REVIEW ARTICLE

Parkinson disease

R. Balestrino[a] and A.H.V. Schapira[b]

[a]*Department of Neuroscience, University of Turin, Turin, Italy; and* [b]*Department of Clinical and Movement Neurosciences, UCL Queen Square Institute of Neurology, London, UK*

Keywords:
clinical, genetics, movement disorders, neurodegeneration, Parkinson disease, pathophysiology, treatment

Received 2 July 2019
Accepted 14 October 2019

European Journal of Neurology 2020, **27:** 27–42

doi:10.1111/ene.14108

Parkinson disease (PD) is the most common neurodegenerative movement disorder. In Europe, prevalence and incidence rates for PD are estimated at approximately 108–257/100 000 and 11–19/100 000 per year, respectively. Risk factors include age, male gender and some environmental factors. The aetiology of the disease in most patients is unknown, but different genetic causes have been identified. Although familial forms of PD account for only 5%–15% of cases, studies on these families provided interesting insight on the genetics and the pathogenesis of the disease allowing the identification of genes implicated in its pathogenesis and offering critical insights into the mechanisms of disease. The cardinal motor symptoms of PD are tremor, rigidity, bradykinesia/akinesia and postural instability, but the clinical picture includes other motor and non-motor symptoms. Its diagnosis is principally clinical, although specific investigations can help the differential diagnosis from other forms of parkinsonism. Pathologically, PD is characterized by the loss of dopaminergic neurons in the pars compacta of the substantia nigra and by accumulation of misfolded α-synuclein, which is found in intra-cytoplasmic inclusions called Lewy bodies. Currently available treatments offer good control of motor symptoms but do not modify the evolution of the disease. This article is intended to provide a comprehensive, general and practical review of PD for the general neurologist.

Introduction

Parkinson disease (PD) is the most common neurodegenerative movement disorder [1]. Its cardinal motor symptoms are tremor, rigidity, bradykinesia/akinesia and postural instability, but the clinical picture includes other motor and non-motor symptoms (NMSs). The diagnosis is principally clinical, although specific investigations can help the differential diagnosis from other forms of parkinsonism.

The pathological hallmarks of PD are loss of dopaminergic neurons in the substantia nigra (SN) pars compacta (SNpc) and accumulation of misfolded α-synuclein, which is found in intra-cytoplasmic inclusions called Lewy bodies (LBs). When patients are first diagnosed, a substantial proportion of dopaminergic neurons in the SNpc has already been lost, and neurodegeneration has spread to other central nervous system regions. The aetiology of the disease in most patients is unknown, but different genetic causes have been identified in approximately 5%–10% of cases. Current treatment of PD is based on the replacement of dopamine, although alternative approaches such as deep brain stimulation (DBS) are suitable for later-stage disease. Currently available treatments offer good control of motor symptoms but do not halt the progression of neurodegeneration, the evolution of the disease and the increasing disability. This article is intended to provide a comprehensive, general and practical review of PD for the general neurologist.

Correspondence: Anthony H.V. Schapira, Department of Clinical and Movement Neurosciences, UCL, Queen Square Institute of Neurology, UCL Royal Free Campus, Rowland Hill Street, London NW3 2PF, UK. (tel: +44 020 7830 2012; fax: +44 020 7472 6829; e-mail: a.schapira@ucl.ac.uk).

Epidemiology and risk factors

In industrialized countries the estimated prevalence of PD is 0.3% in the general population, 1.0% in people older than 60 years and 3.0% in people older than

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80 years; incidence rates of PD are estimated to range between 8 and 18 per 100 000 person-years [2]. In Europe, estimated prevalence and incidence rates for PD range between 65 and 12,500 per 100 000 and between 5 and 346 per 100 000 person-years respectively [3]. Age is the most important risk factor for the disease [2]; male gender confers a moderate risk [4]. Some environmental factors have been linked to the risk of PD, including certain pesticides and rural-living [5]. It is of interest that some substances such as 1-methyl-4-phenyl tetrahydropyridine (MPTP) [6] and annonacin can cause nigrostriatal cell death and a form of atypical parkinsonism [7,8]. Exposure to toxic levels of manganese, trichloroethylene, carbon monoxide and other agents can likewise sometimes lead to a type of parkinsonism, but with clinical and pathological features distinct from PD. β2-adrenoreceptor antagonists have been linked to an increased risk for PD, whilst in contrast β2-adrenoreceptor agonists seem to reduce it [9]. Conversely, there is an inverse association between the risk of PD and cigarette smoking [5], coffee drinking [10] calcium channel blockers [11] and statins [12], whilst contrasting evidence is available regarding the use of nonsteroidal anti-inflammatory drugs [13,14] and uric acid levels or gout [15,16].

Family history is a risk factor for PD and the relative risk in first-degree relatives of PD cases increases by approximately two- to three-fold compared to controls [17]. Familial forms of PD account for 5%–15% of cases. The most important genes linked to PD are summarized in Table 1.

Pathophysiology of PD

The main pathological features of PD are the loss of dopaminergic neurons with subsequent depigmentation of the SNpc and the presence of LBs. LBs are intraneuronal, round, eosinophilic inclusions with a hyaline core and a pale peripheral halo that are composed of more than 90 proteins [18]; their main components are α-synuclein and ubiquitin [19]. α-synuclein has the propensity to misfold, become insoluble and form β-sheet-rich amyloid aggregates that accumulate and form intracellular inclusions. The intermediates in this aggregation process are

Table 1 Summary of genes associated with Parkinson disease (PD)

Gene	Locus name	Protein name	Chromosome	Inheritance	Clinics	Frequency in PD	Protein function
SNCA	PARK1/4	α-synuclein	4q21–23	AD	EOPD	<1%	Synaptic
PRKN	PARK2	Parkin	6q25–27	AR	EOPD, slow progression, + dystonia	1%–5% (up to 44% in EOPD)	Ubiquitin-ligase
UCHL1	PARK5	UCHL-1	4p14	AD	EOPD, LOPD	<1%	Uncertain
PINK1	PARK6	PTEN-induced putative kinase I	1p35–37	AR	EOPD, slow progression	2%–5%	Mitochondrial kinase
DJ-1	PARK7	Protein DJ-1	1p36	AR	EOPD, slow progression	1%	Cellular sensor of oxidative stress
LRRK2	PARK8	Leucine-rich repeat serine/ threonine-protein kinase 2	12p11–q13	AD	LOPD, slow progression	1%–5% (up to 40% in North African Berber Arab patients)	Multiple functions domain dependent
ATP13A2	PARK9	ATPase type 13A2	1p36	AR	Atypical parkinsonism, Kufor Rakeb syndrome	<1%	Lysosomal protein
PLA2G6	PARK14	A2 phospholipase	22q13	AR	EOPD, dystonia-parkinsonism	<1%	Unknown
FOXB7	PARK15	F-box protein 7	22q12–13	AR	EOPD, atypical parkinsonism	<1%	Unknown
VPS35	PARK17	Vacuolar protein sorting-associated protein 35	16q11	AD or risk	LOPD	<1%	Unknown
GBA					Glucocerebrosidase	1q21	Risk factor
Earlier onset +	dementia	5%–25% (10%–30% in Ashkenazi Jewish patients)	Lysosomal protein				

AD, autosomal dominant; AR, autosomal recessive; EOPD, early onset PD; LOPD, late onset PD.

the toxic oligomeric and proto-fibrillar forms that impair mitochondrial [20], lysosomal and proteasomal [21] function, damage biological membranes [22] and the cytoskeleton [23], alter synaptic function [24] and cause neuronal degeneration. It has been estimated that at the time of the diagnosis up to 60% of dopaminergic neurons have already been lost [25].

