

# The Evolving Landscape of Parkinson's Disease Research: Current Challenges and Future Outlook

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## Abstract

Parkinson's disease (PD) is a progressive neurodegenerative disorder that primarily affects movement. It occurs due to gradual loss of dopamine-producing brain cells, particularly in the substantia nigra. The exact cause of Parkinson's disease is not fully understood, but it is believed to involve a combination of genetic and environmental factors. Currently available treatments provide symptomatic relief but do not halt disease progression. Research efforts are currently focused on developing disease-modifying therapies that target the underlying pathological mechanisms of PD. Breakthroughs in PD biomarkers hold immense promise: earlier diagnosis, better monitoring, and targeted treatment based on individual response could significantly improve patient outcomes and ease the burden of this disease.

Research into PD is an active and evolving field, with ongoing efforts focused on understanding disease mechanisms, identifying biomarkers, developing new treatments, and improving patient care. In this paper, we analyze data from the CAS Content Collection to summarize the research progress in PD. We examine the publication landscape in effort to provide insights into current knowledge advances and developments. We also review the most discussed and emerging concepts and assess the strategies to combat the disease. We explore genetic risk factors, pharmacological targets, and comorbid diseases, inspect clinical applications of products against PD with their development pipelines and efforts for drug repurposing. The objective of this review is to provide a broad overview of the evolving landscape of current knowledge regarding PD, to outline challenges, and evaluate growth opportunities to further efforts in combating the disease.

**Keywords:** Parkinson's disease; pathogenesis; aging; dopaminergic neuron; alpha-synuclein; Lewy bodies; protein aggregation; biomarker

## Introduction

Parkinson's disease is a progressive neurodegenerative disorder that primarily affects movement.<sup>1-3</sup> It is characterized by the gradual loss of dopamine-producing neurons in the brain, particularly in a region called the substantia nigra. Dopamine is a neurotransmitter involved in coordinating movement, and its deficiency leads to the characteristic motor symptoms of Parkinson's disease, including tremors, bradykinesia (slowness of movement), muscle rigidity, and postural instability.<sup>4</sup> Additionally, Parkinson's disease can cause a range of non-motor symptoms, such as cognitive impairment, depression, and sleep disturbances.<sup>5</sup> While the exact cause of Parkinson's disease is not fully understood, it is believed to involve a combination of genetic, environmental, and age-related factors. There is currently no cure for Parkinson's disease, but treatments are available to help manage its symptoms and improve quality of life for affected individuals.

Parkinson's disease (PD) is the second most common neurodegenerative disorder after Alzheimer's disease.<sup>6</sup> Its prevalence increases with age, with the majority of cases occurring in individuals over the age of 60. Estimates of prevalence vary globally, but it is generally reported to affect around 1-2% of individuals over the age of 65.<sup>7</sup> Prevalence rates tend to be higher in industrialized countries compared to developing nations. While most cases of PD are sporadic, a small percentage (~5-10%) are believed to have a genetic component.<sup>8</sup> Certain genetic mutations have been linked to familial forms of Parkinson's disease, which may present at an earlier age and have a stronger family history. Parkinson's disease prevalence rates can vary across different regions and countries.<sup>9</sup> Factors such as environmental exposures, lifestyle habits, and access to healthcare may contribute to these variations with some studies suggesting higher prevalence rates in certain regions, such as Europe and North America, compared to other parts of the world.<sup>9</sup> Research into the epidemiology of Parkinson's disease continues to evolve, with efforts to understand regional differences and trends over time.

In this paper, we analyze data from the CAS Content Collection to summarize the research progress in Parkinson's disease. We examine the publication landscape in the area in effort to provide insights into current knowledge advances and developments. We review the most discussed and emerging concepts and assess the strategies to combat the disease. We explore the genetic risk factors, pharmacological targets, and comorbid diseases. Finally, we inspect clinical applications of products against PD with their development pipelines and efforts for drug repurposing. The objective of this review is to provide a broad overview of the evolving landscape of current knowledge regarding the class of PD, to outline challenges, and evaluate growth opportunities to further efforts in combating the diseases.

The objective of this review is to provide a broad outline of the evolving landscape of current knowledge regarding PD, to delineate challenges, and evaluate growth opportunities, to further efforts in solving the problems that remain. The novelty and merit of the article stem

from the extensive, wide-ranging coverage of the most up-to-date scientific information accumulated in the CAS Content Collection allowing unique, unmatched breadth of landscape analysis and in-depth insights.

