

Parkinson's disease

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Parkinson's disease is a recognisable clinical syndrome with a range of causes and clinical presentations. Parkinson's disease represents a fast-growing neurodegenerative condition; the rising prevalence worldwide resembles the many characteristics typically observed during a pandemic, except for an infectious cause. In most populations, 3–5% of Parkinson's disease is explained by genetic causes linked to known Parkinson's disease genes, thus representing monogenic Parkinson's disease, whereas 90 genetic risk variants collectively explain 16–36% of the heritable risk of non-monogenic Parkinson's disease. Additional causal associations include having a relative with Parkinson's disease or tremor, constipation, and being a non-smoker, each at least doubling the risk of Parkinson's disease. The diagnosis is clinically based; ancillary testing is reserved for people with an atypical presentation. Current criteria define Parkinson's disease as the presence of bradykinesia combined with either rest tremor, rigidity, or both. However, the clinical presentation is multifaceted and includes many non-motor symptoms. Prognostic counselling is guided by awareness of disease subtypes. Clinically manifest Parkinson's disease is preceded by a potentially long prodromal period. Presently, establishment of prodromal symptoms has no clinical implications other than symptom suppression, although recognition of prodromal parkinsonism will probably have consequences when disease-modifying treatments become available. Treatment goals vary from person to person, emphasising the need for personalised management. There is no reason to postpone symptomatic treatment in people developing disability due to Parkinson's disease. Levodopa is the most common medication used as first-line therapy. Optimal management should start at diagnosis and requires a multidisciplinary team approach, including a growing repertoire of non-pharmacological interventions. At present, no therapy can slow down or arrest the progression of Parkinson's disease, but informed by new insights in genetic causes and mechanisms of neuronal death, several promising strategies are being tested for disease-modifying potential. With the perspective of people with Parkinson's disease as a so-called red thread throughout this Seminar, we will show how personalised management of Parkinson's disease can be optimised.

Introduction

Parkinson's disease has a large effect on society. In terms of the number of people affected, this disease is a common condition, with approximately 6·1 million people who had been affected worldwide in 2016.¹ For reasons that are not yet fully understood, the incidence and prevalence of this disease have risen rapidly in the past two decades (panel 1).^{1–3} The personal effect of Parkinson's disease is enormous. Unique to a degenerative disease, the disease duration can span decades. The typical presentation includes a slow progression with accumulating disability for affected individuals. Parkinson's disease also has profound consequences for caregivers, most experiencing excessive strain.⁴ For society, Parkinson's disease conveys a mounting socioeconomic burden.⁵

Various observations suggest that Parkinson's disease might not exist as a single entity. First, many different causes can manifest as a similar appearing clinical syndrome, referred to as parkinsonism.⁶ Some causes are known, such as the less than ten well established genes that can unequivocally cause parkinsonism when mutated. Second, even when a specific cause is uncovered, the disease frequently manifests highly variable symptoms and patterns of progression. For example, the presentation can vary considerably across individuals with an identical toxic cause for their parkinsonian signs, such as exposure to the neurotoxin, 1-methyl-4-phenyl-1,2,3,6-tetrahydropyridine (MPTP), a heroin analogue.⁷ Third, the wishes, needs, and priorities of each person with Parkinson's disease vary widely. A

prominent resting tremor might be hardly noticeable for a labourer accustomed to carrying heavy objects, but a similar tremor intensity could be debilitating for a calligraphist. As such, every person has their own unique Parkinson's disease. Considering all three arguments, an extreme notion would be to say that there are over 6 million different variations of Parkinson's disease in the world.

Acknowledging this marked heterogeneity in causes, presentation, and personal preferences has implications for clinical practice. This heterogeneity makes Parkinson's disease an ideal disease for precision medicine in which the various treatments—pharmacotherapy, neurosurgery, and rehabilitation—should be individually tailored to match each person's priorities and needs, and eventually their genetic or other specific biological make-up.⁸ However, this important development towards personalised precision medicine should not be oversold: people with Parkinson's disease also share common pathophysiological pathways, such as neuroinflammation or mitochondrial dysfunction, so some treatments will probably benefit many seemingly different individuals. Moreover, unique therapies for each person with Parkinson's disease will not be available, but there will probably be particular clusters of people that respond to specific types of treatment. The challenge will be to make these clusters as fine-grained as possible.

Four individual histories (appendix p 14) exemplify the range of clinical presentations and personal differences in treatment priorities. We use this personal perspective

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See Online for appendix

Search strategy and selection criteria

We searched for literature via the Cochrane Library and MEDLINE between Jan 1, 2017, and Dec 30, 2020. We used Medical Subject Headings and free text search term "Parkinson* disease" and restricted our search to the English language. This search resulted in 23 058 articles that were screened on the basis of the title and, partially, by the abstract review. Articles included in our selection of the top 100 Parkinson's disease articles from January, 2017, to December, 2020, were chosen on the basis of one or both of the following criteria: relevance for practising clinicians caring for people with Parkinson's disease (eg, diagnosis, counselling, treatment); or novelty, with clear potential to improve or change our understanding of Parkinson's disease or its management. We generally did not include case reports, smaller-scope articles (such as genetic studies restricted to some populations), articles reporting preliminary (unconfirmed) data, and basic science literature without any clear translational aspect. When multiple relevant papers were identified that related to a particular topic, we selected the parent publication. When topics were surrounded by considerable debate, we selected a meta-analysis, if it was available.

The selection of articles was further informed by a group of 15 international expert colleagues, who were individually requested via email to assemble and send a list of the most relevant papers published in the field of Parkinson's disease in the past 3-5 years. This collective strategy resulted in a selection of 138 articles that were then fully reviewed. Articles overlapping with those selected on the basis of the literature review were counted only once. We then voted on the selection of the most important references published since 2017 by ranking articles as A (must be included), B (very important article), or C (interesting and important but not top priority). Articles that were also recommended by one or more of the 15 international experts for the top 100 selection obtained an additional vote. In addition, we voted on suggested articles that had not previously been considered by the literature review and subsequent selection. None of these papers reached a high enough priority to be included into the list of the top 100 articles. The voting was carried out independently, followed by a discussion of discrepant votes by all three authors and a consensus decision. This process resulted in the selection of 82 articles. During the writing process, an additional 18 publications were added to the selection, collectively amounting to the top 100 references (appendix pp 1-2, 16).

In addition to the top 100 references, the authors included 65 further publications that encompass important older publications (n=28) and publications within the selected timeframe, but not included within the top 100 (n=37). Notably, the number of published articles per year almost doubled from 2017 (n=5380) to 2020 (n=9904, extrapolated from 4952 articles published in the first 6 months of 2020).

In this Seminar, we cite the original publications when discussing new findings that have appeared since the *Lancet* Seminar from 2015. We refer to recent reviews or international consensus guidelines when discussing generic background information about Parkinson's disease. We covered an overall body of literature on Parkinson's disease (approximately 23 000 published articles since 2017). The selected top 100 Parkinson's disease articles from the literature and expert opinion review thus represent approximately 0-4% of the available Parkinson's disease literature during this period. On average, we highlight almost three published papers per month over the past 3-5 years.

as a figurative red thread throughout this Seminar (figure 1). We also address the many misconceptions that can affect a Parkinson's disease diagnosis (table 1).

Clinical presentation of Parkinson's disease

Clinical spectrum

The motor features of Parkinson's disease are hard to miss. The video shows the complete motor examination

of people with recently identified Parkinson's disease. However, the clinical spectrum also contains many less visible components, including non-motor features, such as cognitive decline, depression, and pain (appendix pp 3-4). These non-motor features contribute substantially to the disability of affected individuals.⁹ A rating scale can measure this non-motor burden.¹⁰

The earliest stages of Parkinson's disease can be difficult to recognise, as reflected by the long delay (average 10 years) that typically separates the person's first noticeable symptom from the timing of diagnosis.¹¹ Early symptoms include constipation (the most common symptom), acting out dreams during the rapid eye movement (REM) phase of sleep (suggesting a REM sleep behaviour disorder), hyposmia, asymmetric vague shoulder pain, or depression.⁶ General practitioners should not be blamed for missing the diagnosis at such an early stage: no initial manifestation is by itself enough to diagnose Parkinson's disease, and each manifestation also occurs as part of many other conditions. Delays are particularly common when tremor is absent, when the legs are predominantly affected, and in people with young-onset disease.¹²

Diagnostic criteria

Except for genetic testing in selected cases, a definitive diagnosis can only be established on the basis of post-mortem identification of hallmark neuropathological changes in the brain (appendix p 17). Pathologically, Parkinson's disease is defined by the accumulation of α -synuclein in Lewy bodies and Lewy neurites. This Lewy pathology is characterised by a crowded environment of membranes, including vesicular structures and dysmorphic organelles, such as dysmorphic mitochondria, and high lipid content.¹³ A new insight is that even in early disease stages, similar pathological changes can occur in multiple organs, including the skin, colon, and salivary glands, suggesting that Parkinson's disease is a multi-system disease.¹⁴ This recognition might ultimately yield new diagnostic avenues, because these systemic tissues are better accessible than tissue from the brain when a person is alive.

In daily practice, Parkinson's disease is a clinical diagnosis, and is based on history taking and neurological examination. Although intended primarily for use in clinical research, following the International Parkinson and Movement Disorder Society's diagnostic criteria for Parkinson's disease can guide clinicians in establishing the diagnosis (figure 2).¹⁵ The diagnostic process is shown in figure 3. A gratifying response to an adequate dose of dopaminergic therapy supports a diagnosis of Parkinson's disease;¹⁵ if needed, the levodopa dose should be escalated to 1000 mg daily for 4 weeks before concluding that people with Parkinson's disease are not responsive.