A sequential model of the formation of LBs and deposition of α-synuclein, starting in the dorsal motor nucleus of the glossopharyngeal and vagal nerves and anterior olfactory nucleus, with progressive spread to the brain stem and, in later stages, to the mesocortex and allocortex and finally to the neocortex, has been proposed [26] (Fig. 1). α-synuclein tends to spread through neurons in a prion-like manner, and this mechanism of transmission probably underlies the progression of pathological alterations previously described [27]. Furthermore, some data suggest that α-synuclein aggregation may begin in the autonomic plexi of the gut and spread rostrally [28] and that this could be influenced by the gut microbiome [29].

Mechanisms of disease and genetics

SNCA, the gene encoding for α-synuclein, was the first gene linked to PD, and A53T was the first pathogenic *SNCA* mutation identified [30] This mutation, as other pathogenic mutations, confers to α-synuclein a greater tendency to misfold and aggregate than the wild-type; other pathogenic mutations of *SNCA* affect the quantity of α-synuclein (either through duplications or triplications, either altering its expression or its clearance), and alter its post-transcriptional modifications, and/or its interaction with other cellular organelles and transport systems. Moreover, current evidence has highlighted the role of α-synuclein in activating immunological response, and it has been demonstrated that activated microglial cells directly engulf α-synuclein in an attempt to clear it [31]. Interestingly, upregulation of the expression of α-synuclein has also been found in patients with idiopathic PD [32].

Another key mechanism of disease is impairment of mitochondrial function [33]. Different genes implicated in familial forms of PD regulate mitochondrial functions. PINK1 [34] and Parkin [35] interplay in a mitochondria quality-control pathway: PINK1 is a serine/threonine kinase, which 'marks' damaged mitochondria and activates the mitophagy pathway through the recruitment of Parkin, an E3 ubiquitin ligase. DJ-1 [36] plays a crucial role in regulating calcium flux in the mitochondrion, protecting the cell from oxidative stress produced by the pace-making activity of dopaminergic neurons and dopamine toxicity. There are reports of mitochondrial DNA mutations, probably of somatic origin, in the SNpc of PD brains [37].

An increasing body of evidence links PD to dysfunction in the cellular clearance pathways, and several genes linked to autophagy have been associated with PD [38]. Mutant LRRK2 [39] interferes with autophagy and has been reported to slow α-synuclein degradation, contributing to its accumulation [40]. *ATP132A* mutations determine lysosomal dysfunction [41] and cause a young-onset parkinsonism (Kufor Rakeb syndrome), whilst its expression is upregulated in surviving dopaminergic neurons in idiopathic PD, suggesting its neuroprotective role [42].

Mutations of *GBA1*, which encodes for glucocerebrosidase (GCase), a lysosomal enzyme that metabolizes glucosylceramide and whose defects cause Gaucher disease, constitute the most important genetic risk factor for PD currently known. *GBA1* mutations are highly prevalent amongst PD patients, with an odds ratio of 5.43; between 5% and 25% of PD patients carry *GBA1* mutations. The contribution of GBA to PD pathogenesis is complex, and there are interactions with different pathways implicated in PD pathogenesis: a reciprocal relationship with α-synuclein accumulation, endoplasmic reticulum stress and mitochondrial dysfunction. GBA related PD is clinically undistinguishable from sporadic PD, although patients generally show earlier onset, more rapid deterioration (depending on the mutation) and a higher risk of cognitive impairment. See [43] for a review.

Recently, nine rare *LRP10* variants have been associated with familial PD, PD dementia and dementia with LBs (DLB) [44]. LRP10 is a protein that shuttles between the trans-Golgi network, endosomes and plasma membrane. Other proteins implicated in this network, including VPS35 and GGA1, have been previously linked to PD. Further research is needed to clarify the pathogenetic role of alterations in these pathways in PD and other neurodegenerative disorders with LB pathology [45].

Why dopaminergic neurons of the SNpc are particularly susceptible to neurodegeneration remains unknown; it has been proposed that the autonomous pace-making nature of SNpc dopaminergic neurons and calcium homeostasis play an important role [46].

Recently, the role of the microbiome in the pathogenesis of PD and other neurodegenerative disease has attracted increasing interest. Pathogenetic mechanisms include alteration of dopamine synthesis and metabolism, immune system dysregulation and inflammation, and changes in the permeability of enteral mucosa [47].

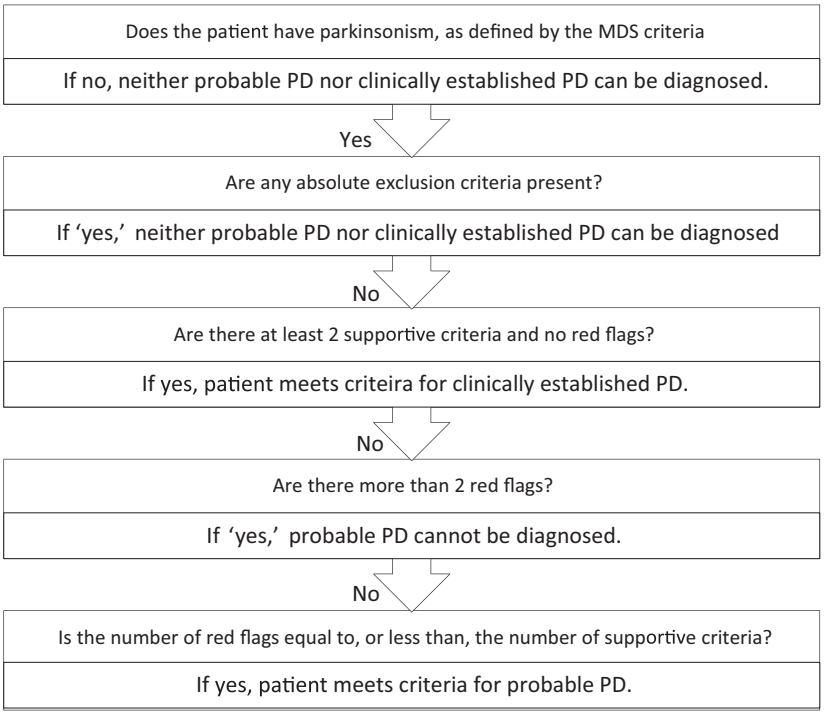

Figure 1 Diagnostic criteria application, from [58]