## Overview of Parkinson's disease

### *Etiology and Risk Factors*

The etiology of Parkinson's disease is complex and not fully understood, but it is believed to involve a combination of genetic, environmental, and age-related factors.<sup>1-3</sup>

- **Aging** is the most significant risk factor for Parkinson's disease, with the majority of cases diagnosed in individuals over the age of 60.<sup>10</sup> As people age, there is a natural decline in the function and integrity of dopamine-producing neurons in the brain, which may contribute to the development of PD.

- While most cases of PD are sporadic (occurring randomly), a small percentage (around 5-10%) are believed to have a **genetic** component.<sup>11-13</sup> Several genes have been implicated in familial forms of PD, including mutations in the SNCA ( $\alpha$ -synuclein), LRRK2 (leucine-rich repeat kinase 2), Parkin (PARK2), PINK1 (PARK6), and DJ-1 (PARK7) genes.<sup>14-17</sup> These genetic mutations can disrupt cellular processes involved in protein degradation, mitochondrial function, and oxidative stress response, leading to neuronal dysfunction and degeneration in the brain.

- Exposure to certain **environmental** toxins and chemicals has been linked to an increased risk of developing PD.<sup>18,19</sup> The most well-known environmental risk factor for PD is exposure to pesticides and herbicides<sup>20</sup>, particularly those containing compounds like rotenone and paraquat. Other potential environmental risk factors include industrial chemicals, heavy metals (e.g., lead, manganese), and certain solvents (e.g., trichloroethylene). Some studies have also suggested a possible association between PD risk and factors such as rural living, well-water consumption, and exposure to certain metals in drinking water.<sup>21</sup>

- Certain medical conditions and **lifestyle** factors have also been implicated as potential risk factors for PD, although their roles are less well-established.<sup>22</sup> These include head injuries, prior exposure to viral infections, smoking, and caffeine consumption. Chronic inflammation and oxidative stress are thought to play roles in the pathogenesis of PD, and factors that contribute to these processes may influence disease risk.<sup>23</sup>

### *Pathophysiology*

The pathophysiology of PD is multifactorial, involving a complex interplay of genetic, environmental, and molecular factors. It involves complex changes in the brain, particularly in regions associated with movement and motor control.

The hallmark feature of Parkinson's disease is the dopaminergic neurodegeneration – progressive loss of dopamine-producing neurons in the substantia nigra, a region of the brain

involved in movement control.<sup>24-26</sup> Dopamine is a neurotransmitter that plays a critical role in regulating motor function and coordination. Its depletion leads to the characteristic motor symptoms of PD, such as tremors, rigidity, and bradykinesia (slowness of movement).

Another characteristic feature of PD is the accumulation of abnormal protein aggregates known as Lewy bodies within neurons.<sup>27-29</sup> Lewy bodies primarily consist of misfolded  $\alpha$ -synuclein protein and are found in various brain regions, including the substantia nigra and other structures involved in motor and cognitive function. The presence of Lewy bodies is thought to contribute to neuronal dysfunction and degeneration, although the exact role they play in the pathogenesis of PD is still under investigation.

Chronic inflammation and oxidative stress are also believed to play significant roles in the progression of Parkinson's disease.<sup>23, 30-32</sup> Inflammatory processes in the brain, mediated by activated microglia and astrocytes, can lead to neuronal damage and contribute to the degenerative cascade. Oxidative stress, resulting from an imbalance between reactive oxygen species (ROS) and antioxidant defenses, can damage cellular components and exacerbate neuronal dysfunction and death.

Dysfunction of mitochondria, the cellular organelles responsible for energy production, has been implicated in the pathophysiology of PD.<sup>33-35</sup> Mitochondrial impairment can lead to energy deficits, increased oxidative stress, and activation of cell death pathways, contributing to neuronal degeneration. Mutations in genes associated with mitochondrial function, such as PINK1 and Parkin, have been linked to familial forms of Parkinson's disease.

Dysfunction in protein clearance mechanisms, including autophagy and the ubiquitin-proteasome system, may contribute to the accumulation of misfolded proteins and the formation of Lewy bodies.<sup>36-38</sup> Impaired clearance of damaged or aggregated proteins can overwhelm cellular defenses and lead to neuronal toxicity and degeneration.