Identification of so-called red flags (ie, specific symptoms or signs that provide a relative argument

See Online for video

against the presence of Parkinson's disease, and that signal the possible presence of an alternative pathology, which occurs in people with a form of atypical parkinsonism) can accelerate the diagnostic process, noting that no single red flag provides definitive certainty of a specific diagnosis.¹⁵ Detailed knowledge of all red flags—and knowing how to interpret their presence—is only required for experts in movement disorders. An example of a straightforward, albeit not highly specific, red flag is a wide-based gait, typically accompanied by an impaired tandem gait—the inability to take 10 consecutive steps along a narrow line—which signals the presence of a form of atypical parkinsonism.¹⁶

Factors complicating the diagnosis

Diagnostic errors are common in daily practice. In clinical trials of early-stage Parkinson's disease, up to 15% of people with the disease are diagnosed incorrectly;¹⁷ this misclassification rate is even higher among non-experts.¹⁸ The presence of comorbidity might complicate the diagnostic process (appendix p 5).^{19–21} One common comorbidity is the presence of concurrent cerebrovascular lesions, which regularly appear on brain imaging during routine diagnostic tests.²² These lesions can produce manifestations similar to lesions in Parkinson's disease, such as gait disturbances, cognitive decline, or urinary incontinence. Another specific comorbidity is a concurrent infection with SARS-CoV-2, causing COVID-19. People with Parkinson's disease are not at increased risk of becoming infected but seem more susceptible to particularly the respiratory complications of COVID-19. These risks are not increased in early Parkinson's disease,²³ but rise for more severely affected individuals, possibly increasing their mortality risk.²⁴ Additionally, many people with the disease have a marked worsening of symptoms because of fewer physical activities and more stress—both acute and chronic stress can worsen parkinsonism.²⁵

Subtypes

Several recognisable subtypes exist, within which some clusters of symptoms coincide. Acknowledging these subtypes is important for various reasons. The first relates to the pathophysiology, as some symptom clusters can suggest where the disease process originally started.²⁶ The second reason relates to prognosis. A 2019 study on people with autopsy-confirmed Parkinson's disease identified the presence of a diffuse malignant subtype that was associated with faster progression towards reaching relevant clinical endpoints and with reduced survival.²⁷ This subtype classification remains far from offering an individual prognosis in clinical practice, as the confidence intervals for the predictions remain wide. The third reason relates to possible implications for personalised treatment, which is not yet a reality in daily practice. Genetically defined subtypes are closest to delivering personalised treatment.

Panel 1: The Parkinson pandemic

The global survey of neurological diseases revealed that the incidence and prevalence of Parkinson's disease has increased rapidly throughout the world.¹ Parkinson's disease might even be the fastest growing neurological condition worldwide.^{1,2} This rapid global growth of new people living with Parkinson's disease has been compared with many of the characteristics typically observed during a pandemic, except for an infectious cause. The growth can be explained in part by the ageing of the population because the incidence of Parkinson's disease increases with age. However, after correction for age-related factors, Parkinson's disease is projected to continue to rise in incidence, being driven by more factors than ageing.¹ Although diagnostic strategies for Parkinson's disease have not changed drastically, improved diagnostic accuracy by experienced clinicians offers a partial explanation.³ However, this more accurate diagnostic process cannot explain why the age-adjusted prevalence of Parkinson's disease is growing faster than other neurological disorders, including diseases such as multiple sclerosis, which has seen substantial advances in diagnostic approaches. Other factors potentially contributing to this rise include prolonged survival and environmental pollution with toxins, such as pesticides (eg, paraquat) or chemicals (eg, trichloroethylene), known to be harmful to Parkinson's disease-related neurons and brain circuits. The larger the societal growth in gross national income, the faster the rise in the incidence of Parkinson's disease,² perhaps because economic growth is a proxy for industrialisation and environmental pollution.

Ancillary testing

According to the International Parkinson and Movement Disorder Society's diagnostic criteria for Parkinson's disease, the outcome of any ancillary test adds little weight to the diagnostic scale, serving as a single supportive criterion to counterbalance a red flag (figure 2).¹⁵ Possible useful diagnostic tests are outlined in table 2.

Epidemiology

Parkinson's disease is an age-related disease, with incidence and prevalence increasing steadily with age.²⁹ However, the misconception that Parkinson's disease exclusively affects older people should be dismissed. The age of onset for almost 25% of affected individuals is younger than 65 years and for 5–10% is younger than 50 years. The term young-onset Parkinson's disease has been introduced when referring to affected individuals with an age of onset younger than 40 years (maybe even younger than 50 years). The disease occurs worldwide, without remarkable epidemiological differences, except for a disproportionately fast increase in new cases in China,² and a fast increase in high-income countries in Europe.³ The global burden of Parkinson's disease—in terms of deaths and disability—has more than doubled in the past two decades.³

Although Parkinson's disease affects both sexes, women might have several advantages over men: their incidence of the disease is lower, particularly for individuals aged 50–59 years,²⁹ and their age at onset is higher. The number of years lived with disability is highest for men.³ However, women are disadvantaged in other ways: they have a higher risk of developing dyskinesia, and motor and non-motor response fluctuations, which might result from

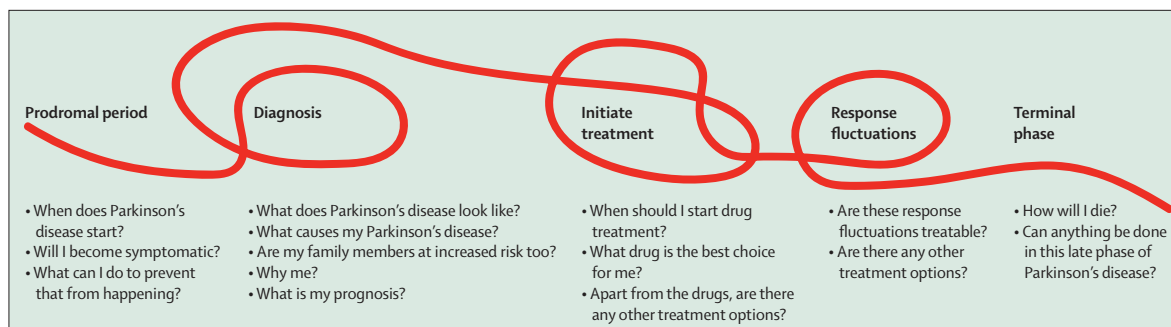


Figure 1: Examples of the various questions that people with Parkinson's disease might have during the consecutive phases of the disease

The various disease phases are connected by a figurative red thread, as graphically depicted here. We will use this red thread of personal perspectives to guide us throughout this Seminar and to show how the personalised management of people with Parkinson's disease can be optimised.

Largely untrue	Mostly true
Parkinson's disease is a single entity, with a single cause and a uniform clinical presentation	Multiple causes (eg, different genes) can lead to a similar appearing Parkinson syndrome, whereas single causes (eg, specific genetic mutations) can produce very heterogeneous manifestations
Parkinson's disease is a disease solely affecting older people	Parkinson's disease is an age-related condition, but might also affect younger people, including those younger than 50 years
Tremor is typical of Parkinson's disease	Up to 20% of people with Parkinson's disease do not have a tremor; however, bradykinesia is always present
Parkinson's disease is characterised only by movement abnormalities	The disease is typically characterised by a combination of both motor features (eg, bradykinesia and tremor) and a range of non-motor features (eg, depression, constipation, and disturbed sleep); these non-motor features can precede the manifestation of the motor syndrome
Men and women with Parkinson's disease present in an identical way	The clinical presentation, disease course, and health behaviour differ between sexes
The diagnosis of Parkinson's disease must be corroborated by an MRI scan, dopaminergic neuroimaging, or both	The clinical diagnosis remains the gold standard; ancillary tests should be applied only under specific circumstances in people presenting with an atypical presentation
Genetic testing is of no clinical relevance	Although not part of routine clinical practice, genetic testing can establish a definitive diagnosis in selected cases; and can be important for family counselling and will probably become increasingly relevant as genetically stratified people with Parkinson's disease enter gene-targeted clinical trials; also, as with cancer, people with Parkinson's disease might receive personalised treatment tailored to their genetic profile in the future
Postpone symptomatic drug treatment for as long as possible, to delay the development and severity of response fluctuations	Postponing treatment does not delay response fluctuations; timely instalment of symptomatic pharmacotherapy can reduce motor symptoms and improve quality of life
Postpone the use of levodopa for as long as possible; dopamine receptor agonists should be the first-line treatment	There is no evidence that withholding levodopa is beneficial to people with Parkinson's disease; compared with other strategies, levodopa is generally tolerated best and is the most effective antiparkinsonian treatment and, therefore, is the first-line treatment for most people with the disease
The medical specialist (ie, neurologist or geriatrician) is the main and often only practitioner necessary for treatment	Optimal management requires a multidisciplinary team approach
People with Parkinson's disease play only a minor role in the management of their own disease	The person with Parkinson's disease is an important member of the multidisciplinary team; self-management and active participation by people with the disease are essential to reach optimal outcomes
The many challenges associated with Parkinson's disease can be solved by the added sum of all ongoing monodisciplinary efforts	Optimal management of Parkinson's disease can only be done by an integrated collaborative effort, with intensive collaboration between professionals of multiple different backgrounds and people with Parkinson's disease as partners in care and science

Table 1: Several common misconceptions about Parkinson's disease, which can lead to delays in diagnosis, suboptimal management, avoidable disability, and unnecessary costs

their usually lower bodyweight (causing relative overdosing).^{30,31} Also, women are more likely to report urinary complaints and depression.³² Conversely, men have a greater risk of cognitive decline.^{32,33} Health behaviour is different for women with Parkinson's disease, with less frequent and delayed access to medical professionals, including specialised care.^{33,34} This behaviour might result in undertreatment, including decreased use of

neurosurgical interventions. Importantly, women are under-represented in Parkinson's disease trials.³⁵

Causes and modifying factors

When discussing the causes of Parkinson's disease, three factors are relevant: genetics, environment, and interactions thereof (figure 4). There is a relatively good understanding of causative genes, and a person's entire