Clinical features

Parkinson disease comprises a range of motor and non-motor features (Table 2), the expression of which may vary to some degree between patients; however, all patients must exhibit the core clinical features and respond to dopaminergic therapy to satisfy the criteria for the diagnosis of PD [48]. The cardinal motor symptoms include tremor, bradykinesia/hypokinesia/akinesia, rigidity – which are usually asymmetric – and postural instability; other motor features are postural abnormalities (camptocormia and Pisa syndrome), gait disturbances and 'freezing', micrography, disturbances of speech, hypomimia, and alteration of blinking and eye movements, amongst others. The responsiveness of motor symptoms to levodopa administration is an important and diagnostic feature of PD.

The clinical picture between PD patients can be highly heterogeneous, allowing the definition of different motor subtypes: 'tremor dominant', 'postural instability and gait difficulty' (PIGD) or 'indeterminate' [49,50]. The interest in identifying/defining PD subtypes is based on their possible association with aetiological or prognostic aspects and with response to treatment: for example, tremor-dominant PD has been associated with a slower progression and less disability compared to PIGD [51]. Even if PD has been historically defined as a movement disorder, NMSs are an important aspect of the clinical picture. NMSs range from dysphagia and sialorrhoea to autonomic, gastrointestinal, sleep, sensorial, cognitive and neuropsychiatric disturbances. NMSs tend to be under-reported by patients and under-investigated by physicians; however, if properly assessed, they are reported by the majority of patients and have a major impact on health-related quality of life (HRQoL) and

Table 2 Motor and non-motor symptoms of Parkinson disease (PD)

Motor symptoms	Non-motor symptoms
Tremor	Hyposmia
Rigidity	Psychiatric symptoms: depression, anxiety, apathy hallucinations, psychosis
Bradykynesia/akinesia/hypokinesia	Dementia/cognitive impairment
Postural instability	Sensory symptoms
Postural abnormalities (camptocormia, Pisa syndrome)	Genitourinary symptoms: urinary frequency, urgency, reduced libido, sexual dysfunction
Gait disturbances (freezing of gait, festination, start/target/obstacle hesitation)	Gastrointestinal symptoms: constipation, delayed/reduced stomach emptying
Alterations in blinking/eye movements	Dysphagia, sialorrhoea, dysarthria, hypophonia
Hypomimia	Disturbances of sleep and wakefulness
Micrographia	Cardiovascular symptoms: blood pression variations (postural, postprandial), dysrhythmias

disability [52–54]. Some other symptoms – referred to as 'prodromal/premotor symptoms' – might arise even 10 years before the diagnosis and the emergence of motor symptoms: hyposmia, depression, constipation and rapid eye movement sleep behaviour disorder (RBD) are the most recognized, but they can include visual changes, anxiety and other autonomic disturbances [55]. The prodromal phase of PD represents a unique opportunity to identify those at high risk of developing PD and before the occurrence of massive neurodegeneration, providing interesting insight on mechanisms of the disease and its progression, and a promising therapeutic window for neuroprotective treatments; therefore, efforts have been made to improve the recognition of this phase. Large population studies such as the PRIPS (Prospective Evaluation of Risk Factors for Idiopathic Parkinson's Syndrome), PARS (Parkinson At-Risk Syndrome Study), the TREND (Tubinger Evaluation of Risk Factors for Early Detection of Neurodegeneration) and the Rotterdam Study have helped to identify prodromal markers of PD, and studies in high risk groups (such as patients with RBD or genetic predisposition, e.g. carriers of GBA or LRKK2 mutations) have enabled the further refinement of clinical features during the prodromal phase (for a detailed review see [56]). Online-based screening studies, such as the PREDICT-PD in the general population and the RAPSODI in GBA mutation carriers, are currently ongoing. Recently, the diagnostic criteria for the prodromal phase of PD have been updated, and a web-based prodromal PD risk calculator that allows the calculation of probabilities of prodromal PD for individuals is now available but should be used with caution and only in research settings [57].

Diagnosis and differential diagnosis

The diagnosis of PD is essentially clinical. The diagnostic criteria for PD have recently been updated by the Movement Disorders Society [58] (Table 3). The main differential diagnoses are summarized in Table 4.

Secondary parkinsonism

Parkinsonism can be secondary to lesions of the basal ganglia of different aetiologies – such as ischaemic, neoplastic or infective. In these cases, an abrupt onset and the coexistence of other symptoms should suggest a diagnosis other than PD. Exposure to toxins (carbon monoxide, manganese) or drugs such as dopamine-blocking agents (anti-psychotics but also metoclopramide), tetrabenazine, calcium channel blockers, amiodarone and lithium can cause parkinsonism; drug-induced parkinsonism (DIP) is the second most common cause of parkinsonism after PD. Accurate diagnosis is crucial for best management and appropriate prognosis. Motor features that can aid the distinction from PD are symmetrical symptoms, oro-mandibular dyskinesias and no or limited response to levodopa; however, motor features of DIP can resemble PD. Hyposmia seems to be the most reliable NMS to differentiate DIP and PD, although confounding factors (age, smoking and cognitive impairment) can complicate its assessment. Withdrawal of the causative drug for 6 months should lead to improvements of symptoms; however, this is not always possible nor effective [59].

Essential tremor (ET)

The main clinical feature of ET is a postural and/or action tremor at 5–12 Hz frequency with symmetrical presentation that involves more often the hands, head ('yes–yes' or 'no–no') and/or voice. Rest tremor can be present, but in contrast to PD it increases during movement. Patients show tremulous handwriting rather than micrography as in PD. In addition to tremor, mild cerebellar signs, cognitive impairment, psychiatric symptoms and sensory disturbances have occasionally been described. The disease is usually slowly progressive; alcohol, propranolol and primidone can mitigate its symptoms, whilst they are ineffective in PD. ET shows an autosomal dominant inheritance, and patients often report a positive familiar history [60]. Some overlapping features between PD and ET have been described and misdiagnosis is relatively common [61].

