to document the presence of rapid eye movement sleep without atonia (ie, sustained or intermittent muscle activity measured by electromyogram) and to rule out mimics (eg, obstructive sleep apnoea, non-rapid eye movement parasomnia, seizure)

**Treatment**
RBD is primarily treated with clonazepam or melatonin at bedtime[10]

**Significance**
RBD can be associated with sleep disruption or injuries to the affected individual or bed partner. Individuals with isolated RBD have an increased risk of developing a neurodegenerative disease (including Parkinson's disease, Lewy body disease, multiple system atrophy): 18–35% risk at 5 years and 40–75% risk at 10 years;[11–13] patients with Parkinson's disease and RBD tend to have a disease subtype characterised by more severe autonomic dysfunction, gait impairment, and dementia

increase risk (in decreasing order of strength of association) were pesticide exposure, prior head injury, rural living, β-blocker use, agricultural occupation, and well-water drinking. Environmental factors found to be associated with a decreased risk (in decreasing order of strength of association) were tobacco smoking, coffee drinking, non-steroidal anti-inflammatory drug use, calcium channel blocker use, and alcohol consumption.[14] The reduced risk of Parkinson's disease with smoking has led to the proposal that smoking might protect against the disease. However, the findings of a more recent large case-control study[31] showed that patients with Parkinson's disease are able to quit smoking more easily than controls, suggesting that the negative association with smoking could instead be due to a decreased responsiveness to nicotine during the prodromal phase of Parkinson's disease. Studies on serum urate concentrations were excluded from the meta-analysis,[14] but results of at least five prospective population-based studies have shown an inverse association between blood urate concentration and Parkinson's disease risk, a finding which might be more robust for men than women.[32] Findings of a separate meta-analysis[33] have confirmed that welding and manganese exposure are not associated with increased risk of Parkinson's disease. Results of single epidemiologic studies[34,35] suggest that use of antipsychotics, specifically phenothiazines, benzamides, haloperidol, or risperidone by elderly people and exposure to solvents, particularly trichloroethylene, might enhance risk of Parkinson's disease, but additional studies are needed to confirm these associations.

The contribution of genetics to Parkinson's disease is suggested by the increased risk of disease associated with a family history of Parkinson's disease or tremor.[14] The most convincing evidence came with the discovery of monogenic forms of Parkinson's disease (table 1). *SNCA*, which encodes the protein α-synuclein, was the first gene to be associated with inherited Parkinson's disease.[36] Mutations in *LRRK2* and *parkin* are the most common causes of dominantly and recessively inherited Parkinson's disease, respectively.[37] The greatest genetic risk factor for developing Parkinson's disease is mutation in *GBA*, which encodes β-glucocerebrosidase, the lysosomal enzyme deficient in Gaucher disease.[38] Results of a large multicentre study[39] of more than 5000 patients with Parkinson's disease and an equal number of matched controls showed an odds ratio greater than 5 for any *GBA* mutation in Parkinson's disease patients versus controls. Advances in genomics and bioinformatics have uncovered additional genetic risk factors for Parkinson's disease. In the past decade, almost 900 genetic association studies have implicated dozens of potential gene loci in Parkinson's disease. These studies include genome-wide association studies that analyse up to 500 000 common genetic variants, single-nucleotide polymorphisms, throughout the human genome in large case-control cohorts and compare the frequency of these single-nucleotide polymorphisms between people with and without Parkinson's disease. Findings of a recent meta-analysis[40] of genome-wide association studies of all existing European-ancestry Parkinson's disease data revealed that 24 loci have clinically significant association with disease risk (figure 2).These loci include *GBA* as well as genes associated with monogenic forms of Parkinson's disease (*LRRK2* and *SNCA*).

### *Panel 3:* Long-term complications of dopaminergic therapies for Parkinson's disease

**Motor fluctuations**
Alterations between periods of good motor symptom control (ie, on-time) and periods of reduced motor symptom control (ie, off-time)

**Non-motor fluctuations**
Alterations between good non-motor symptom control and periods of reduced non-motor symptom control

**Dyskinesia**
Involuntary choreiform or dystonic movements, which occur most frequently when levodopa concentrations are at their maximum (ie, peak-dose dyskinesia); less commonly, these involuntary movements might develop at the beginning or the end of a levodopa dose, or both (ie, diphasic dyskinesia)

**Drug-induced psychosis**
Hallucinations include minor phenomena, such as sense of presence or passage hallucinations (ie, patients report the sensation of someone nearby or of passing in their peripheral visual field, respectively, when no one is actually there); hallucinations also include well-formed visual hallucinations, and less commonly non-visual hallucinations (eg, auditory, tactile, olfactory); other psychotic features might include illusions and delusions (often with paranoia)

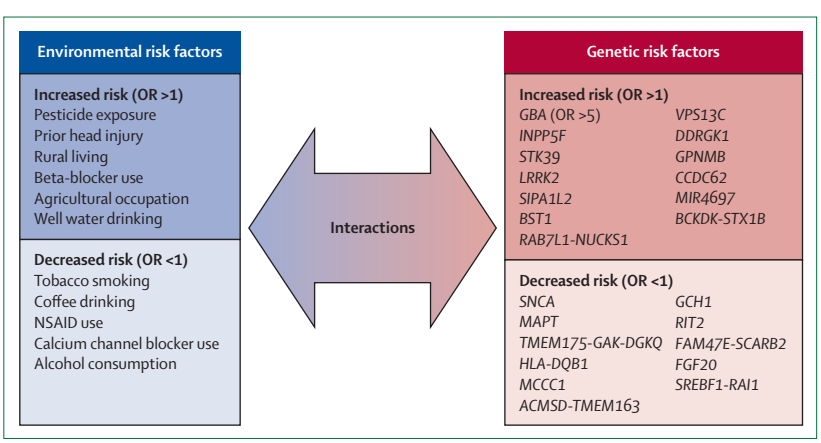


***Figure 2:*** **Risk factors for the development of Parkinson's disease**
Results of epidemiological studies have revealed various environmental exposures that increase (OR >1) or decrease (OR <1) the risk of developing Parkinson's disease (left). Findings of genome-wide association studies have identified genetic risk factors, which are polymorphisms within certain genes that influence risk for developing Parkinson's disease (right). The strongest genetic risk factor is the Asn370Ser mutation of β-glucocerebrosidase, which is associated with an OR greater than 5. The interplay between environmental and genetic risk factors is under investigation. OR=odds ratio.