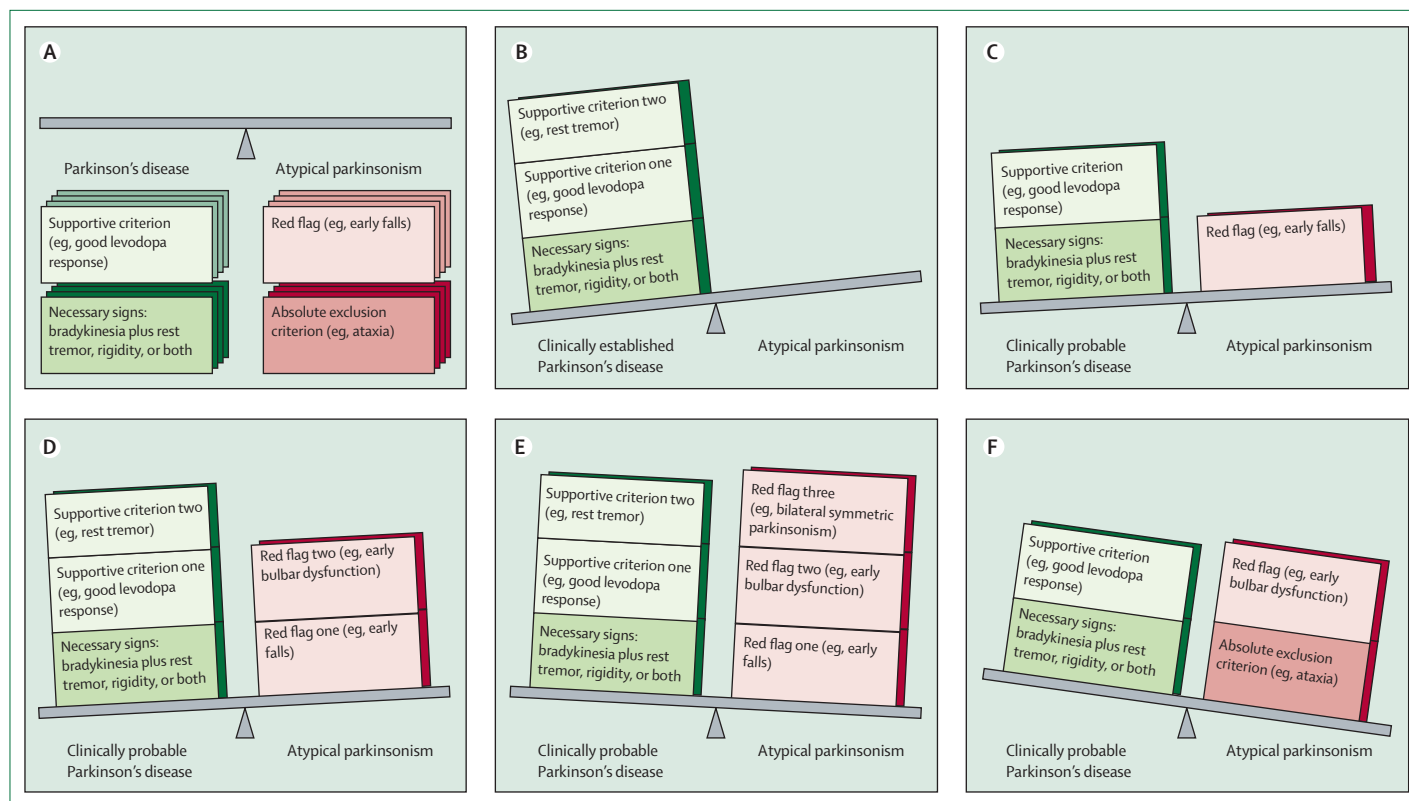


Figure 2: The diagnostic weighting process according to the International Parkinson and Movement Disorder Society diagnostic criteria for Parkinson's disease

According to these criteria,¹⁵ a diagnosis of Parkinson's disease is made on positive grounds on the basis of a combination of symptoms or signs that should be present, and exclusion of symptoms or signs that should not be present. (A) Absolute exclusion criteria refer to highly specific signs of alternative diagnoses that rule out any diagnostic rating of Parkinson's disease. Red flags refer to signs that provide a relative argument against the presence of Parkinson's disease and that are suggestive of alternative pathology, but their specificity is lower or uncertain. (B–D) The various possible scenarios to establish clinically established Parkinson's disease or clinically probable Parkinson's disease. A diagnosis of clinically established Parkinson's disease requires absence of absolute exclusion criteria, presence of at least two supportive criteria, and no red flags. A diagnosis of clinically probable Parkinson's disease requires absence of absolute exclusion criteria, whereas the presence of up to two red flags can be cancelled out by the presence of two supportive criteria. (E, F) Scenarios that suggest the presence of a form of atypical parkinsonism.

genome can readily be deciphered, but the assessment of the so-called environmentome (ie, the sum of all potentially causative and protective factors that are present in our environment) is not possible at present. Moreover, unlike a person's genetic make-up, which is largely stable, their environment is in constant flux. Environmental factors that perhaps had an effect decades ago or that accumulated over time, possibly in interaction with genetic features, is not possible to assess. Inaccessibility of the brain further constrains aetiological studies. We assume there is a continuum between causes and risk factors and counteracting protective factors of different effect sizes that occur in unique constellations. Notably, factors increasing the risk for developing Parkinson's disease are not necessarily identical to those modifying the disease course, which can only be assessed in large-scale longitudinal studies.

Genetics

Although monogenic forms comprise a minority of all Parkinson's disease, they are important for several reasons: (1) in selected cases, identifying a monogenic

cause can establish a definitive diagnosis of a particular type of Parkinson's disease during life; (2) Parkinson's disease genetics can have implications for family counselling; (3) genetics have improved our understanding of Parkinson's disease pathophysiology; and (4) monogenic Parkinson's disease might be amenable to specific gene-targeted treatments, the first of which are being evaluated in trials (this is a concrete example of personalised precision medicine for people with Parkinson's disease). To prepare for trials of these gene-targeted therapies for Parkinson's disease, an international effort is establishing clinical trial-ready genetic cohorts.³⁶

In clinical practice, focus should be on genes that are unequivocally linked to Parkinson's disease (appendix pp 6–8).^{37–41} When suspecting a genetic form of this disease, the best clue is a young age at onset (particularly younger than 40 years). In many countries, genetic counselling is mandatory to offer; establishing the presence of monogenic Parkinson's disease can alleviate anxiety among some individuals but increase concerns for others. Importantly, a negative result does not fully exclude a genetic cause,

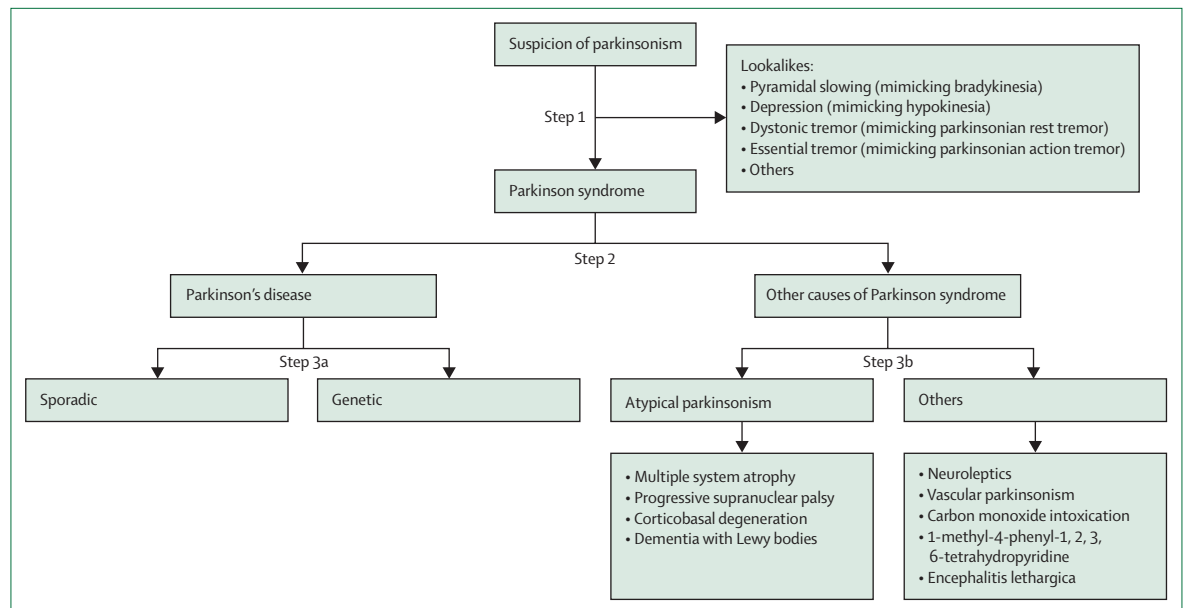


Figure 3: The clinical diagnostic process

Step 1 is defining whether parkinsonism is truly present. For this step, the presence of bradykinesia is required, combined with either rest tremor, rigidity, or both. Step 2 is to distinguish Parkinson's disease from other causes of parkinsonism, which is important because the group of other causes includes neurodegenerative conditions that are jointly referred to as atypical parkinsonism. In comparison with Parkinson's disease, these forms of atypical parkinsonism generally share a much less favourable prognosis, with faster disease progression, a less robust to even absent response to dopaminergic medication, a faster appearance of debilitating complications, such as falls or dementia, and a markedly reduced survival. Additionally, this other group includes potentially fully reversible causes of parkinsonism, including drug-induced parkinsonism.

whereas a seemingly positive result might later prove to represent a rare benign variant.

To date, the most interest is focused on mutations in the genes *SNCA*, *LRRK2*, *PRKN*, *PINK1*, and *GBA*. Shared features of all *SNCA* mutations comprise an earlier age of disease onset, faster progression of motor signs, and presence of prominent non-motor features including rapid cognitive decline.⁴² Seven different *LRRK2* mutations have been clearly linked to Parkinson's disease, NM_198578.4(LRRK2):6055G>A (Gly2019Ser) being the most common, with a founder effect in the Ashkenazi Jewish and north African Arab populations.⁴² *LRRK2* mutations account for 3–41% of familial Parkinson's disease cases but are also observed at a lower rate in apparently sporadic cases. The phenotype of *LRRK2* Gly2019Ser mutations is indistinguishable from sporadic Parkinson's disease. Mutations in *PRKN* and *PINK1* are the major causes of autosomal recessive and early-onset Parkinson's disease, with the frequent *PRKN* mutations accounting for up to 77% of cases of juvenile Parkinson's disease (age of onset being younger than 20 years) and 10–20% of young-onset Parkinson's disease.⁴³ However, there remains a long latency in diagnosing early-onset in people with *PRKN* mutations.¹² *PRKN* and *PINK1* disease are overall slowly progressive, respond well and sustainably to antiparkinsonian treatment, and are commonly complicated by dystonia, but rarely by dementia. Conceptionally falling between a causative genetic factor with highly reduced penetrance

and a strong genetic risk factor, pathogenic *GBA* variants occurred in 8.5% of people with Parkinson's disease in a multi-ethnic sample of more than 1100 individuals.⁴⁴ The characteristic phenotype of *GBA*-linked Parkinson's disease is an earlier onset and a severe course, in particular with rapid cognitive decline.⁴⁵ Addressing genetic variants of typically much lower individual effect sizes, the largest meta-analysis of genome-wide association studies identified 90 independent, genome-wide, statistically significant risk signals that collectively account for 16–36% of the heritable risk of Parkinson's disease.⁴⁶