Atypical parkinsonisms

Multiple system atrophy (MSA) is a neurodegenerative disorder characterized by autonomic failure and parkinsonism and/or cerebellar signs. Motor signs of MSA include an akinetic-rigid parkinsonism, with – differently from PD – a symmetric distribution and no or minimal response to levodopa; pyramidal signs (extensor plantar responses and hyperreflexia), cerebellar signs (dysarthria, dysmetria, nystagmus, ataxia) and oculomotor dysfunction (impaired smooth pursuit movements, dysmetric saccades, suppression of the vestibulo-ocular reflex) can occur. Classic resting tremor is rare; patients rather can show a jerky poly-mini myoclonus. Neck (anterocollis or laterocollis) or orofacial dystonia can occur, especially in response to levodopa administration. Dysautonomic features are common from early stages of the disease; they include uro-genital,

Table 3 New diagnostic criteria for Parkinson disease (PD), from [58]

Movement Disorders Society clinical diagnostic criteria for PD
The essential criterion is parkinsonism defined as: bradykinesia in combination with at least 1 of rest tremor or rigidity
Diagnosis of clinically established PD
1) Absence of absolute exclusion criteria
2) At least two supportive criteria, and
3) No red flags
Diagnosis of clinically probable PD
1) Absence of absolute exclusion criteria
2) Presence of red flags counterbalanced by supportive criteria
If one red flag is present, there must also be at least 1 supportive criterion
If two red flags, at least 2 supportive criteria are needed
No more than two red flags are allowed for this category
Supportive criteria
1) Clear and dramatic beneficial response to dopaminergic therapy. During initial treatment, patient returned to normal or near-normal level of function. In the absence of clear documentation of initial response, a dramatic response can be classified as:
a) Marked improvement with dose increases or marked worsening with dose decreases. Mild changes do not qualify. Document this either objectively (>30% in UPDRS III with change in treatment) or subjectively (clearly documented history of marked changes from a reliable patient or caregiver).
b) Unequivocal and marked on/off fluctuations, which must have at some point included predictable end-of-dose wearing-off.
2) Presence of levodopa-induced dyskinesia
3) Rest tremor of a limb, documented on clinical examination (in past, or on current examination)
4) The presence of either olfactory loss or cardiac sympathetic denervation on MIBG scintigraphy
Absolute exclusion criteria
1) Unequivocal cerebellar abnormalities, such as cerebellar gait, limb ataxia or cerebellar oculomotor abnormalities
2) Downward vertical supranuclear gaze palsy, or selective slowing of downward vertical saccades
3) Diagnosis of probable behavioural variant frontotemporal dementia or primary progressive aphasia, defined according to consensus criteria within the first 5 years of disease
4) Parkinsonian features restricted to the lower limbs for more than 3 years
5) Treatment with a dopamine receptor blocker or a dopamine-depleting agent in a dose and time-course consistent with drug-induced parkinsonism
6) Absence of observable response to high-dose levodopa despite at least moderate severity of disease
7) Unequivocal cortical sensory loss, clear limb ideomotor apraxia, or progressive aphasia
8) Normal functional neuroimaging of the presynaptic dopaminergic system
9) Documentation of an alternative condition known to produce parkinsonism and plausibly connected to the patient's symptoms, or the expert evaluating physician, based on the full diagnostic assessment, feels that an alternative syndrome is more likely than PD
Red flags
1) Rapid progression of gait impairment requiring regular use of wheelchair within 5 years of onset
2) A complete absence of progression of motor symptoms or signs over 5 or more years unless stability is related to treatment
3) Early bulbar dysfunction: severe dysphonia or dysarthria (speech unintelligible most of the time) or severe dysphagia (requiring soft food, nasogastric tube or gastrostomy feeding) within first 5 years
4) Inspiratory respiratory dysfunction: either diurnal or nocturnal inspiratory stridor or frequent inspiratory sighs
5) Severe autonomic failure in the first 5 years of disease. This can include orthostatic hypotension or severe urinary retention or urinary incontinence in the first 5 years of disease (excluding long-standing or small amount stress incontinence in women) that is not simply functional incontinence. In men, urinary retention must not be attributable to prostate disease, and must be associated with erectile dysfunction
6) Recurrent (>1/year) falls because of impaired balance within 3 years of onset
7) Disproportionate anterocollis (dystonic) or contractures of hand or feet within the first 10 years
8) Absence of any of the common non-motor features of disease despite 5 years' disease duration. These include sleep dysfunction (sleep-maintenance insomnia, excessive daytime somnolence, symptoms of REM sleep behaviour disorder), autonomic dysfunction (constipation, daytime urinary urgency, symptomatic orthostasis), hyposmia or psychiatric dysfunction (depression, anxiety or hallucinations)
9) Otherwise unexplained pyramidal tract signs, defined as pyramidal weakness or clear pathological hyperreflexia (excluding mild reflex asymmetry and isolated extensor plantar response)
10) Bilateral symmetric parkinsonism. The patient or caregiver reports bilateral symptom onset with no side predominance, and no side predominance is observed on objective examination

MIBG, metaiodobenzylguanidine; REM, rapid eye movement; UPDRS, Unified Parkinson Disease Rating Scale.

Table 4 Differential diagnosis in parkinsonism

Parkinson disease	Secondary parkinsonism	Atypical parkinsonism	Neurodegenerative diseases	Other diseases
Sporadic	Drug induced	Multi-systemic atrophy	Dementia with Lewy bodies	Wilson disease
Familial/genetic	Vascular	Progressive supranuclear palsy	Alzheimer disease with parkinsonism	Huntington disease
	Toxic	Corticobasal syndrome	Prion disease	Kufor Rakeb syndrome
	Neoplastic		Frontotemporal Dementia	SCA3
	Infective			Dopa-responsive dystonia
	Normal pressure hydrocephalus			X-linked parkinsonism dystonia
	Trauma			Neurodegeneration with brain iron accumulation
	Liver failure			Fragile X–associated ataxia-tremor-parkinsonism

cardiovascular (orthostatic hypotension and its manifestations such as syncope and postural dizziness), respiratory (stridor, sleep-related breathing disorders, respiratory insufficiency), gastrointestinal and sudomotor symptoms. Dementia can occur in later stages of the disease. Pathologically, MSA is a synucleinopathy; the neurodegeneration more often affects the striatonigral and/or olivopontocerebellar systems [62,63].