## **Diagnosis**

The diagnosis of PD requires a comprehensive evaluation by a healthcare professional experienced in movement disorders, incorporating clinical judgment, symptom assessment, and supportive diagnostic tests as needed. Early diagnosis is crucial for initiating appropriate treatment and supportive care to improve outcomes and quality of life for patients with PD.<sup>4, 39, 40</sup>

Diagnosis of PD is primarily based on clinical evaluation, including assessment of motor symptoms, medical history, and neurological examination. While there is no definitive test to diagnose PD, healthcare professionals use established criteria and a combination of diagnostic tools to make an accurate diagnosis. A detailed physical examination is performed to evaluate motor function, including assessment of tremor, bradykinesia (slowness of movement), muscle rigidity, and postural stability. Non-motor symptoms, such as cognitive impairment, psychiatric symptoms, autonomic dysfunction, and sleep disturbances, may also be assessed during the evaluation. Response to dopaminergic medications, particularly levodopa (L-dopa), can provide supportive evidence for the diagnosis of PD.<sup>41-43</sup>

While neuroimaging is not typically required for diagnosing PD, it may be used to support the diagnosis and rule out other conditions that can mimic PD.<sup>44-46</sup> Structural neuroimaging techniques such as magnetic resonance imaging (MRI) may be used to exclude other causes of parkinsonism, such as tumors or stroke. Functional imaging techniques such as dopamine transporter (DAT) imaging with single-photon emission computed tomography (SPECT) or positron emission tomography (PET) can assess dopamine transporter activity in the brain, which is typically reduced in PD.

Several sets of clinical diagnostic criteria have been developed to aid in the diagnosis of PD, including the UK Brain Bank Criteria<sup>47, 48</sup> and the Movement Disorder Society (MDS) Clinical Diagnostic Criteria for Parkinson's Disease<sup>49, 50</sup>. These criteria incorporate clinical features, response to medication, and exclusion of other parkinsonian syndromes to establish a diagnosis of PD.

## **Treatment**

While there is currently no cure for PD, treatments are available to help alleviate symptoms, improve quality of life, and slow disease progression. Therapeutic approaches include pharmacotherapy with dopaminergic medications (e.g., levodopa, dopamine agonists, MAO-B inhibitors)<sup>51</sup>, deep brain stimulation (DBS) surgery<sup>52</sup>, focused ultrasound<sup>53</sup>, physical therapy, occupational therapy, speech therapy, and lifestyle modifications.<sup>54, 55</sup> The specific treatment plan is tailored to each individual based on their symptoms, disease stage, and overall health. Additionally, ongoing research continues to explore potential therapies aimed at slowing or halting the progression of the disease. Early diagnosis and intervention are crucial in managing PD and improving quality of life for affected individuals. Overall, the management of PD is multidisciplinary and requires a collaborative approach involving healthcare professionals, patients, and caregivers. By addressing motor and non-motor symptoms, optimizing medication regimens, promoting healthy lifestyle habits, and providing supportive care, it is possible to enhance quality of life and functional independence for individuals living with PD.

### *Medications and surgical interventions*

- Levodopa (L-dopa) is the most effective medication for managing motor symptoms of PD.<sup>56, 57</sup> It is converted into dopamine in the brain, replenishing dopamine levels and improving motor function.
- Dopamine agonists mimic the action of dopamine in the brain and can be used alone or in combination with levodopa.<sup>58, 59</sup>
- Monoamine oxidase type B (MAO-B) inhibitors help prevent the breakdown of dopamine and prolong its effects, thereby reducing motor symptoms.<sup>60, 61</sup>
- Catechol-O-methyltransferase (COMT) inhibitors prolong the effects of levodopa by inhibiting its breakdown.<sup>62, 63</sup>
- Amantadine can help alleviate dyskinesias (involuntary movements) and may also provide modest benefits for other PD symptoms.<sup>64, 65</sup>
- Anticholinergic drugs may be used to manage tremors and dystonia in some cases.

- Duopa is a gel formulation of levodopa and carbidopa that is delivered continuously through a pump system directly into the small intestine. It can provide more stable levodopa levels and improve motor fluctuations in advanced PD. <sup>66-68</sup>
- Deep Brain Stimulation involves implanting electrodes into specific brain regions and delivering electrical impulses to modulate abnormal neuronal activity. <sup>52, 69</sup> It can help improve motor symptoms and reduce medication-related complications in certain patients.
- Focused ultrasound targets and ablates the globus pallidus to treat mobility symptoms, tremor, rigidity, and dyskinesia in both tremor-dominant and advanced Parkinson's disease patients. <sup>53</sup>

### *Rehabilitative therapies and lifestyle modifications*

Rehabilitation is considered as supplementary to pharmacological and surgical treatments for PD in effort to maximize functional ability and minimize secondary complications. <sup>70-72</sup>