Non-genetic factors associated with an altered Parkinson's disease risk

Several toxins can produce a clinical picture resembling Parkinson's disease, such as parkinsonism resulting from exposure to the neurotoxin MPTP.⁷ In addition to these direct causes, various environmental and lifestyle factors have been evaluated as contributors to the risk of Parkinson's disease. This literature is difficult to interpret: many factors have never been replicated, conflicting results exist, a plausible mechanistic explanation is often scarce, and the observed associations could have been false. One persuasive risk factor is exposure to environmental toxins such as pesticides, for which there is converging and consistent evidence.⁴⁷ The introduction of pesticides after World War 2—which was required to feed a fast-growing world population—could partially explain the current rise of Parkinson's disease. Another well

	Purpose	Indications
MRI	Cerebrovascular lesions (ie, lacunes, white matter hyperintensity, and perivascular spaces); normal pressure hydrocephalus; atypical parkinsonism	Presence of >2 red flags or absolute exclusion criteria
Dopaminergic neuroimaging*†	Identify degeneration of the nigrostriatal system (thus establishing parkinsonism)	Dystonic tremor vs Parkinson's disease; essential tremor vs Parkinson's disease; people with Parkinson's disease with a functional overlay; drug-induced parkinsonism vs (concurrent) Parkinson's disease; vascular parkinsonism; enrichment biomarker—for use in clinical trials only‡
Sympathetic cardiac [123I]-metaiodobenzylguanidine scintigraphy	Differentiate Parkinson's disease and dementia with Lewy bodies (decreased binding) from multiple system atrophy and progressive supranuclear palsy (normal binding)	Diagnostic uncertainty
Transcranial ultrasound of the substantia nigra	Presence of hyperechogenicity predicts Parkinson's disease diagnosis, normal echogenicity predicts atypical parkinsonism and poorer treatment response	Restricted use (by experienced examiner, for people with a sufficient bone window)
Genetic testing	At present, the only way to establish a definitive diagnosis of a particular type of Parkinson's disease during life	Research: identification of candidates for trials of gene-targeted treatments; clinical practice: onset at a young age (younger than 40 years), or positive family history, or both§
Copper (serum, 24 h urine), plasma ceruloplasmin, Kayser-Fleischer rings in peripheral cornea	Exclude Wilson's disease	Age at onset is younger than 50 years
Autonomic function tests	Establish autonomic dysfunction	Might aid in differentiating Parkinson's disease from multiple system atrophy, in which autonomic dysfunction appears earlier and more prominently
Polysomnography	Detection of idiopathic rapid eye movement sleep behaviour disorder	Presence suggests underlying synucleinopathy (Parkinson's disease, multiple system atrophy, Lewy body dementia)
Olfactory tests	Detect hyposmia	Provides supportive criterion to establish diagnosis of Parkinson's disease
Tremor analysis (eg, neurophysiology, accelerometers, wearables)	Classification of tremor (eg, frequency and amplitude)	Aids in differential diagnosis (eg, functional parkinsonism vs Parkinson's disease)

Dopaminergic neuroimaging remains normal in conditions that mimic parkinsonism; note that dopaminergic neuroimaging does not distinguish Parkinson's disease from the various forms of atypical parkinsonism; therefore, dopaminergic neuroimaging is not recommended for routine use in daily clinical practice but can be useful for specific indications. †Individuals with suspected parkinsonism but who have normal dopamine transporter scans have been referred to as having SWEDDS (scans without evidence of extrapyramidal dopaminergic deficit); such a normal scan renders a diagnosis of Parkinson's disease highly unlikely, and most will have alternative diagnoses, such as dystonic tremor or essential tremor; the scan might later become abnormal in a small subgroup who might end up having Parkinson's disease after all. ‡Dopaminergic neuroimaging was approved by both the US Food and Drug Administration and the European Medicines Agency in 2018 as an enrichment biomarker for clinical trials, aiming to ascertain that a higher proportion of people with a presynaptic dopaminergic deficit are included in Parkinson's disease studies. §Results should be considered preliminary and reporting to people with Parkinson's disease is not yet considered standard of care.

Table 2: Ancillary diagnostic tests that can be considered in people presenting with parkinsonism

established risk factor is head injury. Recent studies—one with observational data from a medical claims database,⁴⁸ and a retrospective cohort study among former professional soccer players⁴⁹—showed that traumatic brain injury can be a risk factor of Parkinson's disease.

In the past 6 months, concerns have been expressed over COVID-19 increasing the risk of developing parkinsonism, although at this stage there is only anecdotal evidence supporting this notion.^{50–52} Hyposmia is a feature of both COVID-19 and Parkinson's disease, and SARS-CoV-2 could perhaps trigger a cascade of neurodegeneration following nasal entry into the brain. Careful monitoring will reveal if the already fast-growing incidence of Parkinson's disease accelerates further as a sequel of the worldwide COVID-19 pandemic, just as was seen in the aftermath of the 1918 influenza pandemic.⁵³

Negative associations with the risk of developing Parkinson's disease include smoking, coffee drinking,

anti-inflammatory drug use, high plasma urate levels, or physical activity.⁵⁴ If the negative association between smoking and Parkinson's disease risk is truly causal, then the global tendency to smoke less could partly explain the fast rise in incidence of Parkinson's disease.⁵⁵ However, the association could also be false, because smokers might have higher dopamine levels, which could explain their appetite for cigarettes via a rewards mechanism, whereas also preventing smokers from dropping below a critically low dopamine threshold that is needed to produce manifest parkinsonism. Similar considerations apply to the presumed protective effect of physical activity,⁵⁶ which could directly protect against neurodegeneration, but which might also reflect a generally healthier lifestyle and better fitness.

Some protective factors motivated the design of intervention studies, aiming to modify the course of Parkinson's disease. One example is high plasma urate, which is potentially protective according to biological,

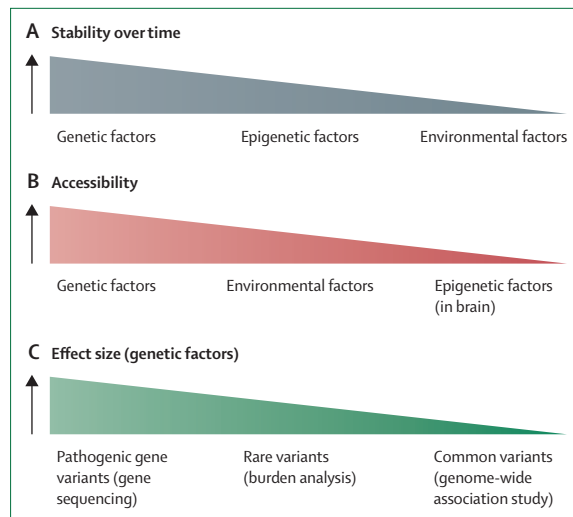


Figure 4: The limitations of studying the causes of Parkinson's disease and modifying factors

(A) Stability over time varies greatly across genetic factors (which are very stable), epigenetic factors (only partially stable), and environmental factors (which are typically in constant flux). (B) Accessibility is likewise highly variable, with genetic factors being easily accessible, environmental factors being more difficult to study—especially in a hypothesis-free manner, longitudinally and retrospectively—and epigenetic factors being mostly inaccessible in the tissue of interest (brain) in living individuals. (C) Effect sizes range from causal (pathogenic variants) to genetic burden conferred by rare variants in Parkinson's disease-linked genes to common variants with relatively small effect sizes, even when combined in polygenic risk scores.

epidemiological, and clinical data. However, a trial (NCT02642393), completed in September, 2019, on the urate precursor inosine in early Parkinson's disease was negative, despite being effective in raising serum and cerebrospinal fluid urate concentrations. Moreover, causality of urate was not identified with mendelian randomisation,⁵⁷ which is a method for exploring observational associations in the context of genome-wide association data and to uncover evidence of causality.⁵⁸ Several factors are being debated, such as the intake of β 2-adrenoreceptor agonists and antagonists.⁵⁹ Other factors await confirmation (eg, ionising radiation in occupationally exposed workers).⁶⁰ Intervention studies are needed to further explore causality.

Pathophysiology

The pathophysiology of Parkinson's disease appears to result from the complex interplay of aberrant α -synuclein aggregation, dysfunction of mitochondria, lysosomes or vesicle transport, synaptic transport issues, and neuroinflammation.⁶¹ These disease mechanisms collectively result in accelerated neuronal death of primarily dopaminergic neurons, but the neuropathology involves multiple other motor and non-motor circuits. Loss of nigrostriatal dopamine cells causes a gradient of striatal dopamine depletion producing an imbalance between direct (facilitatory) and indirect (inhibitory) pathways through the basal ganglia, resulting in bradykinesia.

Neurophysiological recordings conceptualised bradykinesia as an imbalance between different oscillatory rhythms: too much (antikinetic) beta activity and too little (prokinetic) gamma activity. Specifically, beta oscillations are associated with the dopaminergic off state, and disappear with dopaminergic medication or deep brain stimulation.^{62,63} A relatively new insight is that these pathological changes are accompanied by compensatory alterations in brain activity in areas that are initially unaffected by the pathology of Parkinson's disease, such as a shift towards more anterior corticostriatal circuits, and recruitment of cortical regions that are less connected to the basal ganglia.⁶⁴

Monogenic forms of Parkinson's disease have provided important pathophysiological clues but how well these findings can be transferred to non-monogenic Parkinson's disease remains elusive. Adding another caveat, many studies on the pathophysiology of this disease are carried out in animals or cellular models under artificial experimental conditions. Some pathways are well established, such as the link between α -synuclein and lysosomal acid GCase that form a positive feedback loop, leading to a potentially self-propagating disease,⁶⁵ or a pathological cascade beginning with mitochondrial oxidant stress, leading to oxidised dopamine accumulation, resulting in reduced lysosomal acid GCase activity and, in turn, α -synuclein accumulation.⁶⁶ A 2018 study found that the activation of poly [ADP-ribose] polymerase (PARP) 1 accelerates the formation of pathological α -synuclein, which can be prevented with PARP inhibitors.⁶⁷ Additionally, a defined set of peptides derived from α -synuclein act as possible antigenic epitopes and drive helper and cytotoxic T-cell responses. Approximately 40% of people with Parkinson's disease shown immune responses to α -synuclein, similar to classical autoimmune diseases.⁶⁸ Of further note, influenza virus infection results in α -synuclein aggregation, which was prevented by an anti-influenza drug.⁶⁹ Finally, the Parkinson's disease proteins Parkin and PINK1 jointly facilitate the clearance of damaged mitochondria (mitophagy),⁷⁰ a process now also linked to inflammatory processes.⁷¹