Different variants of progressive supranuclear palsy (PSP) have been recognized. The classic PSP phenotype is known as Richardson syndrome; it usually presents with an axial akinetic-rigid parkinsonism with no or mild response to levodopa, postural abnormalities (head and trunk hyperextension/retrocollis, rather than camptocormia as in PD), gait abnormalities (broad-based gait and freezing), postural instability and falls since an initial stage of the disease (rather than in a later stage as in PD). The typical sign of PSP is the supranuclear palsy of vertical gaze, which is absent in PD; other oculomotor dysfunction signs include slowing of vertical saccadic movements (especially downward) and apraxia of eyelid opening (which cause a compensatory overactivity of the frontalis muscle and lead to a typical 'surprised' expression). The vestibulo-ocular reflex is preserved, given the supranuclear nature of the gaze palsy. Other features include pseudobulbar palsy, subcortical-type dementia, frontal release signs and motor perseveration, which are absent in PD. A characteristic feature of patients with PSP is 'motor recklessness', defined as no caution in walking/standing up/moving despite the lack of balance and frequent falls. Pathologically, PSP is a tauopathy, a disorder associated with abnormal aggregates of tau protein, and its hallmark feature is 'tufted astrocytes'; the neurodegeneration affects subcortical structures, such as the SN, the subthalamic nucleus (STN) and the midbrain [62,63].

The most common motor features of corticobasal degeneration (CBD) are asymmetric rigidity and bradykinesia, which can present -differently from PD- together with dystonia and myoclonus (typically distal and stimulus sensitive). A characteristic sign of CBD is the 'alien limb phenomenon', reported by approximately 50% of patients: the limb may involuntarily assume positions, grab objects or interfere with the actions of the unaffected limbs. Tremor is rare and if present is an action/postural tremor rather than a resting tremor as in PD. CBD is also characterized by cortical features such as dementia (usually affecting frontal and parietal functions), apraxia and cortical sensory loss, which are usually absent in PD. However, the presentation of CBD is highly variable and can overlap with other diseases, and its clinical diagnostic accuracy is estimated to be particularly low (<50%). Pathologically CBD is a tauopathy; its hallmark feature is the presence of 'astrocytic plaques'; the neurodegeneration mainly affects the SN and the frontoparietal cortex [62,63].

Other parkinsonisms

The core clinical features of DLB include cognitive decline with fluctuations in alertness and attention, parkinsonism, visual hallucinations and RBD. Parkinsonism is present in almost 85% of patients; it is usually milder than in other atypical parkinsonisms and PD; axial signs such as postural abnormalities, gait impairment and postural instability are prevalent; tremor is uncommon. Importantly, cognitive impairment begins simultaneously or within 1 year of parkinsonism. Cognitive impairment is characterized by deficits in attention, executive function and visuospatial ability, whilst memory and language are relatively spared. Other clinical features include dysautonomic features, frequent falls, excessive daytime sleepiness, neuroleptic sensitivity, hyposmia and mood disorders. Hallucinations are typically very vivid and detailed. Fluctuations in alertness and attention are very characteristic and help to exclude PD. DLB is a synucleinopathy;

its pathological hallmarks are α-synuclein neuronal inclusions (LBs and Lewy neurites) and neuronal loss. In DLB, there are three variations of α-synuclein pathology: brainstem predominant, limbic (or transitional) and neocortical. There is an overlap with Alzheimer disease pathology [64].

Frontotemporal degeneration (FTD) is the second most common cause of neurodegenerative dementia before age 65 (after Alzheimer disease). Different variants of FTD exist, and they are classified based on clinical features. Parkinsonism is more common in the behavioural variant (bvFTD); the most common motor features are bradykinesia, parkinsonian gait, rigidity, postural instability and resting tremor. Parkinsonism is also common in FTD cases with *C9orf72* mutations, a cause of FTD-amyotrophic lateral sclerosis (FTD-ALS); it is typically symmetrical and rigid-akinetic. The occurrence of early behavioural or cognitive symptoms can aid the differential diagnosis. FTD pathology is complex and is classified based on the predominant protein in pathological inclusions: tau (4R and/or 3R tau), TDP-43 or FET [63,65].

Parkinsonism can occur in other degenerative diseases such as Wilson disease (WD) and Huntington disease (HD).

Wilson disease is a monogenic, autosomal recessive condition. The causative gene, *ATP7B*, encodes a copper-transporting P-type ATPase. WD is characterized by hepatic and/or neurological symptoms. Neurological symptoms in WD typically begin in the second or third decade of life; however, both late onset (>70 years old) and childhood onset have been described. The combination of wing-beating tremor or flapping tremor and dysarthria strongly suggests the diagnosis of WD; other neurological symptoms include parkinsonism, other forms of tremor (an irregular, jerky, dystonic tremor; rest, action or intention tremor), dystonia and orofacial dyskinesias. Pyramidal features, seizures, psychiatric symptoms and abnormal vertical smooth pursuit have also been reported. WD can present with acute liver failure or chronic liver disease, although the absence of liver disease does not exclude WD. The presence of Kayser–Fleischer rings and low serum ceruloplasmin concentrations are sufficient to establish the diagnosis. Accurate diagnosis of WD is critical, given that it is a treatable disorder and that pre-symptomatic treatment is also mandatory in relatives with biochemical or genetic evidence of preclinical WD. Treatment options include copper chelators, zinc salts or both; medical therapy must be lifelong. Introduction of therapy in WD may be associated with an initial worsening of clinical features and requires careful monitoring [66].

Huntington disease is a neurodegenerative disease with autosomal dominant inheritance, caused by an expanded CAG trinucleotide repeat in the gene that encodes the protein huntingtin (*HTT*). The disease is characterized by a combination of motor, cognitive and behavioural features. Motor features in HD include involuntary movements, such as chorea, and impairment of voluntary movements, such as incoordination and bradykinesia. Cognitive impairment in HD is characterized by problems of mental flexibility, attention, planning, cognitive slowing and emotion recognition. Psychiatric features include depression, apathy, irritability, obsessive–compulsive behaviours and psychosis. Juvenile HD, also known as Westphal variant, might mimic PD: behavioural and cognitive disturbances are often the first sign, and the motor picture is characterized by hypokinesia and bradykinesia with dystonic traits; chorea is rare in the first decade and only appears in the second decade; epileptic fits are frequent [67]. The current management of HD is focused on symptoms management, but disease-modifying therapies such as antisense oligonucleotides designed to inhibit HTT messenger RNA are giving promising results in trials [68].

Parkinsonism can also occur in neurodegenerative diseases with brain iron accumulation –such as Hallervorden–Spatz disease – and some forms of spinocerebellar ataxias: in these cases, a positive family history, young age at onset, concurrent clinical features and instrumental findings should lead the neurologist to consider other causes than PD.

Imaging

Although PD is a clinical diagnosis, imaging can aid the differential diagnosis. Magnetic resonance imaging (MRI) is not useful to diagnose PD; its utility relies in excluding ischaemic, inflammatory, infective and neoplastic causes or other forms of parkinsonism.

Typical MRI findings in atypical parkinsonism include the 'hot cross bun sign' in MSA, the 'hummingbird sign' and the 'morning glory sign' in PSP, frontotemporal atrophy in FTD and asymmetric cortical atrophy in CBD; fluorodeoxyglucose positron emission tomography (FDG-PET) can reveal hypometabolism in the same areas affected by the atrophy in CBD and FTD [63].