- Physical therapy can help improve mobility, balance, flexibility, and strength in PD patients. It may also include exercises to address gait abnormalities and freezing of gait.
- Occupational therapists can assist PD patients in developing strategies to perform daily activities more independently and safely, as well as recommend assistive devices and modifications to the home environment.
- Speech therapists can work with PD patients to address speech and swallowing difficulties, improve vocal projection, and teach techniques to enhance communication.
- Exercise, including aerobic activities, strength training, and balance exercises, can help improve motor function, mobility, and overall well-being in PD patients.
- A balanced diet rich in fruits, vegetables, whole grains, and lean proteins may support overall health and help manage constipation, a common non-motor symptom of PD.
- Stress management techniques such as mindfulness, relaxation exercises, and stress reduction strategies may help alleviate anxiety and improve coping mechanisms.

## **Landscape analysis of Parkinson's disease research**

### ***Journal publication and patent trends***

The CAS Content Collection <sup>73</sup> is the largest human-compiled collection of published scientific information. It represents a valuable resource to access and keep up to date on the scientific literature all over the world, across disciplines, including chemistry, biomedical sciences, engineering, materials science, agricultural science, and many more. This allows quantitative analysis of global research publications across various parameters including time, geography, scientific area, medical application, disease, and chemical composition. Currently, there are over 220,000 scientific publications (mainly journal articles and patents) in the CAS Content Collection related to the Parkinson's disease. There has been a steady growth of these documents over the last two decades, with an >30% increase since 2019 (Figure 1A). The growth rate in the area of PD research is similar to that in the general class of neurodegenerative diseases, with PD growth being faster in the earlier years (2023-2015), but slightly lagging behind recently (Figure 1B). The scientific journal publications notably dominate (journal/patent

ratio ~4-6), but in the recent three years the number of patents exhibited notable growth, correlating with the initial accumulation of scientific knowledge and its subsequent transfer into patentable applications.

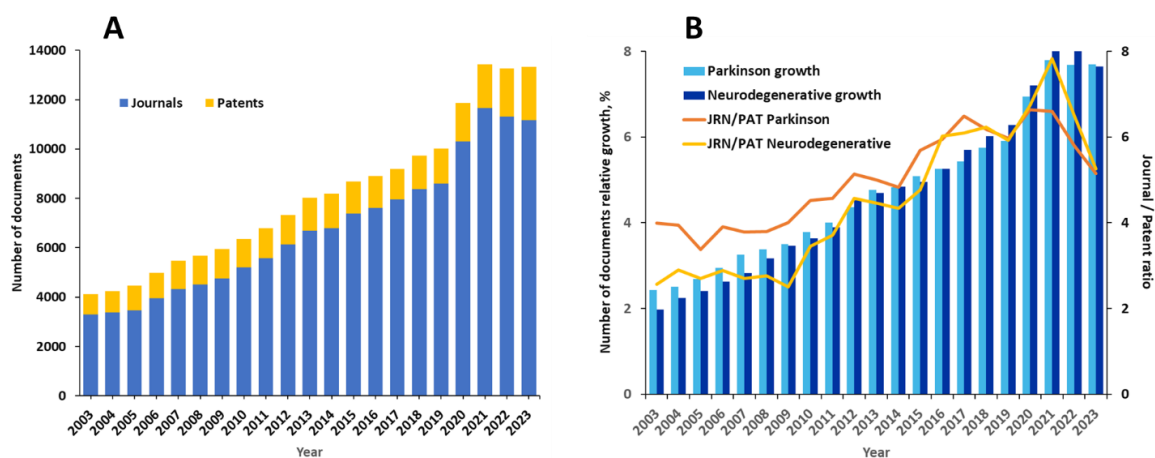


Figure 1. (A) Yearly trend of the number of documents (journal articles and patents) in the CAS Content Collection™ related to PD; (B) comparison between relative growth in the number of documents related to PD (light blue bars) and all neurodegenerative diseases (dark blue bars); orange and yellow lines compare the journal/patent ratio for the class of PD and all neurodegenerative diseases, respectively.

The United States, China, Japan, South Korea, Germany, France, the United Kingdom, Italy, and Canada, are the leaders with respect to the number of published journal articles and patents related to PD research, with ~1/3 of the patents coming from the United States (Figure 2). The journals *Movements Disorders*, *Parkinsonism & Related Disorders*, *Neurology*, and *PLoS One* have published the highest number of articles related to PD research (Figure 3).