The link between early disease processes in the gut and subsequent neurodegeneration in the brain is not fully understood. One clinical hint is that constipation can antedate the appearance of motor parkinsonism by several years,⁷² which is in keeping with the Braak hypothesis (the veracity of which remains a matter of debate) that Parkinson's disease is triggered when a foreign agent enters the CNS, presumably via the gastrointestinal system, spreading via the vagal nerve to the brain.⁷³ An elegant study addressed this issue with a comprehensive multimodal imaging approach to identify dysfunction of the gut, heart, brainstem (locus coeruleus), and nigral projections in people with Parkinson's disease.⁷⁴ Two types of this disease were identified: a body-first type with early gut and cardiac involvement,

followed by brain dysfunction, in line with the Braak hypothesis; and a brain-first type with pathology starting in the nigrostriatal system. People with Parkinson's disease with a brain-first phenotype might have a genetic cause. Conversely, for those with a body-first phenotype, the earliest event of Parkinson's disease pathogenesis could be a change in gut microbiota. One study showed that mice overexpressing *SNCA* only develop parkinsonism and brain pathology in the presence of gut microbiota; germ-free animals were protected against neurodegeneration.⁷⁵ In *PINK1*-deficient mice, intestinal infection with bacteria results in mitochondrial antigen presentation and elicits autoimmune mechanisms.⁷⁶ However, further research is needed to identify whether changes in the microbiome have any causal relationship to Parkinson's disease or whether the microbiome merely reflect secondary changes.

An important message is that insights into the underlying pathophysiology provide potential new targets for diagnostic and possibly intervention strategies. However, given the complexity of the pathophysiology and its unique expression in an individual with Parkinson's disease, modification of the disease course of all forms of the disease by a single intervention is unlikely. Furthermore, pathophysiological processes are different during the prodromal or early symptomatic phase of Parkinson's disease, compared with the later stages, so the nature of the interventions will need to be carefully timed and tailored to the underlying disease processes at play.

Prognosis

Parkinson's disease is a progressive condition, although the rate of deterioration varies considerably across different individuals.⁶ Absence of progression excludes a diagnosis of Parkinson's disease, whereas unusually fast rates of progression—with rapid development of factors, such as falls or dementia—suggest an alternative diagnosis.¹⁵ Life expectancy is decreased overall, yet most people live long with Parkinson's disease, many even decades. Common causes of death include aspiration pneumonia and complications following a hip fracture.

Individual predictions are difficult to make. Several groups attempted to identify predictive factors, specifically in relation to the time taken to reach clinically relevant milestones (panel 2).^{34,77–91} Some predictors include lifestyle factors, such as coffee consumption, smoking, or physical activity.⁷⁷ Others depend on ancillary tests, such as genetics (appendix pp 6–8), MRI,⁷⁸ analyses of cerebrospinal fluid,^{79–81} or kinematic gait analyses.⁸²

Prodromal phase

A long prodromal period might precede the onset of clinically manifest Parkinson's disease.⁹² Various prodromal features are listed in the appendix (pp 3–4). Much relevant information is readily available in primary care medical records—mining these can be used to

identify at risk individuals.⁹³ The prodromal symptom with the highest risk of subsequent phenotypic conversion to overt Parkinson's disease is idiopathic REM sleep behaviour disorder, which is by itself rare but quite specific, and can increase the annual risk of developing parkinsonism or dementia by 6·3%.⁷² This risk is higher for older people and those with additional neurological abnormalities. The more prodromal symptoms, the higher the risk of developing manifest parkinsonism.⁹² New evidence suggests that the prodromal period can start as early as at age 20 years (or possibly more) before the onset of motor parkinsonism.^{94,95} The nature of one's job choice at a young age could be an early reflection of the prodromal phase. Specifically, long before the diagnosis is made, people with Parkinson's disease are more likely to opt for a conventional profession and are less likely to become artists, perhaps because a diminished dopaminergic tone in the prodromal phase is associated with less creativity.⁹⁵ At present, the importance of identifying prodromal Parkinson's disease lies in selecting appropriate candidates for inclusion in trials of experimental disease-modifying interventions, which could potentially delay or even prevent progression to manifest Parkinson's disease when applied early. To support this early identification, a web-based risk calculator has been introduced to calculate the individual probabilities of prodromal Parkinson's disease.⁹²

Symptomatic medical management

Initiating treatment in de-novo Parkinson's disease

Parkinson's disease is treatable. Dopaminergic pharmacotherapy is one of four main strategies (figure 5). People with Parkinson's disease might raise important questions when considering initiation of pharmacotherapy. One argument to postpone treatment is the long-held notion that levodopa could be toxic and hasten disease progression by promoting oxidative stress, fuelling levodopa phobia and motivating both physicians and people with Parkinson's disease to postpone treatment. However, the LEAP study, which used a delayed start design in which people with Parkinson's disease either received levodopa immediately, or after a placebo period of 9 months, showed no evidence of levodopa toxicity, or for neuroprotective effects.⁹⁷ However, early starters manifested fewer motor symptoms and had a better quality of life than the late starters. Moreover, observations in African people with Parkinson's disease, who postponed medication due to a scarcity of access, revealed that delaying treatment did not reduce the likelihood of motor complications and dyskinesias.⁹⁸ The consensus is that there is no rationale to postpone symptomatic treatment in people with Parkinson's disease who develop a disability. Conversely, presence of recognisable symptoms without accompanying disability should not result in initiation of drug therapy.

Once the decision to initiate treatment is made, the strategy must be individualised (figure 6; appendix

Panel 2: Prognosis of Parkinson's disease, expressed as an increased risk of reaching specific clinically relevant endpoints (milestones) with examples of identified predictors

Need for levodopa or other symptomatic treatment

Clinical

- People with Parkinson's disease with functional impairment or embarrassment

Motor worsening

Clinical

- Low frequency of sexual activity*
- Cardiovascular risk profile
- Phenotype characterised by little or no tremor

Brain MRI

- Brain atrophy
- Free water in posterior substantia nigra (diffusion MRI)

Dopaminergic neuroimaging

- Increased deficit

Cerebrospinal fluid

- Low concentrations of cerebrospinal fluid amyloid β and amyloid β -total tau ratio (Alzheimer-like profile)
- High cerebrospinal fluid neurofilament light chain

Cognitive decline and dementia

Clinical

- Higher age (at baseline and at onset of Parkinson's disease)
- Cardiovascular risk profile
- Lower baseline cognitive scores
- Depression
- Hallucinations
- Akinetic-rigid or postural instability-gait disorder subtype

Blood tests

- Higher concentrations of uric acid, C-reactive protein, HDL cholesterol, and glucose
- GBA mutation status

Brain MRI

- Perivascular spaces
- White matter hyperintensity
- Decreased hippocampal volume

Dopaminergic neuroimaging

- Low caudate uptake

Cerebrospinal fluid

- Low concentrations of cerebrospinal fluid amyloid β (1–42)

Recurrent falls

Clinical

- Greater disease severity
- Longer disease duration
- Presence of response fluctuations
- Cognitive impairment
- Depression
- Abnormal gait (including freezing of gait)
- Symptomatic postural hypotension
- Postural instability and gait disability phenotype

First fracture

Clinical

- Postural instability

Loss of independence

Clinical

- Higher age
- Greater motor severity
- Mild cognitive impairment

Dependency on wheelchair

Clinical

- Older age at assessment
- Institutionalisation
- Postural instability

Nursing home admission

Clinical

- Older age
- Psychosis and hallucinations
- Dementia
- More severe motor symptoms
- Living alone
- Falls

Need for nasogastric tube or gastrostomy

Clinical

- Dysphagia
- Aspiration pneumonia

Death

Clinical

- Comorbidities
- Dementia at baseline
- Dysphagia
- Postural instability
- Freezing of gait
- Orthostatic hypotension
- Fracture
- Institutionalisation

Blood tests

- LRRK2 mutations (higher survival rates compared with Parkinson's disease and GBA-related parkinsonism)

Dopaminergic neuroimaging

- Low caudate uptake

Cerebrospinal fluid

- Elevated leukocytes in cerebrospinal fluid

Some of these endpoints^{34,77–95} are potentially amenable to interventions (eg, freezing as predictor for recurrent falls), and others can merely be used for prognostic counselling (eg, abnormalities on brain imaging). *One study related an active sex life to a slower rate of disease progression, although causality cannot be proven; this finding might suggest that more attention should be paid to sexual activity in the overall management of Parkinson's disease.⁸⁹

p 9). A large, real-life observational study suggested that levodopa, a dopamine receptor agonist, or a monoamine oxidase type B inhibitor all were beneficial as the initial therapy, but that in people receiving levodopa, treatment was tolerated best and mobility scores improved most compared with other strategies.⁹⁹ Levodopa is associated with greater motor improvement, but also with more dyskinesias than dopamine agonists. However, dopamine agonists are associated with more side-effects (eg, nausea, orthostasis, and sleep attacks) and are less well tolerated than levodopa, especially in older people with Parkinson's disease. Impulse control disorders might emerge with prolonged use of dopamine agonists, mainly in men and younger people with Parkinson's disease.⁶

There are considerable interindividual variations in response to levodopa, and there is a sizeable subgroup of otherwise typical people with Parkinson's disease who become progressively resistant to levodopa over time, despite an initially beneficial response. Important remediable causes include chronic constipation and avoidance of levodopa intake simultaneously with proteinaceous meals. Two studies published in 2019 identified a further explanation, namely bacterial decarboxylases, which might be abundantly present in the gut of people with Parkinson's disease because of bacterial overgrowth, chronic constipation, enzyme induction by prolonged levodopa use, or combinations thereof.^{100,101} In rodents, small intestinal bacterial decarboxylase can convert levodopa into dopamine, thereby compromising plasma concentrations of dopamine.¹⁰¹ This mechanism might partially explain why some people with Parkinson's disease respond less favourably to levodopa, and why some develop on-off fluctuations earlier and more severely than others with the disease.