Dopaminergic imaging using either single-photon emission computed tomography or PET can reveal features implying dopaminergic denervation, displayed as a reduced and asymmetric uptake of striatal dopaminergic biomarkers, especially in the posterior putamen. Dopaminergic imaging is useful to differentiate PD from conditions with no dopaminergic denervation

such as DIP (if there is no underlying degeneration of nigrostriatal structures) or ET [69], but not from other degenerative causes of parkinsonism. Metaiodobenzylguanidine (MIBG) scintigraphy is useful to document cardiac sympathetic denervation, helping to differentiate PD and DLB from MSA and PSP [70].

Ultrasounds can detect abnormal hyperechogenicity of the SN in patients with PD; however, the sensitivity and specificity of this technique for the diagnosis of PD are suboptimal (respectively, 75% and 70% with atypical parkinsonism and 78% and 85% with ET) [71].

Treatment of PD

The treatment of PD is symptomatic and is predominantly focused on the dopaminergic pathway; there are currently no disease-modifying treatments for PD.

Levodopa

Levodopa is the gold standard for the treatment of PD and the most effective drug for motor symptoms [72]. Levodopa crosses the blood–brain barrier and is converted to dopamine in the remaining dopaminergic neurons of the SNpc. Levodopa is usually given in tablet form multiple times per day but can also be given by duodenal infusion in patients with advanced disease. It provides a significant improvement of symptoms, which can be tested in a pharmacological challenge and can be used to aid the diagnosis of PD. Levodopa causes peripheral dopaminergic side effects (nausea and hypotension) that can be avoided by a decarboxylase inhibitor (carbidopa or benserazide); other side effects include sleepiness, confusion, hallucinations and impulse control disorders, e.g. hypersexuality, compulsive shopping, gambling and punding [73]. However, its most important limitation relates to the development of motor complications: fluctuations, dyskinesia, dystonia and wearing-off. Complications are thought to be linked to the discontinuous phasic stimulation of the striatal dopamine receptors, as opposed to the physiological continuous supply of dopamine [74]. The development of motor complications in response to levodopa is related to the severity of dopaminergic neurodegeneration (more severe, greater the risk), the dose of levodopa (>400 mg daily), female sex and low weight (relates to dose/kg) [75]. An extended-release carbidopa-levodopa formulation (IPX066), in order to reduce motor fluctuations, has been developed and recently approved [76]. In advanced PD, when motor complications become disabling and are poorly managed with classical pharmacological therapy, levodopa can be administered directly into the duodenum by pump through a gastrostomy catheter as a levodopa-carbidopa gel; this formulation has been shown to reduce motor fluctuations significantly in advanced PD; potential adverse events of the treatment are related to the surgical procedure and the infusion system itself [77]. Other formulations of levodopa to target motor fluctuations such as continuous subcutaneous infusion, an inhaled formulation, a levodopa prodrug (XP21279) [78] and an extended release levodopa (DM1992) formulation [79] are currently under investigation.

Dopamine agonists

Dopamine agonists directly stimulate the postsynaptic dopamine D1–3 receptors in the striatum without the requirement for further metabolism within the dopaminergic neurons. Dopamine agonists are not as effective in reversing motor symptoms as levodopa but are associated with a lower risk for dyskinesia; they may be used as monotherapy in earlier phases of the disease or in conjunction with levodopa. Side effects are similar to levodopa but also include leg oedema, more impulse control disorders and excessive daytime sleepiness. Ropinirole and pramipexole are administered orally; immediate and extended release formulations are available. Rotigotine is administered as a transdermal patch, once daily. Apomorphine, which has a short duration of activity, can be administered subcutaneously as an injection for acute OFF episodes, or by continuous infusion to reduced motor fluctuations in advanced PD [80]. Other formulations of apomorphine, such as inhaled (VR040) [81] and sublingual (APL-130277) [82] formulations, are currently being tested.

Monoamine oxidase B (MAO-B) inhibitors and safinamide

The therapeutic potential of MAO-B inhibitors relies in their ability to decrease dopamine metabolism and thereby prolong and potentiate dopaminergic stimulation. Rasagiline and selegiline are irreversible inhibitors. In early/mild PD they are used as they offer mild symptomatic improvement with fewer complications than levodopa, whilst in advanced PD they are used in association with other drugs to reduce motor fluctuations and levodopa requirements. In clinical trials, early treatment with an MAO-B inhibitor seemed to delay the motor deterioration and the need for additional dopaminergic therapy; therefore different mechanisms of neuroprotection (prevention of reactive oxygen species production, increase of neurotrophic and anti-apoptotic factors) have been hypothesized; however, these drugs have not been proven to modify

the natural history of PD [83]. Safinamide is a new option for treating motor fluctuations in mid- and late-stage PD; it is a reversible inhibitor of MAO-B, with additional properties including blockade of voltage-dependent sodium channels, modulating calcium channels and inhibiting glutamate release. It has been shown to provide enhanced symptom control of motor function in advanced PD [84]; moreover, an anti-dyskinetic effect of safinamide has been demonstrated in animal models [85].

Catechol-*O*-methyl transferase (COMT) inhibitors

In the presence of a decarboxylase inhibitor, the metabolism of levodopa is performed by COMT enzymes: the inhibition of these enzymes is used in the treatment of PD as an adjunct to levodopa for the amelioration of motor fluctuations, as it increases the half-life of levodopa [86]. Available COMT inhibitors are tolcapone (which has been associated with fatal liver failure and has therefore to be administered with caution), entacapone and opicapone (which has recently been approved in Europe).

Other compounds

The modulation of the cholinergic system is a double target in PD. Anticholinergic drugs (e.g. trihexyphenidyl, benztropine, orphenadrine, biperiden) improve some motor symptoms such as tremor but induce deficits in cognitive function. In contrast, according to a recent meta-analysis, treatments that improve cholinergic transmission such as acetylcholinesterase inhibitors (e.g. rivastigmine, donepezil and galantamine) improve cognitive function and behavioural disturbances but increase tremor and the incidence of adverse drug reactions [87].

Amantadine is an *N*-methyl-D-aspartate-type (NMDA) glutamate receptor antagonist with anticholinergic activity [88]. Amantadine is used to reduce motor symptoms and complications in PD; however, recommendations for its anti-dyskinetic use are contrasting [72,89,90]. A randomized controlled trial demonstrated a significant decrease in levodopa-induced dyskinesia and improving OFF time with amantadine extended-release capsules [91]. Glutamate receptor modulators (such as NEU-240; dipraglurant and mavoglurant; foliglurax) and adenosine 2a receptor modulators (tozadenant, fipamezole) are currently under evaluation for their potential to ameliorate dyskinesias; one adenosine A2a receptor modulator has already been approved in Japan (istradefylline) whilst another one (preladenant) failed to show clinical efficacy [92].