| | Protein | Pathogenic mutation(s) |
|---|---|---|
| **Autosomal dominant** | | |
| *SNCA* | α-synuclein | Missense mutations (Ala18Thr, Ala29Ser, Ala30Pro, Glu46Lys, His50Gln, Gly51Asp, Ala53Glu, Ala53Thr); multiplications (duplications, triplications) |
| *LRRK2* | Leucine-rich repeat kinase 2 | Missense mutations (Ile1371Val, Asn1437His, Arg1441Cys, Arg1441Gly, Arg1441His, Tyr1699Cys, Gly2019Ser [most common], Ile2020Thr) |
| *VPS35* | Vacuolar protein sorting 35 | Missense mutation (Asp620Asn) |
| *EIF4G1* | Eukaryotic translation initiation factor 4-γ 1 | Missense mutations (Arg1205His, Ala502Val) |
| *DNAJC13* | Receptor-mediated endocytosis 8 (REM-8) | Missense mutation (Asn855Ser) |
| *CHCHD2* | Coiled-coil-helix-coiled-coil-helix domain containing 2 | Missense mutations (Thr61Ile, Arg145Gln); splice-site alteration |
| **Autosomal recessive** | | |
| *Parkin* | Parkin | Exon rearrangements, including exon deletions or multiplications (most common); missense mutations, nonsense mutations, small deletions or insertions; splice-site alterations |
| *PINK1* | PTEN-induced putative kinase 1 | Missense or nonsense mutations (most common); exon rearrangements, including exon deletions or duplications |
| *DJ-1* | DJ-1 | Missense mutations or exon rearrangements (most common); splice-site alterations |

***Table 1:*** **Monogenic forms of Parkinson's disease, by gene**

### *Panel 4:* Braak staging of Lewy pathology in Parkinson's disease[55]

The Braak model proposes that Lewy pathology in Parkinson's disease progresses temporally and spatially through the following stages:

**Stage 1**
Peripheral nervous system (autonomic neurons), olfactory system (olfactory bulb, anterior olfactory nucleus), medulla (dorsal motor nuclei of vagal and glossopharyngeal nerves)

**Stage 2**
Pons (locus ceruleus, magnocellular portions of reticular formation, posterior raphe nuclei), spinal cord grey matter

**Stage 3**
Pons (pedunculopontine nucleus), midbrain (substantia nigra pars compacta), basal forebrain (magnocellular nuclei including nucleus basalis of Meynert), limbic system (central subnucleus of amygdala)

**Stage 4**
Limbic system (accessory cortical and basolateral nuclei of amygdala, interstitial nucleus of stria terminalis, ventral claustrum), thalamus (intralaminar nuclei), temporal cortex (anteromedial temporal mesocortex, CA2 region of hippocampus)

**Stages 5 and 6**
Multiple cortical regions (insular cortex, association cortical areas, primary cortical areas)

Risk of developing Parkinson's disease is clearly multifactorial, but the elaborate interplay between the various factors is just beginning to be deciphered. For example, the findings of a case-control study[41] revealed that exposure to the pesticide Paraquat (1,1′-dimethyl-4,4′-bipyridinium dichloride) and a history of head injury act synergistically to increase Parkinson's disease risk. Additional studies have identified genetic modifiers of environmental risk factors. For instance, the risk reduction associated with coffee consumption is affected by single-nucleotide polymorphisms in *CYP1A2* (encoding the cytochrome P450 isoform most responsible for caffeine metabolism)[42] or *GRIN2A* (encoding a subunit of the N-methyl-D-aspartate receptor).[43] Also, the size of a polymorphic mixed dinucleotide repeat (Rep1) in the promoter region of *SNCA* modifies the risk of Parkinson's disease associated with head injury.[44] A further understanding of Parkinson's disease risk factors and their interactions is expected to have broad implications for the elucidation of pathogenic mechanisms, identification of biomarkers, and individualisation of treatment.

## Pathology

The crucial pathological feature of Parkinson's disease is loss of dopaminergic neurons within the SNpc. The most profoundly affected area of the SNpc is typically the ventrolateral tier, which contains neurons that project to the dorsal putamen of the striatum. Results of clinical-pathological correlation studies[45] showed that moderate to severe dopaminergic neuronal loss within this area is probably the cause of motor features, bradykinesia and rigidity in particular, in advanced Parkinson's disease. Recent findings[46] from pathology confirm that moderate loss of nigral neurons is also present in early stages of the disease but also provide evidence for a population of potentially salvageable dopaminergic neurons. Neuronal loss in Parkinson's disease occurs in many other brain regions, including the locus ceruleus, nucleus basalis of Meynert, pedunculopontine nucleus, raphe nucleus, dorsal motor nucleus of the vagus, amygdala, and hypothalamus.[47]

Another hallmark of Parkinson's disease is Lewy pathology. Aggregation of abnormally folded proteins has emerged as a common theme in neurodegenerative diseases, including Parkinson's disease. Each neurodegenerative disease is categorised according to the protein that is most abundant in the associated protein inclusions.[48] In Parkinson's disease, this protein was identified as α-synuclein following the discovery that mutations in its gene, *SNCA*, cause a monogenic form of the disease.[36,49] In a misfolded state, α-synuclein becomes insoluble and aggregates to form intracellular inclusions within the cell body (Lewy bodies) and processes (Lewy neurites) of neurons.[50] Lewy pathology is not restricted to the brain but can also be found in the spinal cord and peripheral nervous system, including the vagus nerve, sympathetic ganglia, cardiac plexus, enteric nervous system, salivary glands, adrenal medulla, cutaneous nerves, and sciatic nerve.[51–54]

Lewy pathology has been hypothesised to progress in a stereotyped pattern over the course of Parkinson's disease. Braak and colleagues[55] have proposed six stages, starting in the peripheral nervous system and progressively affecting the central nervous system in a caudal-to-rostral direction within the brain (panel 4). The

Braak model has gained traction, in part, because the proposed temporal and spatial progression seems to explain the clinical course of Parkinson's disease. Specifically, stages 1 and 2 could correspond with onset of premotor symptoms, stage 3 would be when motor features present due to nigrostriatal dopamine deficiency, and stages 4–6 would occur with the non-motor symptoms of advanced disease (figure 1). Evidence for an association between Lewy pathology and non-motor symptoms is most convincing for cognitive impairment in Parkinson's disease. Findings from several pathological studies[56–58] have shown a strong correlation between dementia and severity of cortical Lewy pathology. Further studies are needed to confirm the association of other non-motor symptoms with the Braak staging system, which seems to apply to a large proportion of Parkinson's disease cases studied post mortem, but certainly not all.[59,60]