The National Institutes of health (NIH), USA, the Capital Medical University, China, the University of California, USA, Juntendo University School of Medicine, Japan, and the University of Cambridge, UK, have the largest number of published articles in scientific journals (Figure 4A). Patenting activity is dominated by corporate players as compared to academics (Figure 4B,C). F. Hoffmann-La Roche, AstraZeneca, Merck (MSD), Neurosearch, and Pfizer have the highest number of patent applications among commercial organizations (Figure 4B), while the University of California, CNRS (France), Korea Institute of Science and Technology, Massachusetts General Hospital, and Johns Hopkins University lead among the non-commercial organizations (Figure 4C).

The class of organic/inorganic small molecules dominate the PD field (Figure 5). There is considerable variation in the distribution of substance classes between journal articles and patents. While small molecules strongly dominate in the patents (>70%), in the journal articles small molecules, nucleic acids, and proteins/peptides are nearly equally represented (28%, 39%, and 27%, respectively) (Figure 5, inset). That difference is not unexpected, since small molecule drugs are of certain commercial interest and thus more represented in patents, while journal articles generally discuss more fundamental features of the disease thus discussing all three classes of substances.

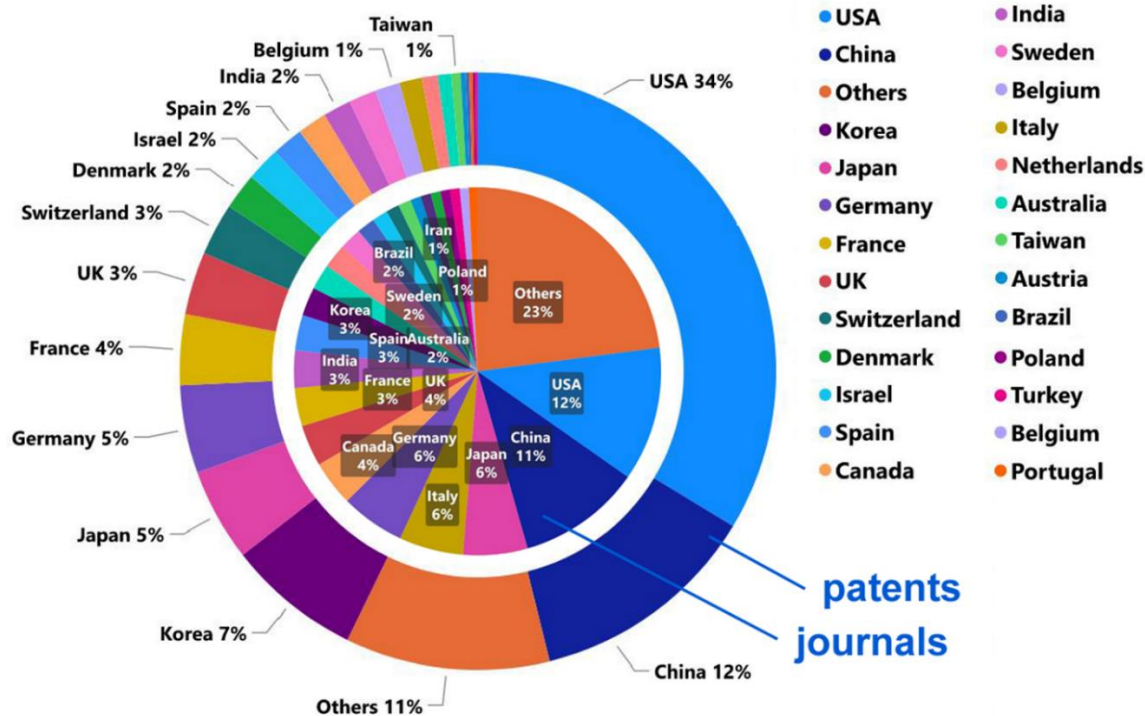


Figure 2. Top countries with respect to the percentage of PD-related journal articles (inner pie chart) and patents (outer donut chart) in the CAS Content Collection.