Serotonin (5-HT) transmission is another emerging therapeutic target in PD. Buspirone is a combined 5-HT1A and α1-adrenergic receptor agonist, already used for the treatment of depression, which is currently undergoing clinical trial for the treatment of motor fluctuations in PD, following some anecdotal observation of its anti-dyskinetic properties. Eltoprazine is a mixed 5-HT1A and 5-HT1B agonist; its anti-dyskinetic properties were assessed in a phase I/II study and it should enter a phase II study soon [93]. The 5-HT2A inverse agonist pimavanserin has recently been approved for the treatment of dopamimetic-induced psychosis in PD [94].

Some compounds are being evaluated for their effect on gait and balance impairment and falls in PD. These include varenicline, a partial α4β2 agonist and full α7 agonist, and droxidopa, a precursor of noradrenaline, which is also being tested for its effects on orthostatic hypotension and fatigue in PD.

Deep brain stimulation (DBS)

Another option for treating advanced PD is DBS; DBS is based on the use of chronic, high-frequency direct electrical current on a target that, based on clinical features, can be the STN (the most used target in PD), the globus pallidus internus or the thalamus. The mechanism of action of DBS seems to rely on both excitatory and inhibitory effects; a current hypothesis is that DBS exerts its therapeutic effects by dissociating input and output signals in the stimulated target and disrupting the abnormal information flow through the corticobasal ganglia loop [95]. STN-DBS is effective in controlling motor symptoms, motor complications, some NMSs, reducing doses of antiparkinsonian drugs, decreasing disability and improving HRQoL. Randomized controlled trials have shown that STN-DBS is superior to pharmacological treatment in reducing motor complications and improving HRQoL in patients with advanced PD [96]. Different variables interplay in determining a positive outcome of DBS: patient selection, surgical procedure and electrode placement, postoperative setting of stimulation parameters and adjustment of pharmacological therapy. Careful patient selection is pivotal for the success of DBS: it should be performed by a multidisciplinary team experienced in DBS and should follow the core assessment programme for surgical interventional therapies in PD (CAPSIT-PD): the most important aspects to consider are disease duration, age, levodopa responsiveness, type and severity of levodopa-unresponsive symptoms, cognitive and psychiatric issues, comorbidities, and brain MRI findings [97]. DBS side effects include intraoperative and hardware related adverse events, worsening of cognitive function, psychiatric symptoms, and ocular and speech disturbances; moreover, motor signs that do

not respond to levodopa, such as freezing, falling and axial signs, do not show a marked improvement with DBS.

Although most of the studies have been performed in advanced PD, the EARLYSTIM trial suggested that DBS might be useful in patients with recent onset of levodopa-induced motor complications [98].

Natural history

Currently available treatments are symptomatic and do not stop neurodegeneration. Although in initial stages of the disease pharmacological therapy provides a good control of symptoms, in the later stages of the disease some levodopa-resistant symptoms (such as falls and freezing, dysarthria, dysphagia and choking, dementia, hallucinations, daytime sleepiness and urinary incontinence) arise, causing the increase in disability in advanced PD. Moreover, complications associated with pharmacological treatment add further difficulties in managing the advanced stages of PD. PD is associated with an increased risk of all-cause mortality and a reduction in life expectancy [99,100] and severe disability. The majority of patients lose autonomy in the advanced phase of the disease; the most reliable predictors of nursing home placement and mortality are levodopa-resistant symptoms [101,102].

Parkinson disease is a progressive and disabling disease with emotional, economic and social burdens for both the patients and the caregivers; therefore, it might be helpful to refer them to non-profit associations that offer support for patients with PD and their families, providing useful information and initiatives.

Future therapeutic directions

Currently, no disease-modifying drug is available for PD, although several compounds are under active investigation (Table 5).There are significant limitations to clinical trial design of disease modification in PD. Validated biomarkers reflecting progression of the disease are still lacking; therefore disease modification can be assessed only by a delay in symptom progression. The heterogeneity in clinical phenotype and disease progression in PD probably reflects different pathogenetic mechanisms which may respond differently to therapeutic approaches. Therefore, the correct stratification of patients in order to reach a targeted and precise treatment might be pivotal for the success of the development of disease-modifying therapies in future. However, validated and defined criteria to identify PD clinical subtypes have not yet been established, although patients may be stratified on genetic grounds. There is no accurate animal model of PD and its progressive pathology and this limits the ability to test compounds in pre-clinical studies.

By the time of diagnosis, dopaminergic degeneration in the SNpc is already well established. The identification of pre-clinical populations represents an interesting target for clinical trials for disease-modifying drugs but is probably only practical when based on genetic grounds.

Trials testing potential disease-modifying treatments such as MAO inhibitors (selegiline and rasagiline), substances that reduce oxidative stress and improve mitochondrial function (coenzyme Q10 and creatine monohydrate) or reduce microglial activation (pioglitazone), and therapy with neurotrophic factors [neurturin and glial cell line derived neurotrophic factor (GDNF)] failed to provide any evidence for disease modification [103–108]. A recent clinical trial with intermittent convection-enhanced delivery of GDNF failed to prove clinical benefit after 40 weeks [109]. Other therapeutic strategies include glutathione and an anti-apoptotic compound that inhibits the protein FAF-1 (KM-819).

Substances that were shown to reduce the risk of developing PD in epidemiological studies such as caffeine, inosine (as a precursor of urate), calcium channel blockers and nicotine have been tested: basic science studies suggest that nicotine and caffeine can influence α-synuclein aggregation and that urate and isradipine have antioxidant properties. Recently, a clinical trial on isradipine failed to show clinical efficacy [110]. Exenatide, a glucagon-like peptide 1 receptor agonist with neuroprotective effects in pre-clinical models of PD, demonstrated a slight motor improvement in a clinical trial in patients with moderate PD. Further research is needed to clarify whether the result is due to a symptomatic or disease-modifying effect [111]. Following the finding of iron deposition in PD brains, especially in the SN, iron chelation has been proposed as a neuroprotective strategy for PD and its effects on motor function and oxidative damage have been demonstrated in animal models of PD. One phase 2 randomized double-blinded placebo controlled clinical trial of iron chelation in PD patients showed a trend for improvement in motor Unified Parkinson's Disease Rating Scale (UPDRS) score and HRQoL [112]. Other clinical trials on iron chelation in PD are currently ongoing. Immunotherapy targeting α-synuclein aims to reduce and/or limit the spread of α-synuclein; both active and passive immunotherapeutic strategies showed promising results in cellular and animal models, and they are therefore being tested in patients. Active immunotherapy is based on the development of immune response against α-synuclein using small peptides that mimic parts of the molecule, whilst