Newer treatment options might address this source of treatment variability through bypassing the gut via alternative routes of levodopa delivery (appendix p 9). Alternative delivery routes appear feasible, as shown by a large randomised, double-blind, placebo-controlled, phase 3 trial that tested the efficacy of CVT-301, a self-administered levodopa oral inhalation powder in people with Parkinson's disease who had substantial off periods under oral levodopa.¹⁰² The immediate improvement after receiving a dose exceeded that of a placebo during in-clinic assessments.

Treatment of non-motor manifestations

Some non-motor symptoms (eg, depression and anxiety) can fluctuate between on and off states, similar to motor symptoms, so dopaminergic drugs can be considered as treatment. However, other non-motor manifestations (eg, orthostatic hypotension or psychosis) are worsened by dopaminergic medication. This emphasises the importance of a multifaceted approach, with the use of both pharmacological and non-pharmacological interventions. Various strategies exist, based on evidence and expert opinion (appendix pp 10–12).^{103,104}

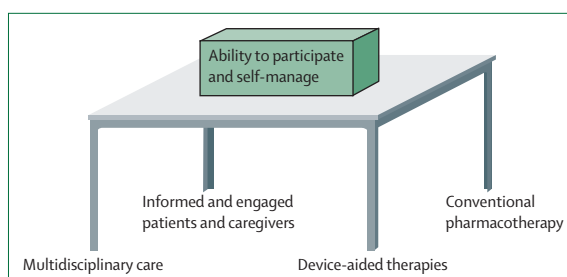


Figure 5: Overall management approach of Parkinson's disease

The overall management approach of Parkinson's disease can be visualised as a table resting on four legs that are needed for all people with Parkinson's disease, except for neurosurgery, which is indicated for only a subgroup. In line with a modern definition of health,⁹⁸ the ultimate goal is to support people with Parkinson's disease in their ability to participate in activities that are meaningful to them, and to support them in self-management.

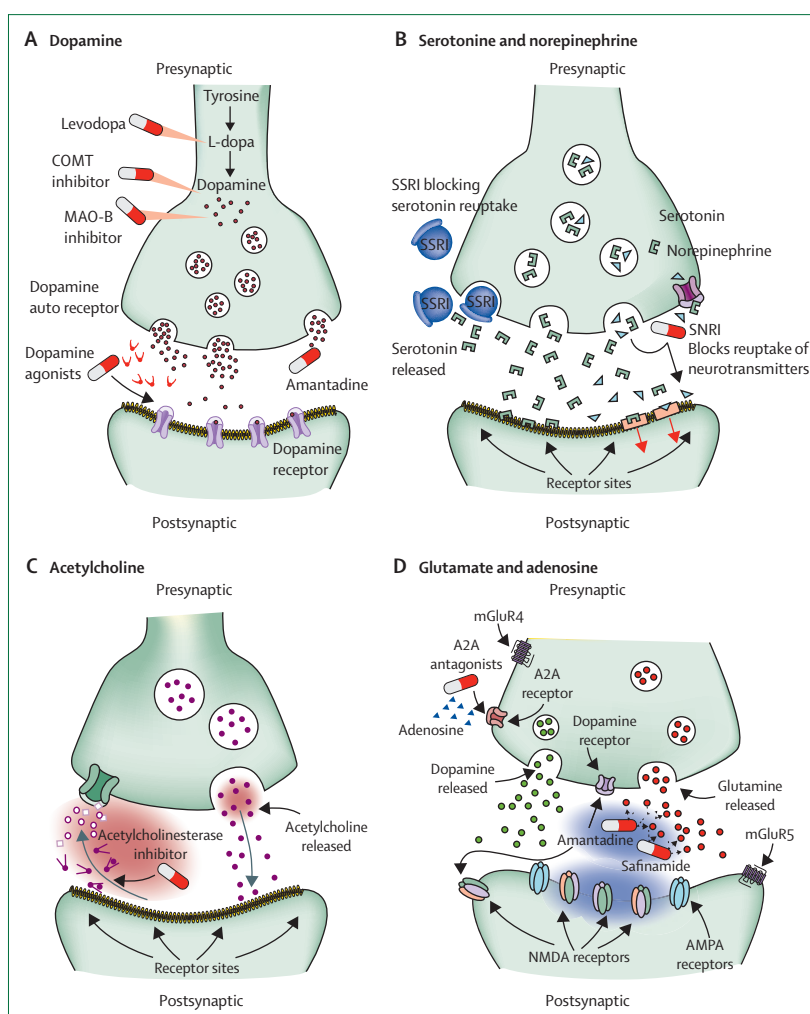


Figure 6: Sites of action for the various antiparkinsonian drugs

Various neurotransmitters that are involved with their respective working mechanism are described. AMPA=α-amino-3-hydroxy-5-methyl-4-isoxazolepropionic acid. COMT=catechol O-methyltransferase. MAO-B=monoamine oxidase type B. NMDA=N-methyl-D-aspartate. SNRI=serotonin-noradrenalin reuptake inhibitor. SSRI=selective serotonin reuptake inhibitor.

Treatment of response fluctuations

Fluctuations in the response to dopaminergic pharmacotherapy typically develop after several years of treatment (appendix p 15).⁶ Several strategies can reduce their severity and effect (appendix p 13). A common approach is to adjust the timing and dosing of oral levodopa. There are also various ways to enhance the half-life of levodopa between doses;⁶ although the working mechanism of these approaches differs, the overall effect is typically a 1 h increase in good on time (ie, when the symptoms of Parkinson's disease are relatively well controlled because of the medication), combined with an equivalent reduction in poor off time (ie, when the symptoms of Parkinson's disease are pronounced and the patient develops a disability because the dopaminergic medication is providing insufficient relief). Reducing off time might be accompanied by increased dyskinesias, which can be accepted if not debilitating.

Unpredictable off periods require a different approach. Treating constipation and improving gastrointestinal motility are crucial first steps. Rapidly acting rescue medications (eg, inhaled levodopa) that bypass the gut can be used.¹⁰² The short-acting dopamine agonist, apomorphine, was already available as a rescue medication via a subcutaneous shot, and now also when delivered as a dissolvable sublingual film.¹⁰⁵

Device-aided therapies

Even when oral treatments are optimally tuned, many people with Parkinson's disease continue to have debilitating response fluctuations, which triggered the development of three types of device-aided therapies that aim at reaching a continuous type of dopaminergic stimulation. The first approach involves neurosurgical interventions targeting the basal ganglia, with either high-frequency stimulation (deep brain stimulation [DBS]) or lesion surgery. The US Food and Drug Administration (FDA) has approved the subthalamic nucleus and globus pallidus internus as potential brain targets for DBS, and the thalamus as target for tremor-dominant Parkinson's disease (although thalamic DBS is rarely used). DBS is usually used bilaterally, but people with quite asymmetric symptoms might only require unilateral surgery. Lesion therapies might also be effective, with the advantage of offering a permanent solution that is not dependent on subsequent finetuning of stimulation settings and occasional battery replacement. Unlike DBS, lesion therapies are usually not applied bilaterally due to risks of speech, swallowing, and cognitive deficits. Unilateral focused ultrasound delivered at high frequencies is a newer FDA-approved lesion technique that can be applied to the thalamus. This therapy is most effective against tremor, but not for bradykinesia and rigidity, and can only be applied unilaterally.^{106–109}

Another approach to address complex response fluctuations is with the use of levodopa–carbidopa intestinal

gel pump therapy. This intervention aims to reach stable plasma levodopa concentrations by ascertaining a continuous levodopa delivery via a percutaneous endoscopic gastrojejunostomy. New work addressed the long-term effects in an open-label sequel to a randomised controlled trial (RCT) with mean follow-up at 4·1 years and a maximum follow-up at 6·9 years.¹¹⁰ Annual discontinuation rate was 10%, but those who continued treatment had less off time and more on time. The main adverse effects were related to the pump therapy (tube replacements). Some people with Parkinson's disease developed severe polyneuropathies due to vitamin B12 deficiency, an issue which will require continuous monitoring.

The third approach is again a pump therapy, with apomorphine delivered subcutaneously during waking hours (approved for use in Europe). The efficacy and safety of 12 weeks of apomorphine infusion have been studied in a double-blind RCT.¹¹¹ The results showed a clinically significant reduction in off time and the treatment was well tolerated.

Multidisciplinary care

Non-pharmacological interventions

Many features of Parkinson's disease do not respond adequately to optimal pharmacotherapy. This issue increases with disease progression because neurodegeneration progressively involves non-dopaminergic brain areas. Moreover, dose-limiting side-effects hamper a successful deployment of pharmacotherapy. This recognition fuelled a drive toward an integrated multidisciplinary management approach, with potentially useful contributions by many different disciplines. The evidence base has increased since the publication of the last *Lancet* Seminar on Parkinson's disease in 2015 (table 3),^{61,112–113} but mainly for the isolated contribution of specific disciplines such as physiotherapy, and less for the bundling of different interventions within an integrated team approach. Several developments are highlighted below.

The role of people with Parkinson's disease in the multidisciplinary team

The question, how can I contribute to my own health, is common in daily practice. As part of the participatory health model, clinicians not only care for people with Parkinson's disease but also encourage individuals to participate in their own care plan. As such, people with Parkinson's disease should be regarded as members of the multidisciplinary team (figure 7). There are many ways people with Parkinson's disease can contribute to their health, including adopting a healthy lifestyle that involves regular exercise and an appropriate diet. Participatory health also means involving people with Parkinson's disease in important medical decisions made on the basis of digestible information tailored to their needs and educational level, and combining

scientific evidence with the physician's experience and the preferences of people with Parkinson's disease.¹³⁴

Physiotherapy

Various physiotherapy strategies are beneficial (summarised in a recent guideline¹²⁰ and meta-analysis¹³⁵). Understanding and applying this evidence in daily practice is important: physiotherapists who received Parkinson's disease-specific training and who treat large numbers of people with Parkinson's disease can have better outcomes at lower costs when compared with generically trained physiotherapists.¹²¹ Many physiotherapy strategies exploit the ability of people with Parkinson's disease to compensate for their motor disability, with alternative motor programmes that bypass defective basal ganglia circuitries. A well known example is that of a person with Parkinson's disease grounded by severe freezing of gait, but who can still effortlessly ride a bicycle. An inventory of the various compensatory approaches that were self-developed by people with Parkinson's disease found seven common underlying strategies that can be disclosed to people with the disease and therapists as basis for personalised treatment.¹¹⁴

Several studies emphasised the benefits of aerobic exercise as symptomatic treatment. Combining aerobic exercise (treadmill walking) with immersion in a three-dimensional virtual reality environment was more effective than aerobic exercise alone in reducing falls.¹¹⁵ As with pharmacotherapy interventions, dose-finding is required. Higher intensities of exercise seem more effective in suppressing symptoms than lower intensities.¹¹² Yet, many people with Parkinson's disease find it difficult to adopt a suitable exercise regime that matches their abilities, or to comply with exercise for long periods of time. Excellent compliance with a home-based exercise programme was done by introducing gamification elements (rewarding participants for engaging in regular exercise) and by coupling people with Parkinson's disease to a personal coach.¹¹³ The results showed that cycling three times per week on a stationary bicycle helped to maintain motor function, whereas the control group who had stretching exercises had their motor functions worsened over time. Whether these effects are merely symptomatic or reflective of a possible disease-modifying effect requires further study.