Lewy pathology is hypothesised to be a biological marker for neurodegeneration in Parkinson's disease. This hypothesis is often extended further to propose that Lewy bodies have a causal role in neuronal loss. However, important findings over the past several years have revealed that Parkinson's disease pathology is more complex than neurodegeneration due to Lewy pathology alone. First, α-synuclein is now known to form a variety of different aggregate types, including small dot-like or thin thread-like structures,[61,62] very fine presynaptic deposits,[63] and soluble oligomers composed of 2–100 α-synuclein monomers.[64] These alternate forms of α-synuclein aggregates might play an important part in neurodegeneration in Parkinson's disease; in particular, certain oligomeric forms of α-synuclein could be toxic to neurons.[65] Second, pathologies distinct from α-synuclein aggregates, such as inclusions composed of other types of proteins, are often seen in the brains of patients with Parkinson's disease. For instance, β-amyloid plaques and tau-containing neurofibrillary tangles, the protein inclusions characteristic of Alzheimer's disease, can be found in the brains of patients with Parkinson's disease at comparable amounts and distribution as in the brains of patients with Alzheimer's disease. Concomitant Alzheimer's disease pathology is associated with a greater burden of Lewy pathology,[58] correlates with a shorter latency to onset of dementia in Parkinson's disease,[66] and occurs in up to 50% of patients with Parkinson's disease and dementia.[58,67] Thus, inclusions of proteins other than α-synuclein might synergise with Lewy pathology and contribute to the clinical expression of Parkinson's disease. Finally, with the identification and characterisation of monogenic forms of Parkinson's disease, clinical Parkinson's disease has been found to occur without Lewy pathology. Several neuropathological reports have documented an absence of Lewy pathology in most patients with Parkinson's disease who have *parkin*-related disease[68,69] and in a smaller proportion of those patients with *LRRK2* mutations.[69,70] These observations all suggest that alternate forms of α-synuclein aggregates other than Lewy bodies, as well as inclusions containing proteins other than α-synuclein, are important features of pathology in Parkinson's disease.

Neuroinflammation is another feature of Parkinson's disease pathology.[71] The presence of an active inflammatory response in the brain mediated primarily by resident astrocytes and microglia has been long recognised, but somewhat overlooked, in Parkinson's disease. Both reactive gliosis resulting from activated astrocytes and microgliosis resulting from microglial activation occur within areas of neurodegeneration in Parkinson's disease. Astrocytes and microglia are both involved in clearance of extracellular debris, which might aid in the survival of neurons. Activated microglia can release trophic factors, such as brain-derived neurotrophic factor and glial-derived neurotrophic factor, but also harmful reactive oxygen and nitrogen species and pro-inflammatory cytokines. Whether the balance of these actions is beneficial or harmful to neurons is not yet established.[72]

## Genetics

The past 15 years have been marked by important discoveries in the genetics of Parkinson's disease. Early investigations used linkage analysis in rare kindreds with inherited parkinsonism to find genes related to Parkinson's disease. The first gene identified was *SNCA*,[36] and *SNCA* mutations are associated with autosomal dominant parkinsonism. Disease-causing mutations include missense mutations, which result in aminoacid substitutions, and multiplications of the gene locus.[73] Aminoacid substitutions due to these missense mutations, or increased protein expression resulting from gene locus multiplications render α-synuclein prone to aggregating. *SNCA*-related Parkinson's disease is rare, but recognition of *SNCA* mutations as a genetic cause of Parkinson's disease led to the identification of α-synuclein as the major component of Lewy bodies and neurites.[49] Furthermore, this finding ushered in the discovery of a growing list of genes associated with monogenic forms of Parkinson's disease (table 1).[37]

Six genes have been proposed to mediate autosomal dominant forms of Parkinson's disease: *SNCA*, *LRRK2*, *VPS35*, *EIF4G1*, *DNAJC13*, and *CHCHD2* (table 1). *LRRK2* encodes the leucine-rich repeat kinase 2, a large multidomain protein involved in multiple cellular processes, including neurite outgrowth and synaptic morphogenesis, membrane trafficking, autophagy, and protein synthesis. LRRK2 may also have a role in the innate immune system.[74–78] LRRK2 activity is conferred, in part, by its dual enzymatic functions (GTPase and serine-threonine kinase). At least eight disease-causing mutations in *LRRK2* have been identified, all mostly clustered within the catalytic domains of the protein.[79–81] *LRRK2* mutations are the most frequent cause of genetic Parkinson's disease, in that they are found in about 4% of familial Parkinson's disease and account for 1% of sporadic Parkinson's disease

worldwide.[80] The most common *LRRK2* mutation results in a Gly2019Ser aminoacid substitution, which increases the kinase activity of the protein. Parkinson's disease associated with the Gly2019Ser substitution is especially prevalent among Ashkenazi Jews (30% of familial Parkinson's disease, 13% of sporadic Parkinson's disease)[82] and North African Arab Berbers (37% of familial Parkinson's disease, 41% of sporadic Parkinson's disease).[83]

*VPS35*,[84,85] *EIF4G1*,[86] *DNAJC13*,[87] and *CHCHD2*[88] are the most recent genes to be associated with dominantly inherited Parkinson's disease. *VPS35* encodes vacuolar protein sorting 35 (VPS35), a component of a multisubunit complex that associates with endosomes, intracellular membrane-bound compartments that traffic proteins between the plasma membrane, Golgi apparatus, and lysosomes.[89] *EIF4G1* mutations have been linked to Parkinson's disease,[86] but reports[90,91] describing several unaffected mutation carriers exist. Therefore, further studies are needed to establish the contribution of *EIF4G1* to the disease. *DNAJC13* encodes a chaperone protein named receptor-mediated endocytosis 8 (REM-8), which, like VPS35, localises to endosomes and regulates transmembrane protein trafficking. A mutation in *DNAJC13* has been identified in patients with Parkinson's disease of Dutch-German-Russian Mennonite ancestry.[87] Mutations in *CHCHD2* have very recently been discovered in Japanese patients with familial Parkinson's disease.[88] *CHCHD2* encodes coiled-coil-helix-coiled-coil-helix domain containing 2 (CHCHD2), which is a mitochondrial protein. Independent identification of other familial or sporadic Parkinson's disease patients with mutations in *DNAJC13* or *CHCHD2* is still needed.

*Parkin*, *PINK1*, and *DJ-1* are associated with autosomal recessive forms of Parkinson's disease (table 1). Unlike autosomal dominant Parkinson's disease, which tends to have an age of onset similar to sporadic Parkinson's disease, recessively inherited parkinsonism is more frequently associated with early onset (age less than 40 years).[92] Mutations in *parkin* are the most common cause of autosomal recessive Parkinson's disease. In patients with Parkinson's disease onset before age 45 years, *parkin* mutations are seen in up to 50% of familial cases and about 15% of sporadic cases.[93,94] Mutations in *PINK1* and *DJ-1* are less common causes (1–8% and 1–2% of early-onset sporadic Parkinson's disease, respectively).[95] Autosomal recessive Parkinson's disease might result from either homozygous or compound heterozygous mutations in these genes. In some patients, only a single heterozygous mutation is detected,[96] an intriguing phenomenon that needs further investigation.The proteins encoded by *parkin*, *PINK1*, and *DJ-1* are all implicated in mitochondrial health.[97] Parkin, an E3 ubiquitin ligase, and PINK1, a serine-threonine protein kinase, work in concert to dispose of damaged mitochondria in a process called mitophagy. The function of DJ-1 is less well characterised, but it seems to protect mitochondria from oxidative stress.