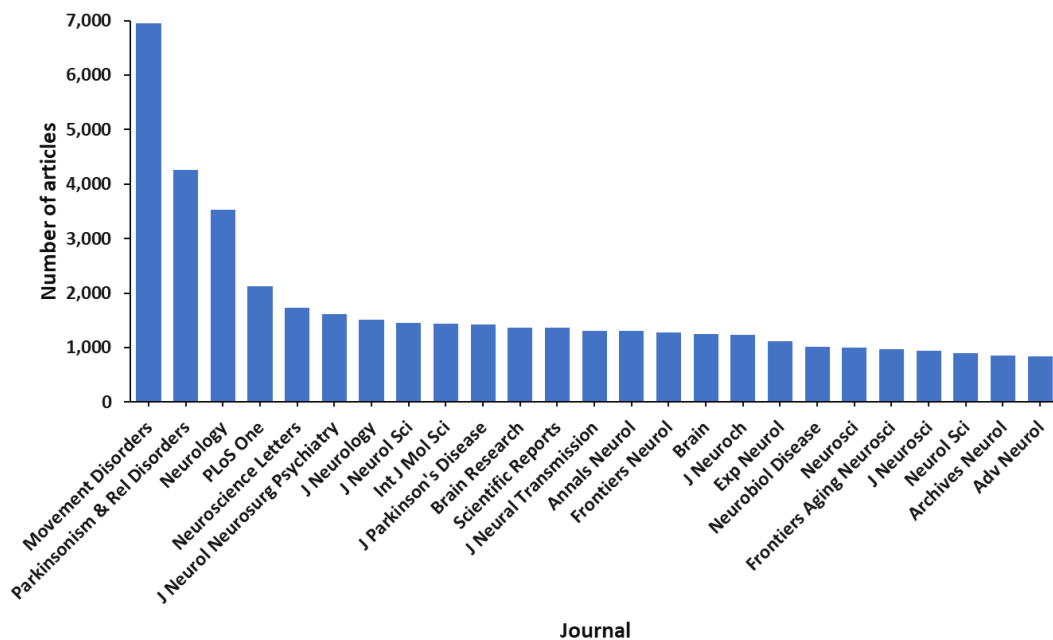


Figure 3. Leading scientific journals in the field of PD research based on journal publication data from the CAS Content Collection for the period 2003-2023.



A Journal articles			B Patents			C		
Organization	Country	Number of articles	Organisation (commercial)	Country	Number of patents	Organisation (non-commercial)	Country	Number of patents
National Institutes of Health USA	USA	593	F. Hoffmann-La Roche	Switzerland	463	University of California	USA	259
Capital Medical University	China	454	AstraZeneca	UK	271	CNRS	France	152
University of California	USA	422	Merck Sharp & Dohme	USA	258	Korea Inst. Sci. Technol.	S. Korea	109
Juntendo University School of Medicine	Japan	409	Neurosearch	Denmark	242	Massachusetts General Hospital	USA	103
University of Cambridge	UK	409	Pfizer	USA	237	Johns Hopkins University	USA	101
Central South University	China	367	Janssen Pharmaceutica	Belgium	214	Vanderbilt University	USA	95
Emory University	USA	364	Sanofi-Aventis	France	171	CSIC	Spain	87
Chinese Academy of Sciences	China	356	Vertex Pharmaceuticals	USA	160	Harvard College	USA	72
Lund University	Sweden	349	H. Lundbeck	Denmark	145	Leland Stanford Junior University	USA	72
University of Pennsylvania	USA	344	Abbott Laboratories	USA	143	Massachusetts Inst. Technol.	USA	71
Huazhong University of Science and Technology	China	321	Wyeth	USA	118	Sichuan University	China	70
Harvard Medical School	USA	320	Gruenenthal	Germany	97	Duke University	USA	67
Fudan University	China	300	Taisho Pharmaceutical	Japan	96	China Pharmaceutical University	China	65
King's College	UK	288	Les Laboratoires Servier	France	95	Emory University	USA	65
University of Pittsburgh	USA	280	Bristol-Myers Squibb	USA	91	Shanghai Inst., Chinese Acad. Sci.	China	64
University College London	UK	267	Genentech	USA	85	Seoul National University	S. Korea	59
University of British Columbia	Canada	265	Novartis	Switzerland	81	Scripps Research Institute	USA	57
University of Toronto	Canada	249	Merck KGaA	Germany	74	University of South Florida	USA	56
Sichuan University	China	247	Elan Pharmaceuticals	Ireland	73	INSERM	France	55
Karolinska Institutet	Sweden	246	Sunshine Lake Pharma	China	68	Yale University	USA	51
Mayo Clinic	USA	246						
Columbia University	USA	242						
McGill University	Canada	225						
Nanjing Medical University	China	224						
University of Oxford	UK	224						

Figure 4. Leading organizations in the field of PD in terms of number of published journal articles (A) and patents by commercial (B) and non-commercial (C) organizations.