Nurses for people with Parkinson's disease

Many feel that specialised nurses who care for people with Parkinson's disease can play a crucial role in optimising management of Parkinson's disease—for example, by serving as the first point of access for people with Parkinson's disease, or by acting as a coordinator for the multidisciplinary team. However, there was hitherto little evidence to support these contributions by these specialised nurses. A 2018 trial studied the role of these

	Quality according to GRADE system*
Physiotherapy	
Aerobic exercise ^{112,113}	High
Alternative movement strategies ¹¹⁴	Low
Virtual-reality enhanced gait and balance training ^{115,116}	Moderate
LSVT-BIG ¹¹⁷	Low
Dual task training ¹¹⁸	High
Cognitive training for freezing ¹¹⁹	Moderate
Combined approaches ^{120,121}	Moderate
For people with multiple system atrophy ¹²²	Low
Occupational therapy ¹²³	Moderate
Speech and language therapy ¹²⁴	Moderate
Nurses for people with Parkinson's disease	
Home visits ^{125,126}	Low
Care management ¹²⁷	High
Mindfulness and yoga ¹²⁸	Moderate
Dance ¹²⁹	Low
Bright light therapy ^{130,131}	Low
Palliative care ¹³²	Moderate
Pain management ¹³³	Low
GRADE=grading of recommendations, assessment, development, and evaluations. High=high confidence that the estimate of the effect from the available literature is very close to the true effect. Low=the estimate of the effect might be substantially different from the true effect. Moderate=the estimate of the effect is close to the true effect, but there might be substantial differences. *GRADE is a rating system (based on four rankings) developed to address shortcomings from previous grading systems and rates the quality and strength of a specific intervention before its recommendation for clinical practice. †LSVT-BIG is a variant of the Lee Silverman Voice Treatment in which the therapist instructs the person with Parkinson's disease to purposely make very large (big) amplitude movements.	
Table 3: Non-pharmacological interventions for people with Parkinson's disease, supported by new, graded evidence	

specialised nurses in making home visits by sending nurses into the homes of people with Parkinson's disease, whereas the control group received traditional outpatient visits to the neurologist.¹²⁵ Quality of life improved for those receiving home visits, but accessibility was an issue—many people with Parkinson's disease were ineligible because of long travel distances. New developments in telemedicine will be supportive in this instance, allowing professionals to pay virtual home visits via secure video conferencing. Remote care by a neurologist was associated with similar outcomes, but with much greater efficiency.¹³⁶ A next step is to develop this telemedicine approach for other disciplines. Another project involved sending a neurologist, a social worker, and a specialist nurse on quarterly home visits.¹²⁶ Various undetected problems were identified, stimulating new multidisciplinary interventions. Participants enjoyed the programme, whereas uncontrolled before and after comparisons showed modest reductions in hospitalisation rates and emergency department visits. This approach deserves further evaluation.

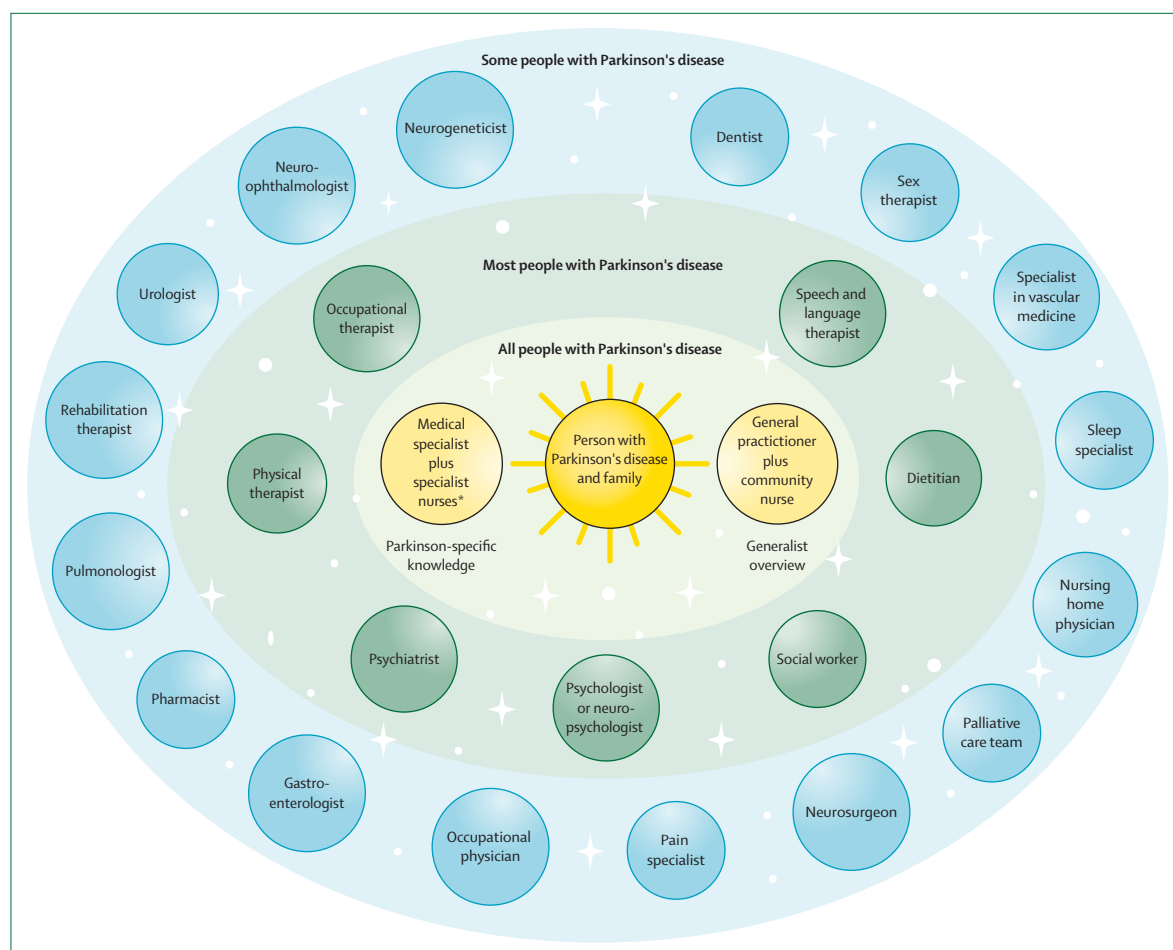


Figure 7: Professional disciplines involved in the multidisciplinary care for people with Parkinson's disease

There are no individual stars within the multidisciplinary team, but the person with Parkinson's disease can be seen as the sun around which the various professionals revolve to deliver their support. Some professionals are always involved in the care of people with Parkinson's disease, which includes the medical specialist (neurologist or geriatrician, depending on the specific setting) supported by a specialist nurse, and the family practitioner who, being a generalist, oversees issues, such as comorbidity and polypharmacy. Other professionals are involved in the care for most people with Parkinson's disease, whereas some are involved with only a smaller group of individuals. This model sketches an ideal situation in which each people with Parkinson's disease has access to each of these disciplines, which unfortunately is not the case in most places in the world. *Nurses who care for people with Parkinson's disease.

Late-stage Parkinson's disease

There is a heightened interest in the most severe stages of Parkinson's disease. New studies identified considerable disabilities, but also recognised remaining treatment options.^{137,138} Adjusting levodopa can alleviate some symptoms in advanced Parkinson's disease, albeit at the risk of worsening dyskinesias or psychosis.¹³⁷ Further insights came from a multicentre study of late-stage parkinsonism, which included a pragmatic RCT that tested the merits of remote advice by a movement disorders expert, delivered to the primary physician of people with Parkinson's disease.¹³⁸ There was no difference in primary outcome (activities of daily living), but quality of life was better for treated people with Parkinson's disease compared with usual care.

An area of largely unmet need relates to end-of-life issues and palliative care. Obvious palliative care needs are often present in people with Parkinson's disease,¹³⁹

but many have great difficulties accessing palliative services. This issue was addressed by a non-blinded trial, in which people with parkinsonism plus caregivers received either outpatient multidisciplinary palliative care or standard care.¹³² Quality of life was significantly better for the palliative care group compared with the standard care group at 6 months, although group differences did not reach the prespecified threshold for clinical relevance. Group differences were no longer visible after 12 months. This study was important in drawing attention to the possible benefits of outpatient palliative care for people with Parkinson's disease. Further work should address how the effects can be amplified and maintained over time.

Future directions for Parkinson's disease research

Despite the progress since the previous *Lancet* Seminar on Parkinson's disease,⁶¹ much remains to be discovered.

Stimulated by the most poignant questions that we, as authors, commonly encounter in our clinical practices, we highlight several directions for future research here.