Additional genes associated with parkinsonism identified from kindreds or patient cohorts include *ATP13A2*, *C9ORF72*, *FBXO7*, *PLA2G6*, *POLG1*, *SCA2*, *SCA3*,[98] *SYNJ1*,[99,100] *RAB39B*,[101] and possibly one or more genes affected in 22q11.2 microdeletion syndrome.[102] Parkinsonism due to mutations in these genes is quite rare and usually associated with features atypical for Parkinson's disease (eg, prominent cognitive impairment, ophthalmologic abnormalities, pyramidal signs, or ataxia).

## Pathogenesis

Substantial advances in the understanding of the pathogenesis of Parkinson's disease have resulted from the epidemiological findings, pathological observations, and genetic discoveries described above. For example, key molecular pathways presumed to be important in both familial and sporadic Parkinson's disease have been identified by fitting genes that are associated with the disease into common intracellular networks.[103] Impairments in cellular processes involved in the regulation of protein homoeostasis, or proteostasis, seem to be implicated in Parkinson's disease pathogenesis. These include abnormalities in protein aggregation, intracellular protein and membrane trafficking, and protein disposal by the ubiquitin-proteasome and lysosome-autophagy systems (figure 3). The genetics of Parkinson's disease has also suggested a role for aberrations in synaptic structure and function in the pathogenic process of Parkinson's disease and has confirmed the importance of mitochondrial dysfunction previously shown in toxin models of Parkinson's disease (eg, 6-hydroxy-dopamine (6-OHDA) and 1-methyl-4-phenyl-1,2,3,6-tetrahydropyridine (MPTP); figure 3).[104]

Pathologists have also yielded testable hypotheses regarding the pathogenesis of Parkinson's disease. For instance, the Braak staging of Parkinson's disease[55] proposed that the pathologic process spreads in a stereotyped pattern from one susceptible brain region to the next (panel 4). Braak and colleagues[55,105] hypothesised that this process begins peripherally, possibly gaining access to the CNS via a nasal or gastric route, and spreads between neurons trans-synaptically. Findings from four separate cases of patients with Parkinson's disease who received transplants of embryonic mesencephalic neurons into their putamen showed that Lewy body-like inclusions could develop within the grafted neurons.[106–108] This finding spurred the suggestion that spreading of Parkinson's disease pathology is mediated by a prion-like transmission of α-synuclein between neurons (figure 3).[109] Efforts to test this hypothesis with in-vitro and in-vivo models are underway. Injection of synthetic α-synuclein fibrils into various brain regions of transgenic mice overexpressing α-synuclein or wild-type mice leads to the formation of Lewy body-like inclusions in locations both near and distant from the injection sites.[110–113] Furthermore, injection of Lewy body-enriched homogenates from the SNpc of patients with Parkinson's disease into the

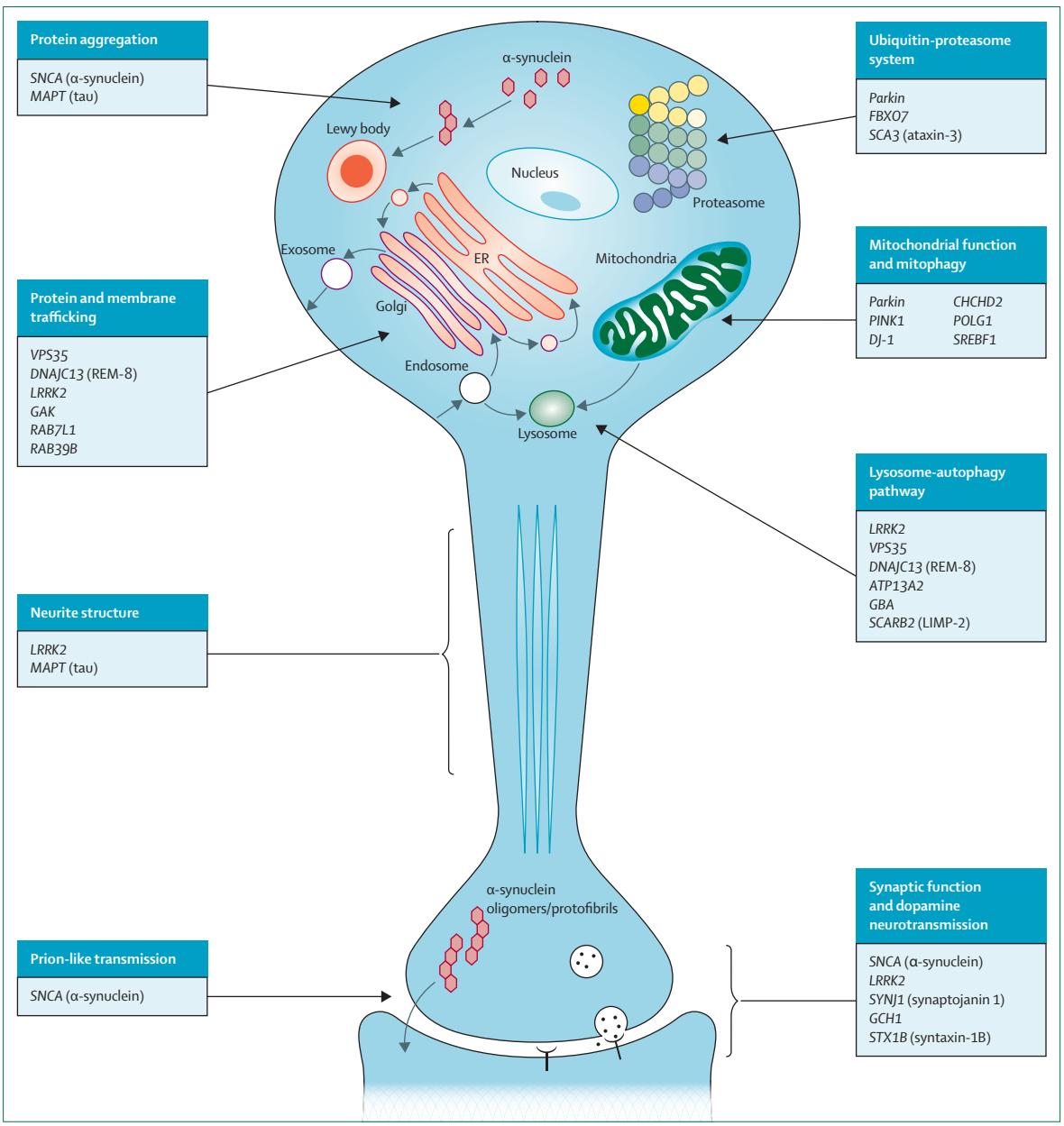


***Figure 3:*** **Cellular processes involved in the pathogenesis of Parkinson's disease**
Multiple genes have been implicated in Parkinson's disease based on mutations identified as causes of familial Parkinson's disease or polymorphisms found to be risk factors for sporadic Parkinson's disease. The gene products drive key cellular processes, the disruption of which might underlie the pathogenesis of Parkinson's disease.