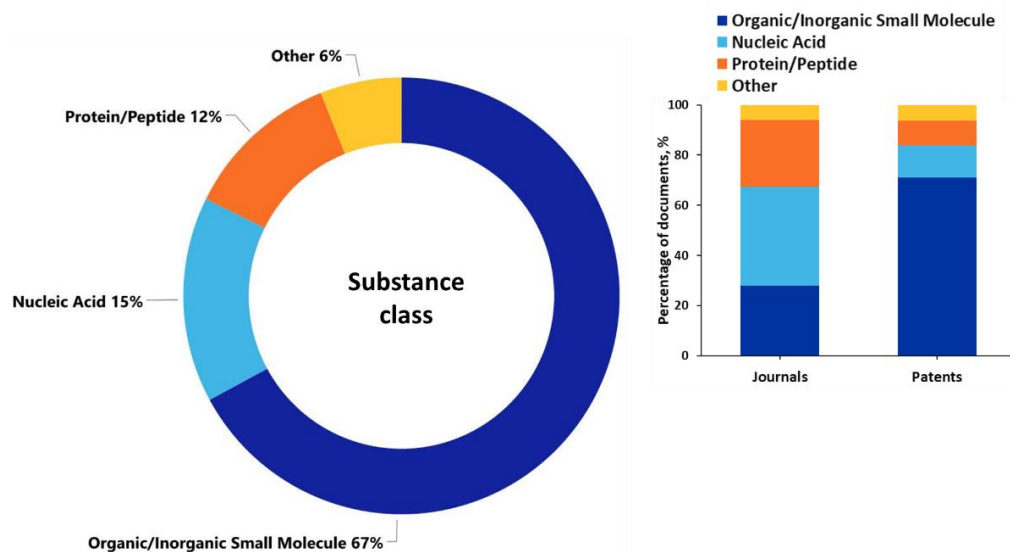


Figure 5. Distribution of the major substance classes in the documents related to the PD; Inset: variation of the substance class distributions in journal articles and patents.

### ***Ageing is the most widely explored concepts in the Parkinson's disease research***

We further explored distribution of the assortment of PD-related concepts in the published documents (journal articles and patents) (Figure 6A). Ageing is the most widely explored concept, it has been discussed in nearly 1/3 of the PD-related published documents (Figure 6A). **Ageing** is a leading risk factor for developing PD, as it is for most neurodegenerative diseases,

including Alzheimer's disease, Huntington's disease, and frontotemporal lobar dementia.<sup>74, 75</sup> Whilst PD involves a complex range of symptoms, a key **brain** region affected by critical cell loss in PD is the **substantia nigra**, which is also the main reason for the motor symptoms associated with this disease. Specifically, it is the **dopaminergic neurons** of the pars compacta within the substantia nigra that are lost.<sup>10</sup> The substantia nigra neurons are specific dopaminergic neurons in certain ways: they are pigmented (contain the pigment neuromelanin), exhibit autonomous pacemaking activity and increased susceptibility to oxidative stress.<sup>10, 76-78</sup> They are also thought to be particularly susceptible to the mitochondrial dysfunction which accumulates within them with advancing age. Thus, understandably, brain, neuron, and substantia nigra are also in the top concepts considered in the PD research (Figure 6).

It has been explicated that the pathogenesis of PD and other neurodegenerative diseases is closely associated with the major hallmarks of ageing.<sup>79-83</sup> Specifically, mitochondrial dysfunction, inflammation, and impaired protein clearance are essential attributes of aging and PD (Figure 6B).