Lifestyle interventions

The incidence and prevalence of Parkinson's disease are rising fast, but we must now identify the most relevant risk factors, especially modifiable ones, thus offering targets to potentially mitigate the risk of developing Parkinson's disease. People with Parkinson's disease tell us that this area should increasingly focus on lifestyle factors. A meta-analysis showed that moderate to vigorous exercise, but not light exercise, is associated with a reduced risk of developing Parkinson's disease,⁵⁶ but intervention studies must show that this association does not result from reverse causation (eg, because people with prodromal parkinsonism have subtle manifestations that keep them from exercising), and that promoting physical activity lowers the risk of Parkinson's disease. The same applies to experimental manipulations of dietary factors, such as the Mediterranean diet,¹⁴⁰ or consumption of coffee, tea, alcohol, or dairy products.⁷⁷

Restoring dopamine loss

Many people with Parkinson's disease have questions about the prospect of cell transplants. The idea is that transplantation of dopamine-producing cells, derived from human embryonic stem cells or from induced pluripotent stem cells, into the putamen could selectively restore dopamine loss. Most work focused on transplantation of human fetal ventral mesencephalic tissue. The trials produced variable outcomes, and unexpected findings. First, graft survival and outgrowth was not necessarily accompanied by corresponding clinical improvements.¹⁴¹ Second, after some transplants, a unique side-effect emerged in the form of so-called runaway dyskinesias: post-transplantation iatrogenic hyperkinetic movements occurring in both the dopaminergic on or off states. Important new insights are expected from the ongoing TRANSEURO study, which assesses the efficacy and safety of human fetal ventral mesencephalic tissue transplants in people with young-onset Parkinson's disease who have been tested for pathogenic variants in genes linked to Parkinson's disease (to exclude that specific genetic deficits could explain unexpectedly good or bad outcomes).¹⁴² Other cellular-based therapies should be explored further, including delivering infusions of glial cell line-derived neurotrophic factor or other neurotrophic factors into the brain, knowing that these growth factors have neurorestorative and neuroprotective effects in non-human primate models of Parkinson's disease. One RCT examined a novel approach, in which glial cell line-derived neurotrophic factor was infused directly into the putamen with a bilaterally implanted, convection-enhanced delivery system.¹⁴³ People with Parkinson's disease in the

intervention group improved considerably, but so did the control group (perhaps because this complex intervention elicited a strong placebo response), without statistically significant group difference in outcomes. Further work should explore whether higher doses, prolonged interventions, or targeting earlier disease phases will afford clinically meaningful improvements.

Slowing down Parkinson's disease

Pending a cure, people with Parkinson's disease place their hopes on the arrival of disease-modifying


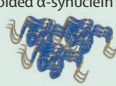




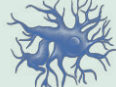
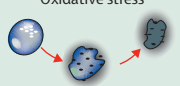

Target	Therapy	
	Preclinical studies	Clinical studies
SNCA 	Beta-2 adrenergic receptor, siRNA, non-steroidal anti-inflammatory drugs, antistreptolysin O	Thiazolidinedione (glitazones)
Misfolded α -synuclein fibrils 	Anti-LAG3 antibody, small molecule inhibitors, CLR01, KYP	Active or passive immunotherapy (eg, BIlB065), nilotinib, deferiprone
Autophagy lysosomal pathway 	LTI-291, AT3375	Ambroxol, glucosylceramide synthase inhibitors
Calcium ion homeostasis 	Calcium ion channel blockers	Calcium ion channel blockers (eg, isradipine)
Mitochondria dysfunction 	Ursolic acid, mitochondrial division inhibitor 1, MIRO reduction, sirolimus	11-dehydrosinulariolide, MitoQ, exenatide, LRRK2 small molecule kinase inhibitors
Neurotrophic factors 	Brain-derived neurotrophic factors, vascular endothelial growth factor	Cerebral dopamine neurotrophic factor, glial cell line-derived neurotrophic factor, neurturin
Inflammation 	Anti-inflammatory (eg, non-steroidal anti-inflammatory drugs)	Sargramostim, exenatide, liraglutide, lixisenatide, AZD3241
Oxidative stress 	DJ-1 chaperones	Deferiprone, inosine, coenzyme Q10, caffeine, nicotine, creatine
Therapies under investigation		
 Vaccines, neuroinflammatory therapies, diets and microbiome, cannabinoids, novel druggable targets, gene therapy, and next generation adaptive deep brain stimulation Emerging future therapies		

Figure 8: Emerging future therapies for Parkinson's disease

These therapies are aimed at slowing down disease progression in people with Parkinson's disease, or at postponing onset of disease manifestations in people with a prodromal phase of Parkinson's disease. The pipeline of planned or ongoing trials aiming at disease modification is broad and deep, including many targets and, in many cases, multiple drugs for each target.

treatments. Many ongoing efforts focus on the possibility to slow the progression of Parkinson's disease, or to postpone disease onset in people with a prodromal phase (figure 8). Some interventions have been custom-made, aiming to directly target the underlying disease pathology. One main group specifically targeted the pathologically misfolded α -synuclein, aiming to reduce its production, limit its prion-like spread, or promote its clearance. Other interventions were identified following a process of drug repurposing: identifying existing medications that were used previously for another indication, but that should theoretically also target the disease process underlying Parkinson's disease.¹⁴⁴ One example involves treatment focused specifically on carriers of *GBA* mutations, a genetic risk factor for Parkinson's disease. The cough suppressant, ambroxol, increases lysosomal acid GCase enzyme activity and reduces α -synuclein concentrations. The first studies (NCT02914366 and NCT02941822) evaluating the safety, tolerability, and pharmacodynamics of ambroxol are underway.^{145,146} Other repurposed drugs include nilotinib (used originally to treat leukaemia, but possibly relevant for Parkinson's disease because it is a tyrosine kinase inhibitor),^{147,148} the antidiabetic drug, exenatide (a GLP-1 agonist with neuroprotective effects in experimental models of parkinsonism),¹⁴⁹ and the prostate drug, terazosin (which increases cellular ATP concentrations by stimulating glycolysis via enhanced activity of phosphoglycerate kinase 1).¹⁵⁰ Exenatide showed signs of efficacy in a clinical trial¹⁴⁹ and is being tested further in a carefully designed trial. However, the field has also witnessed disappointments, including unconvincing outcomes for nilotinib, inosine, isradipine and simvastatin.

Biomarker development

The success of future trials will crucially depend on much-needed innovations. First, there is a need for reliable biomarkers to improve the diagnostic accuracy in early disease phases. Various biomarkers have been proposed,^{78,151–154} but these remain investigational. Second, increased recognition of many clinical scales that document the outcome of experimental interventions that are imperfect: subjective scoring introduces large variability, assessments are typically administered in clinics where many people with Parkinson's disease respond differently than at home, and the scales are usually administered episodically, providing at best a snapshot of the complex and fluctuating response at home. Answers might come from better patient-reported outcomes than from simple interviews done in the examination room, or from remote digital measurements, which theoretically allow for an objective, continuous, and home-based assessment. Various trajectories seem promising, including use of sensors (body-worn or incorporated into homes), dedicated smartphone apps, or analysis of keyboard typing behaviour.^{155–158}

Underserved populations

Another research area relates to the need to ascertain improved access to services for people with Parkinson's disease in underserved areas of the world. Depending on where you live, the clinical presentation of Parkinson's disease might vary because of factors such as regional genetic differences or specific dietary habits that cause differences in comorbidity.¹⁵⁹ Even straightforward interventions, such as levodopa, are not readily available for many people with Parkinson's disease, or are inaccessible due to costs. Knowledge about Parkinson's disease is scarce in numerous places, sometimes with substantial consequences. For example, in South Africa, some people think that Parkinson's disease results from witchcraft, and that affected individuals should not be allowed to live in the community.¹⁶⁰ This undesirable way of thinking highlights the tremendous importance of global educational efforts.

Conclusion

Parkinson's disease has been recognised for over 200 years. Together, the various forms of Parkinson's disease create fast-growing health-care issues with enormous global impact. Fortunately, Parkinson's disease is treatable, particularly when the interventions are delivered with a personalised approach, and by well trained experts.¹⁶¹ Encouraged by the many exciting developments highlighted here, we have hope that treatments and services will continue to evolve, with a tangible effect on people with Parkinson's disease worldwide.

Contributors

BRB and CK developed the outline for this Seminar. CK did the literature search, with subsequent input from BRB and MSO. BRB wrote the first draft for most sections, except for the sections on aetiology and pathophysiology that were initially drafted by CK. MSO provided crucial input on all sections of the manuscript. All authors have verified the underlying data from the literature review.

Declaration of interests

BRB serves as the coeditor in chief for the *Journal of Parkinson's Disease*, serves on the editorial board of *Practical Neurology* and *Digital Biomarkers*, has received fees from serving on the scientific advisory board for Biogen and UCB (paid to the institute), has received fees for speaking at conferences from AbbVie, Biogen, UCB, Zambon, Roche, GE Healthcare, and Bial (paid to the institute), and has received research support from the Netherlands Organization for Health Research and Development, Michael J Fox Foundation, UCB, AbbVie, Stichting Parkinson Fonds, Hersenstichting Nederland, Parkinson's Foundation, Verily Life Sciences, Horizon 2020, Topsector Life Sciences and Health, and the Parkinson Vereniging, outside the submitted work. BRB does not hold any stocks or stock options with any companies that are connected to Parkinson's disease or to any of the topics in this paper. MSO serves as a consultant for the Parkinson's Foundation, and has received research grants from US National Institutes of Health (NIH), Parkinson's Foundation, the Michael J Fox Foundation, the Parkinson Alliance, Smallwood Foundation, the Bachmann-Strauss Foundation, the Tourette Syndrome Association, and the UF Foundation. MSO's DBS research is supported by NIH R01NR014852 and R01NS096008. MSO is the principal investigator of the NIH R25NS108939 Training Grant. MSO has received royalties for publications with Demos, Manson, Amazon, Smashwords, Books4Patients, Perseus, Robert Rose, Oxford, and Cambridge

(movement disorders books). MSO is an associate editor for *JAMA Neurology* and for *New England Journal of Medicine Journal Watch Neurology*. MSO has participated in continuous medical education and educational activities on movement disorders funded by the Academy for Healthcare Learning, PeerView, Prime, QuantiaMD, WebMD and Medscape, Medicus, MedNet, Einstein, MedNet, Henry Stewart, American Academy of Neurology, Movement Disorders Society, and by Vanderbilt University. The institution (not MSO) receives grants from Medtronic, AbbVie, Boston Scientific, Abbott, and Allergan and the principal investigator has no financial interest in these grants. MSO has participated as a site principal investigator, or coinvestigator, or both for several NIH, foundation, and industry funded trials over the years but has not received honoraria. Research projects at the University of Florida receive device and drug donations. MSO does not hold any stocks or stock options with any companies that are connected to Parkinson's disease or to any of the topics in this paper. CK is deputy editor of *Movement Disorders* and associate editor of *Annals of Neurology*. CK serves as a medical adviser to Centogene for genetic testing reports in the fields of movement disorders and dementia, excluding Parkinson's disease and does not hold any stocks or stock options with any companies that are connected to Parkinson's disease or to any of the topics in this paper.

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