substantia nigra or striatum of wild-type mice or macaque monkeys gave similar findings and caused progressive nigrostriatal neurodegeneration.[114]

Neuroinflammation is a characteristic feature of Parkinson's disease pathology, but whether neuroinflammation promotes or protects from neurodegeneration has yet to be established. Findings from meta-analysis of genome-wide association data[40] have identified a single-nucleotide polymorphism within the human leucocyte antigen region that affects the risk of developing Parkinson's disease, suggesting an immune-related genetic susceptibility to Parkinson's disease (figure 2). Furthermore, results of epidemiological studies[14] showing reduced risk of Parkinson's disease with the use of anti-inflammatory medications, specifically non-steroidal anti-inflammatory drugs, support the hypothesis that inflammation might promote an underlying disease process. Use of calcium channel blockers and elevated concentrations of serum urate are also associated with reduced risk of Parkinson's disease.[14] The ability of calcium channel blockers and urate to reduce oxidative stress in neurons that are susceptible to

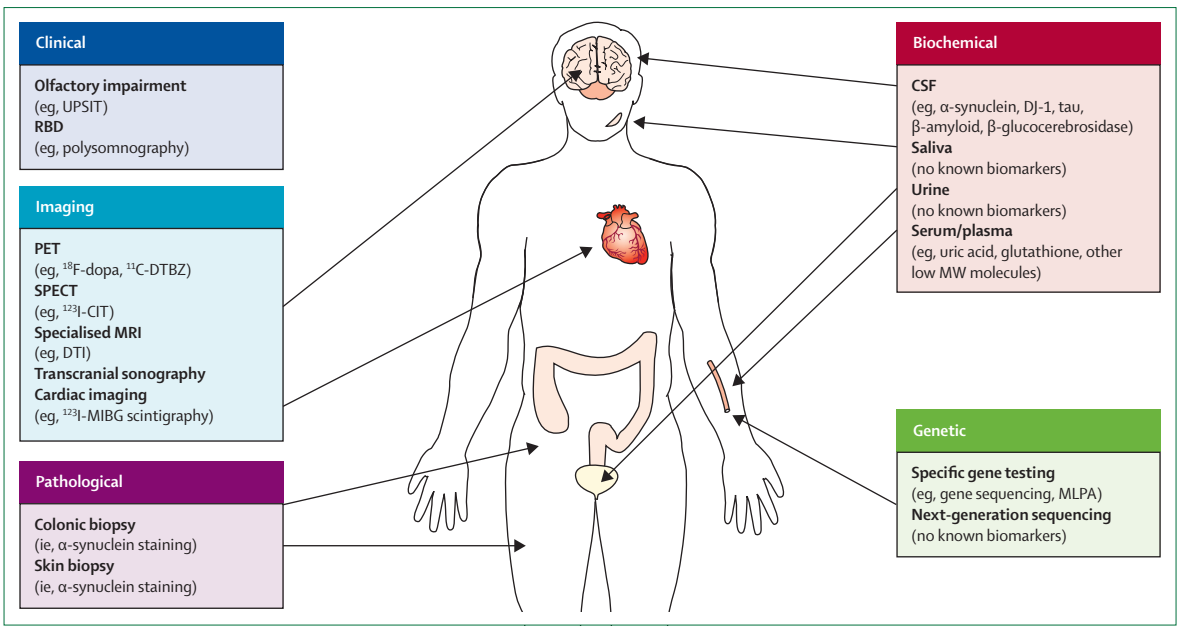


***Figure 4:*** **Potential biomarkers for diagnosis of Parkinson's disease**
A variety of biomarkers for Parkinson's disease diagnosis are currently under investigation. These biomarkers can be classified as clinical, imaging, pathological, biochemical, and genetic. Midbrain hyperechogenicity detected by transcranial sonography is a proposed diagnostic biomarker for Parkinson's disease, but many experts have found this method to have reliability and replicability issues. Combinations of biomarkers are likely to be necessary for accurate diagnosis of premotor or early PD. $^{11}$C-DTBZ=$^{11}$C-dihydrotetrabenazine. CSF=cerebrospinal fluid. DTI=diffusion tensor imaging. $^{123}$I-CIT=$^{123}$I-2β-carbomethoxy-3β-(4-iodophenyl)tropane. $^{123}$I-MIBG=$^{123}$I-metaiodobenzylguanidine. MLPA=multiplex ligation-dependent probe amplification. MW=molecular weight. PET=positron emission tomography. RBD=rapid eye movement sleep behaviour disorder. SPECT=single photon emission computed tomography. UPSIT=University of Pennsylvania's smell identification test.

death in Parkinson's disease has been proposed to explain these observations. Indeed, results of earlier research[115] suggested that SNpc neurons are particularly prone to higher levels of basal mitochondrial oxidative stress because they have elevated intracellular calcium loads that cause increased mitochondrial activity. Therefore, calcium channel blockers, which reduce calcium influx, or urate, a potent antioxidant, might protect neurons by decreasing concentrations of reactive oxygen species.[32,115,116] Other more controversial hypotheses that attempt to link increased oxidative stress to the susceptibility of SNpc neurons to cell death in Parkinson's disease propose that excessive cytotoxic free radicals result from oxidation of cytosolic dopamine and its metabolites[117] or from an overload of free iron within the SNpc.[118] Taken together, converging evidence supports the roles of inflammation and oxidative stress in Parkinson's disease pathogenesis, although the mechanistic details have yet to be elucidated.