Table 5 Examples of disease-modifying compounds in development

Target	Examples of compounds	Effect
Mitochondria	PPAR-γ activators (resveratrol, rosiglitazone, pioglitazone, troglitazone, bezafibrate)	⇧ Mitochondrial biogenesis
	Glucagon-like peptide 1 (GLP-1) agonists (exenatide, liraglutide), exendin-4 (EX-4)	⇧ Cellular growth, ⇧ mitochondrial biogenesis, ⇩ apoptosis, ⇩ inflammation
	Engrailed	Complex I regulator
Calcium homeostasis	Calcium channel blocking agents (isradipine), selective Ca(v)1.3 channel inhibitors	⇩ Mitochondrial-mediated oxidative stress during autonomous activity of dopaminergic neurons
Kinases pathways	Inhibitors of LRRK2 kinase	⇩ Autophosphorylation or phosphorylation of other proteins
Protein handling	Chaperones for α-synuclein	⇧ Refolding and clearance of misfolded proteins
	RNA interference (RNAi) or antisense oligonucleotides (ASO)	⇩ α-synuclein expression and aggregation
Clearance	Rapamycin	⇧ Autophagy
	DNL-201	⇩ LRRK2 activity
GBA pathway	Ambroxol, LTI-291, venglustat, isofagomine	⇧ GCase function, ⇧ lysosomal function, ⇩ α-synuclein aggregation
Immune modulation	Vaccination with α-synuclein or similar peptides (PD01A and PD03A)	⇩ α-synuclein aggregation
	Monoclonal antibodies (PRX002, BIIB054)	⇩ α-synuclein aggregation ⇧ Clearance of extracellular α-synuclein by microglia
	Modulators of granulocyte macrophage activity (sargramostim)	⇧ Immune response against aberrant α-synuclein
Prion-like spreading	Polyphenols (circumin)	Binding α-synuclein and ⇩ aggregation
	Inhibitors of endocytosis	⇩ Aberrant α-synuclein transfer
Neurotrophic factors	GDNF	⇧ Neuronal growth and viability
Neuroprotective factors	Caffeine	Adenosine-receptor antagonist ⇩ α-synuclein aggregation, ⇩ inflammation
	Nicotine	Cholinergic modulation ⇧ Anti-apoptotic proteins ⇩ α-synuclein aggregation
	Glutathione	Ubiquitous intracellular thiol ⇩ Oxidative stress
	Inosine	Precursor of urate ⇩ Oxidative stress, ⇧ levels of urate (protective role in epidemiological studies)
	GM1 ganglioside	Component of neuronal plasma membranes, ⇧ reparation and recovery
	AZD3241	Mieloperoxidase (MPO) inhibitor, ⇩ oxidative stress, ⇩ inflammation
	KM-819	⇩ FAF-1 (proapoptotic protein)
Microbiota	Antibiotics (rifaximin, ceftriaxone), dietary fibres (maltodextrin), orally administered lyophilized faecal microbiota product (PRIM-DJ2727)	Changing drug-metabolizing bacteria, ⇩ dopaminergic neurons loss

GCase, glucocerebrosidase; GDNF, glial cell line derived neurotrophic factor; PPAR, peroxisome proliferator-activated receptors.

passive immunotherapy is based on the use of antibodies against α-synuclein, which can increase its clearance. Positive results have been reported from phase 1 studies on Affitope PD01A and PD03A, two vaccines that target α-synuclein. There are ongoing trials on the antibodies PRX002 and BIIB054 [113]. Other attempts to exploit the immune response in PD involve granulocyte macrophage stimulators such as sargramostim.

Given the important role of autophagy in the pathogenesis of PD, enhancing this pathway has been proposed as a potential therapeutic target. Stimulation of autophagy showed positive effects in stopping or reversing neurodegenerative processes of PD *in vitro* and in animal models [114]. Drugs targeting the GBA pathway (such as ambroxol, isofagomine, LTI-291, venglustat) showed promising outcomes in pre-clinical studies, and are currently under evaluation for clinical use [43]. A phase 1 trial with a small molecule inhibitor of LRRK2 (DNL201) is currently ongoing.

Gene therapy is an interesting tool to accomplish different therapeutic strategies for PD, such as release of neurotrophic factors, modification of basal ganglia circuits, cellular reprogramming, improving levodopa efficacy, enhancing glucocerebrosidase activity and α-synuclein aggregation [115]. In a viral-vector-mediated gene delivery system, several viral vectors such as recombinant adeno-associated virus, lentivirus, non-lentivirus vectors and adenovirus can carry target genes for injection into the brain of PD patients. A small-scale phase I/II open-label study using OXB-101, a viral vector that transfers three genes for dopamine synthesis [aromatic amino acid decarboxylase (AADC), tyrosine hydroxylase and guanosine triphosphate cyclohydrolase], showed positive results, and a trial with OXB-102 is currently ongoing. The VY-AADC vector, which targets the loss of DOPA decarboxylase, is currently under evaluation in phase I and phase II studies. Concerns regarding gene therapy include the onset of other diseases or the occurrence of insertional mutagenesis.

Gene-silencing mechanisms have demonstrated efficacy in other neurodegenerative diseases and represent an interesting opportunity for the treatment of PD. The potential of small interfering RNA (siRNA) to reduce α-synuclein expression has been demonstrated in primate brain [116].

The transplantation of foetal nigral cells showed positive results in animal models of PD and was therefore tested in clinical trials. Despite the initially promising results, longer follow-up failed to show significant clinical efficacy; moreover, patients developed particular motor complications after the procedure ('graft-induced dyskinesias') [117,118]. In addition, years after the procedure α-synuclein accumulation and neurodegeneration were found in grafted cells [119]. The TRANSEURO trial (http://www.transeuro.org.uk), a European Union funded multicentre clinical trial of foetal nigral cell transplantation, is currently ongoing. Other cell types are under evaluation for their replacement potential in PD: allogeneic bone marrow derived mesenchymal stem cells, neural stem cells, human embryonic stem cell derived neural precursor cells, autologous bone marrow derived stem cells, autologous peripheral nerve grafts, autologous adipose derived stromal cells and xenotransplantation of NTCELL [immunoprotected (alginate-encapsulated) choroid plexus cells] [120]. Human-induced pluripotent stem cells are another promising source of dopaminergic neurons to transplant in PD patients: pre-clinical studies showed encouraging results, but further safety studies are necessary before entering clinical phases [121].

Disclosure of conflicts of interest

Roberta Balestrino: None. Anthony H.V. Schapira: editor-in-chief, *European Journal of Neurology*.

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