## Diagnosis

Clinical diagnosis of Parkinson's disease is based on the presence of parkinsonian motor features, namely bradykinesia plus rigidity and resting tremor. Postural instability is typically a feature of more advanced disease. There should be no red flags that suggest an alternate cause of parkinsonism, including other neurodegenerative diseases, such as progressive supranuclear palsy, multiple system atrophy, and corticobasal degeneration. The UK Parkinson's Disease Society Brain Bank criteria[2] are used in the clinic and in clinical research to make a diagnosis of Parkinson's disease (panel 1). Sensitivity of these criteria can be as high as 90%.[119] Although the gold standard for diagnosis of Parkinson's disease is the neuropathological assessment, there are no generally accepted standard pathological diagnostic criteria for Parkinson's disease.[45] In general, diagnosis of Parkinson's disease depends on the presence of moderate-to-severe neuronal loss in the SNpc with Lewy bodies in surviving SNpc neurons, and no pathological evidence for other diseases that produce parkinsonism.[2,120] The International Parkinson and Movement Disorder Society has established a task force to define diagnostic criteria for Parkinson's disease.[121] Any new criteria will need to address the non-motor manifestations of the disease, the absence of Lewy pathology or presence of alternate pathology in certain cases, and the genetic contributions to the disease.[45,121,122]

Strategies to develop biomarkers for the diagnosis of Parkinson's disease are under investigation, especially to enable diagnosis early in the disease course, even before the onset of motor symptoms (figure 4). Drugs that can slow or stop the neurodegenerative process in Parkinson's disease are not yet available, but such disease-modifying drugs are anticipated to be most effective if patients can be diagnosed and treated during this prodromal premotor period. Potential clinical markers include olfactory impairment measured by standard methods, such as the

University of Pennsylvania's smell identification test and rapid eye movement sleep behaviour disorder diagnosed by polysomnography (panel 2).[8]

Candidate imaging markers include positron emission tomography (PET) or single photon emission computed tomography (SPECT) methods to measure reduction in SNpc dopaminergic nerve terminals projecting to the striatum (panel 5).[127] These imaging technologies can help differentiate Parkinson's disease with motor symptoms from disorders without loss of SNpc neurons (eg, essential tremor). The ability of these imaging markers to make this differentiation in early Parkinson's disease was questioned following unexpected clinical trial results. The results of these trials[123–126] showed larger than expected numbers of patients who were given a clinical diagnosis of early Parkinson's disease had scans without evidence of dopaminergic deficit, termed SWEDD (panel 5). Longitudinal follow-up suggests that most of the SWEDD patients probably do not have Parkinson's disease, and thus normal PET or SPECT might accurately rule out the diagnosis of Parkinson's disease.[128] However, dopaminergic imaging with PET or SPECT are abnormal only when there is substantial loss of dopaminergic neurons in the SNpc,[129] and a goal is to be able to diagnose the disease before this degeneration has occured. Indeed, in some cases, evidence of cardiac denervation has been shown to precede imaging findings of nigrostriatal dopaminergic damage.[130,131] Dopamine imaging approaches alone are not sufficient to diagnose Parkinson's disease because they do not reliably distinguish Parkinson's disease from other parkinsonian syndromes associated with nigral degeneration, such as atypical parkinsonism. Standard MRI has a marginal role in Parkinson's disease diagnosis, but high and ultra-high-field (7 Tesla) MRI combined with advanced techniques, such as diffusion tensor imaging, are being explored for early diagnosis of Parkinson's disease.[132–134]

Proposed pathological markers are being tested on the basis of earlier findings of α-synuclein within the peripheral nervous system. Much of the focus has been on the enteric nervous system.[135] Three cases of positive staining for α-synuclein in colonic biopsy tissue prior to the onset of Parkinson's disease have been reported.[136] However, positive α-synuclein staining has also been noted in the colon of control populations,[137,138] and despite earlier promise, a recent study[139] has provided strong evidence that colonic deposition of α-synuclein is not a useful diagnostic test for Parkinson's disease. Phosphorylated α-synuclein in both somatic and autonomic nerve fibres has been identified in skin biopsies from patients with symptomatic Parkinson's disease,[140] which suggests that this approach could help to assess individuals in the prodromal stages. The concentration of α-synuclein, DJ-1, tau, and β-amyloid$_{1–42}$, as well as activity of β-glucocerebrosidase in cerebrospinal fluid are being tested as potential biochemical biomarkers of early Parkinson's disease.[141,142] Low molecular weight molecules, including blood uric acid, are being investigated.[32] Biomarkers in saliva or urine are also being studied, but good candidates have still not been identified.[143,144] A single biochemical marker in one of these biological fluids is unlikely to be sufficient for early diagnosis of Parkinson's disease, but panels of these markers might be useful.[145,146]

For people with family members with a known monogenic form of Parkinson's disease, genetic testing can assist in diagnosis. However, most of the monogenic causes of Parkinson's disease are incompletely penetrant, so positive genetic testing in an asymptomatic individual does not provide a definitive diagnosis. As genetic studies become cheaper, specific genetic signatures will likely be explored as genetic biomarkers for diagnosis of Parkinson's disease. A single measure might not suffice for an accurate and early diagnosis of such a complex disease. Instead, a combination of imaging, biochemical, and genetic biomarkers might be required.

### *Panel 5:* Dopaminergic imaging as a biomarker in Parkinson's disease

**Methods**

Positron emission tomography (PET) or single photon emission computed tomography (SPECT) are methods to assess the density of presynaptic dopaminergic terminals within the striatum (as a surrogate of substantia nigra pars compacta [SNpc] neurodegeneration) with the following measures:

- Activity of aromatic aminoacid decarboxylase with $^{18}$F-dopa PET
- Availability of presynaptic dopamine transporters with $^{123}$I-2β-carbomethoxy-3β-(4-iodophenyl)tropane ($^{123}$I-CIT) SPECT or $^{123}$I-2β-carbomethoxy-3β-(4-iodophenyl)-N-(3-fluoropropyl)nortropane ($^{123}$I-FP-CIT) SPECT
- Amount of vesicular monoamine transporter (VMAT2) with $^{11}$C-dihydrotetrabenazine ($^{11}$C-DTBZ) PET or $^{18}$F-dihydrotetrabenazine ($^{18}$F-DTBZ) PET

**Advantages**

Non-invasive in-vivo methods that are useful for the differentiation of PD from disorders without presynaptic dopaminergic terminal deficiency (eg, essential tremor, functional or psychogenic movement disorder, dystonic tremor, vascular parkinsonism, normal pressure hydrocephalus, dopa-responsive dystonia, Alzheimer's disease)

**Disadvantages**

Cannot distinguish Parkinson's disease from other disorders associated with SNpc neurodegeneration (eg, progressive supranuclear palsy, multiple system atrophy, corticobasal degeneration, dementia with Lewy bodies)

**Scan Without Evidence of Dopaminergic Deficit (SWEDD)**

*Definition*

Patients with SWEDD are those with newly diagnosed, untreated Parkinson's disease who were enrolled in clinical trials (CALM-PD,[123] ELLDOPA,[124] PRECEPT,[125] REAL-PET[126]) and had normal $^{18}$F-dopa PET or SPECT imaging

*Significance*

Longitudinal follow-up of SWEDD patients suggests that the majority of these people do not have Parkinson's disease but instead were accurately assessed by PET or SPECT to have a disorder without presynaptic dopaminergic terminal deficiency

| | Treatment of motor symptoms | | Treatment of motor complications | |
|---|---|---|---|---|
| | Monotherapy | Adjunct to levodopa | Fluctuations | Dyskinesia* |
| **Levodopa** | | | | |
| Levodopa-carbidopa | + | .. | + | – |
| Levodopa-benserazide | + | .. | + | – |
| **Dopamine agonists (non-ergot)** | | | | |
| Apomorphine | – | + | + | – |
| Piribedil | + | + | – | – |
| Pramipexole | + | + | + | – |
| Ropinirole | + | + | + | – |
| Rotigotine | + | + | + | – |
| **Dopamine agonists (ergot)** | | | | |
| Bromocriptine | + | + | + | – |
| Cabergoline | + | + | + | – |
| **Monoamine oxidase type B inhibitors** | | | | |
| Rasagiline | + | + | + | – |
| Selegiline | + | –§ | –§ | – |
| **Catechol-O-methyltransferase inhibitors** | | | | |
| Entacapone | .. | + | + | – |
| Tolcapone | .. | + | + | – |
| **Others** | | | | |
| Amantadine | + | + | – | + |
| Anticholinergics† | +‡ | +‡ | – | – |
| Clozapine | +‡ | +‡ | – | + |

+ indicates efficacious or likely efficacious. – indicates non-efficacious or insufficient evidence. .. indicates not applicable. *Responses to peak dose dyskinesia (diphasic dyskinesia might respond to drugs used for motor fluctuations, particularly dopamine agonists). †Includes benztropine, ethopropazine, trihexyphenidyl, and others. ‡For treatment of tremor. §There is insufficient evidence but, in practice, selegiline is used and can be effective.

*Table 2:* **Pharmacological treatments for motor symptoms and complications**

## Treatment

### Neuroprotection and disease modification

Available therapies for Parkinson's disease only treat symptoms of the disease. A major goal of Parkinson's disease research is the development of disease-modifying drugs that slow or stop the underlying neurodegenerative process. In hindsight, earlier expectations that a single agent could be capable of achieving this might have been naive. The underlying causes of the disease are heterogeneous, and multiple cellular processes are variably involved in neurodegeneration in Parkinson's disease (figure 3). Thus, a more effective strategy might be to target selected dysfunctional molecular pathways in specific patients and to target several molecular pathways with several drugs. Potential pharmacological targets for disease modification in Parkinson's disease include neuroinflammation, mitochondrial dysfunction and oxidative stress, calcium channel activity, LRRK2 kinase activity, as well as α-synuclein accumulation, aggregation, and cell-to-cell transmission (including immunotherapy techniques).[147,148] Potential surgical interventions include targeted gene therapy,[149,150] cell transplantation,[151,152] and deep brain stimulation of subthalamic nuclei.[153]

### Initiation of symptomatic therapy

Drugs that enhance intracerebral dopamine concentrations or stimulate dopamine receptors remain the mainstay of treatment for motor symptoms. These drugs include levodopa, dopamine agonists, monoamine oxidase type B inhibitors, and, less commonly, amantadine (table 2).[154,155] Since none of these drugs have proven to be neuroprotective or disease-modifying, therapy does not need to be started at time of diagnosis for all patients. However, there is little justification for delay. Treatment should be initiated when symptoms cause the patient disability or discomfort, with the goal of improving function and quality of life. Bradykinesia and rigidity reliably respond to dopaminergic treatments early in the disease. Monoamine oxidase type B inhibitors are at best only moderately beneficial. Dopamine agonists or levodopa are needed for more severe symptoms and progressive disability. In contrast to bradykinesia and rigidity, tremor is inconsistently responsive to dopamine replacement therapy, especially in lower doses. Anticholinergic drugs, such as trihexyphenidyl, or clozapine can be effective for tremor (table 2).

Drug-induced adverse reactions need to be regarded when deciding on the initial treatment for Parkinson's disease. Dopamine agonists and levodopa are both associated with nausea, daytime somnolence, and oedema, but these side-effects tend to be more frequent with dopamine agonists. Impulse control disorders, including pathological gambling, hypersexuality, binge eating, and compulsive spending, occur much more often with dopamine agonists. Dopamine agonists should therefore be avoided in patients with a history of addiction, obsessive-compulsive disorder, or impulsive personality because these patients are at high risk for developing impulse control disorders. Dopamine agonists are also more commonly associated with hallucinations and are therefore usually not prescribed for elderly patients, especially those with cognitive impairment. Levodopa provides the greatest symptomatic benefit, but long-term use is associated with motor complications (dyskinesia and motor fluctuations; panel 3). To delay the onset of these complications, a levodopa-sparing initial therapy with a monoamine oxidase type B inhibitor or dopamine agonist can be considered. However, the findings of an open-label randomised trial[156] of treatment of newly diagnosed patients with Parkinson's disease showed no major long-term benefit of a levodopa-sparing strategy, although younger onset patients (age <60 years), who are at greater risk of developing dyskinesia than older onset patients, were not well represented in this study.[157]

### Management of complications of long-term therapy

Complications of long-term dopaminergic treatment are features of advanced disease. Complications include motor and non-motor fluctuations, dyskinesia, and psychosis, which can limit function and reduce quality of life (panel 3). Fluctuations and dyskinesia are believed to

| | Drug class | Drug name |
|---|---|---|
| **Cognitive impairment** | | |
| Dementia | Acetylcholinesterase inhibitor | Rivastigmine |
| **Psychiatric symptoms** | | |
| Depression | Dopamine agonist | Pramipexole |
| | Serotonin reuptake inhibitor | Citalopram, escitalopram, fluoxetine, paroxetine, sertraline |
| | Serotonin and norepinephrine reuptake inhibitor | Venlafaxine extended release |
| | Tricyclic antidepressant | Desipramine, nortriptyline |
| Psychosis | Atypical antipsychotic | Clozapine, quetiapine |
| | Acetylcholinesterase inhibitor | Rivastigmine |
| **Sleep disorders** | | |
| REM sleep behaviour disorder | Benzodiazepine | Clonazepam |
| | Hormone | Melatonin |
| **Autonomic dysfunction** | | |
| Constipation | Osmotic laxative | Polyethylene glycol |
| | Chloride channel activator | Lubiprostone |
| Gastrointestinal motility | Peripheral dopamine antagonist | Domperidone |
| Orthostatic hypotension | Peripheral dopamine antagonist | Domperidone |
| | Mineralocorticoid | Fludrocortisone |
| | Vasopressor | Midodrine |
| | Acetylcholinesterase inhibitor | Pyridostigmine |
| | Norepinephrine prodrug | Droxidopa |
| Sialorrhoea | Anticholinergic | Atropine drops, glycopyrrolate |
| | Neurotoxin | Botulinum toxin A, botulinum toxin B |
| **Other** | | |
| Fatigue | Stimulant | Methylphenidate, modafinil |

REM=rapid eye movement.

***Table 3:*** **Pharmacological treatments for non-motor symptoms**

result, in part, from pulsatile stimulation of striatal dopamine receptors, which occurs later in the disease when intracerebral levodopa concentrations become more closely linked to plasma levodopa concentrations. Available pharmacological strategies to reduce the wide fluctuations in dopamine concentrations include the addition of a dopamine agonist, monoamine oxidase type B inhibitor, or catechol-O-methyltransferase inhibitor (table 2).[154] Long-acting levodopa formulations that maintain stable dopamine concentrations are under development. A novel extended-release oral levodopa, IPX066 (Rytary, Impax Pharmaceuticals, Hayward, CA, USA), has been shown to reduce off-time in advanced Parkinson's disease (panel 3) and recently received FDA approval for use in Parkinson's disease.[158] An alternate approach to achieve constant plasma levodopa concentrations is direct delivery of a stable concentrated levodopa-carbidopa gel (Duodopa, Abbott Laboratories, Chicago, IL, USA) into the duodenum via a percutaneous endogastric gastrostomy tube attached to a portable infusion pump. Results from a double-blind randomised trial[159] showed that this approach in advanced Parkinson's disease shortened the off-time and lengthened the on-time (panel 3) without troublesome dyskinesia in advanced Parkinson's disease. Subcutaneous infusion of the potent dopamine agonist, apomorphine, can also have an important effect on severe motor fluctuations. Non-dopaminergic treatments can be useful for motor complications. For example, amantadine and clozapine have effects on multiple neurotransmitter systems and can be effective in treating dyskinesia (table 2).[154] Drugs with serotonergic or nicotinic properties and drugs that inhibit glutamatergic signalling or adenosine A2A receptors are being tested as potential treatments for motor complications.[160]

Psychosis in Parkinson's disease is most effectively treated with clozapine (table 3), but regular monitoring of haematological status is necessary because clozapine can be associated with potentially life-threatening agranulocytosis, an idiosyncratic adverse drug reaction. However, with periodic monitoring of haematological status, the occurrence of agranulocytosis is very rare, with a risk as low as 0·38%.[161] Quetiapine is less effective, but monitoring of haematological status is not needed. Other neuroleptics should be avoided because they frequently worsen parkinsonism. Cholinesterase inhibitors, such as rivastigmine, might reduce visual hallucinations and delusions in patients with Parkinson's disease who have dementia.[162] The selective serotonin 5-HT2A inverse agonist, pimavanserin (Nuplazid, Acadia Pharmaceuticals, San Diego, CA, USA), has been shown to reduce positive psychotic symptoms without worsening motor function and is being considered for FDA approval for this indication.[163] Unlike clozapine, no substantial safety concerns exist for pimavanserin, and monitoring of haematological status is not needed.

### Management of non-motor features

Unlike most motor features of Parkinson's disease, non-motor symptoms often have limited treatment options or response. However, a variety of treatments are available, and for some patients, these treatments can effectively control or improve disability from non-motor symptoms, such as psychiatric symptoms, sleep disorders, autonomic dysfunction, and fatigue (table 3).[155,164]

Depression associated with Parkinson's disease is typically treated with antidepressants. Evidence supports the efficacy of tricyclic antidepressants, specifically desipramine and nortriptyline, for treatment of Parkinson's disease-related depression. In practice, selective serotonin reuptake inhibitors, including citalopram, escitalopram, fluoxetine, paroxetine, and sertraline, are the most commonly used medications to treat depression in Parkinson's disease, although there is no evidence to support the use of a specific selective serotonin reuptake inhibitor. The extended release formulation of venlafaxine, a serotonin and norepinephrine reuptake inhibitor,[165] and the dopamine agonist pramipexole[166] have been shown to be effective in treating depression in Parkinson's disease patients. Electroconvulsive therapy and repetitive transcranial magnetic stimulation are non-pharmacological interventions used for treatment of depression in patients without Parkinson's disease, but there are no randomised controlled trials to support their use in Parkinson's disease.

### Management of late-stage disease

The motor and non-motor symptoms of late-stage Parkinson's disease typically respond poorly to levodopa. Abnormalities in non-dopaminergic neurotransmitters, including acetylcholine, glutamate, norepinephrine, and serotonin, contribute to the symptoms of Parkinson's disease. Expression of these levodopa-resistant symptoms probably involves some of these other neurotransmitter systems.[160] In particular, reduction in acetylcholine due to degeneration of cholinergic structures might be associated with dementia as well as gait dysfunction and falls in late-stage Parkinson's disease.[167] Accordingly, the cholinesterase inhibitor rivastigmine is efficacious for the treatment of dementia in Parkinson's disease (table 3).[168] Variable results have come from studies using donepezil, another cholinesterase inhibitor. Findings from a small trial[169] of donepezil for treatment of falls support the hypothesis that a rise in cholinergic tone might improve postural stability in Parkinson's disease. The effects of rivastigmine on gait, balance, and falls are being investigated.[170]

### Surgical treatment

Deep brain stimulation is a well established treatment for the motor symptoms of Parkinson's disease. Findings of several clinical trials[171] have shown that deep brain stimulation of either the subthalamic nucleus or globus pallidus internus is effective in moderate-to-severe Parkinson's disease. Thalamic deep brain stimulation is also an option for treatment of tremor. Surgical treatment is an option when the parkinsonian motor features continue to respond to levodopa but motor fluctuations and dyskinesia become disabling. Specific non-motor features, including non-motor fluctuations, sleep-related symptoms, and behavioural abnormalities, can improve with deep brain stimulation, although further study is needed to establish the contributions of the stimulation versus the effect of improvement in motor function and reduction in dopaminergic drugs that accompany deep brain stimulation.[172] The average time to surgical treatment is about 10–13 years after diagnosis of Parkinson's disease. Findings of a multicentre randomised trial, the EARLYSTIM trial,[173] showed that deep brain stimulation of the subthalamic nucleus early in the disease course (mean disease duration 7·5 years, with motor fluctuations for <3 years) improved patient quality of life and several secondary outcome measures more than best medical therapy. The results of this trial will probably change the current practice of delaying surgical interventions until later in the disease course.

## Conclusion

Parkinson's disease is complex in its clinical expression and treatment. Lessons from epidemiology, pathology, and genetics have directed investigations of the pathogenesis of Parkinson's disease. Further understanding of the molecular and cellular pathways involved in the neurodegenerative process are expected to yield useful biomarkers for the diagnosis of early prodromal disease, although a single biomarker is likely to be insufficient. The ultimate deliverable from ongoing research is the development of disease-modifying therapies, which we anticipate will need to be combined, and possibly individualised, to be effective.

#### Contributors

LVK planned the outline of the manuscript, performed the literature search, drafted the text, designed the tables and figures, and approved the manuscript. AEL planned the outline of the manuscript, contributed to and edited the text, contributed to the tables and figures, and approved the manuscript. AEL had final responsibility for the decision to submit this article for publication.

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