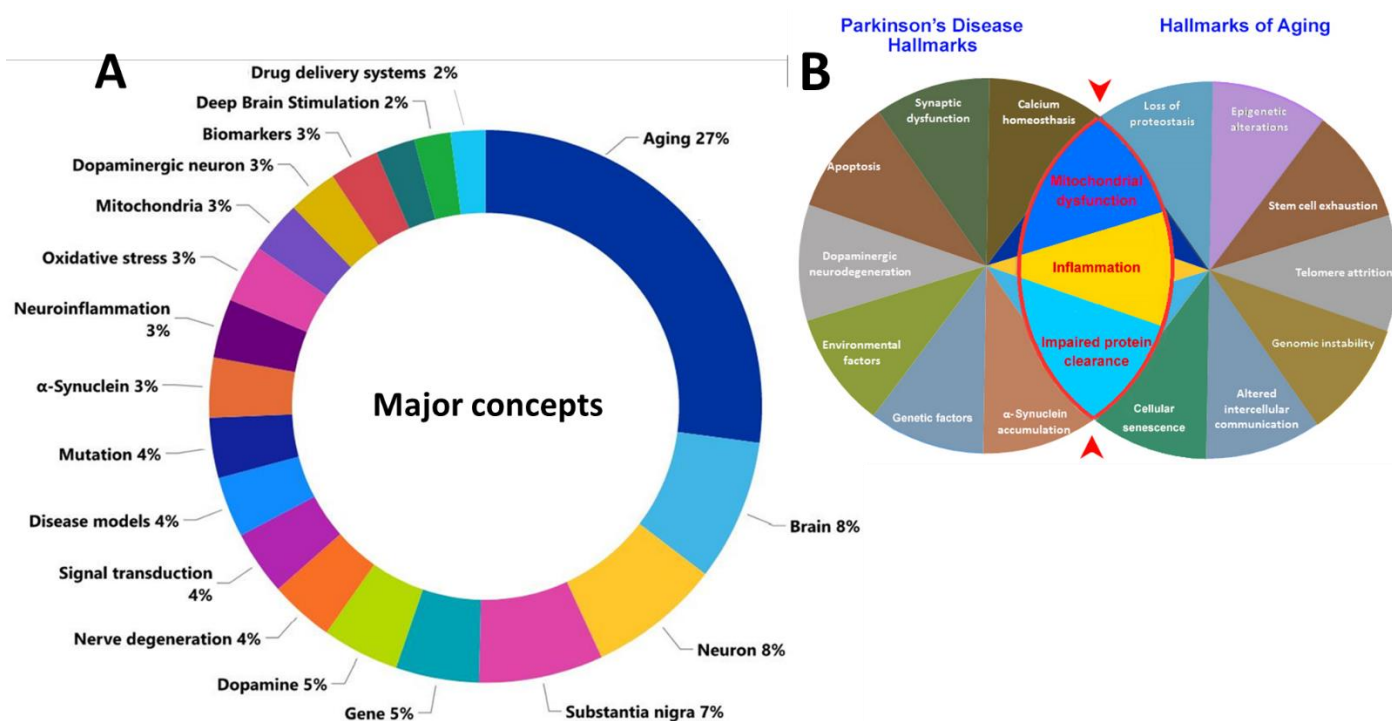


Figure 6. (A) Key concepts related to PD explored in the scientific publications found in the CAS Content Collection; (B) Intersection between PD hallmarks and the hallmarks of aging.

### ***Association of Parkinson's disease with other diseases***

A large assortment of comorbid diseases is associated with PD. Emerging evidence shows that chronic diseases such as diabetes, depression, anemia, and cancer may be associated with

the pathogenesis and progression of PD. <sup>84-90</sup> Studies have identified comorbid conditions such as bone fractures, cancer, dementia, diabetes, and stroke in PD patients. <sup>85, 86, 88</sup> Recent research indicates that certain comorbidities may enhance the risk of PD and precede the manifestation of motor symptoms. Furthermore, medications for treating diabetes and cancer have prompted neuroprotective effects in PD models. Yet, the mechanisms underlying the co-occurrence of these diseases remain unclear.

We examined the co-occurrence of certain diseases with PD as reflected by the co-occurrence of the concepts in the documents of the CAS Content Collection (Figure 7A). Dementia and inflammation are between the expected co-occurrences. Several studies have shown that patients with PD suffer frequently from depression. <sup>91</sup> Moreover, depression has been proposed to be a risk factor for PD. Inflammation has been commonly associated with both depression and neurodegeneration. Proinflammatory cytokines cause modifications in serotonin and dopamine neurotransmission leading to depression and PD. <sup>92</sup> Yet the precise mechanism underlying the relationship between depression and PD remains unclear. Relationship between PD and diabetes has been reported more than three decades ago <sup>92</sup> and confirmed by multiple studies later on. <sup>84</sup> PD and diabetes share similar dysregulated pathways such as inflammation, mitochondrial dysfunction, impaired autophagy and insulin signaling <sup>93</sup>, as well as certain genetic and environmental risk factors <sup>94-96</sup>. Medications used to treat diabetes have indicated promise in alleviating motor symptoms in PD patients. <sup>97</sup> Studies have reported association between cancer and PD, indicating a decreased risk of PD among most of the cancer types, e.g., analysis have shown that diagnosis of PD is associated with a 27% decreased risk of cancer <sup>98</sup>; another study reported a 17% decreased risk of cancer in PD patients <sup>99</sup>. Prostate, lung, bladder, colorectal, blood and uterus cancers have been reported as the most reduced in PD patients. <sup>100</sup>

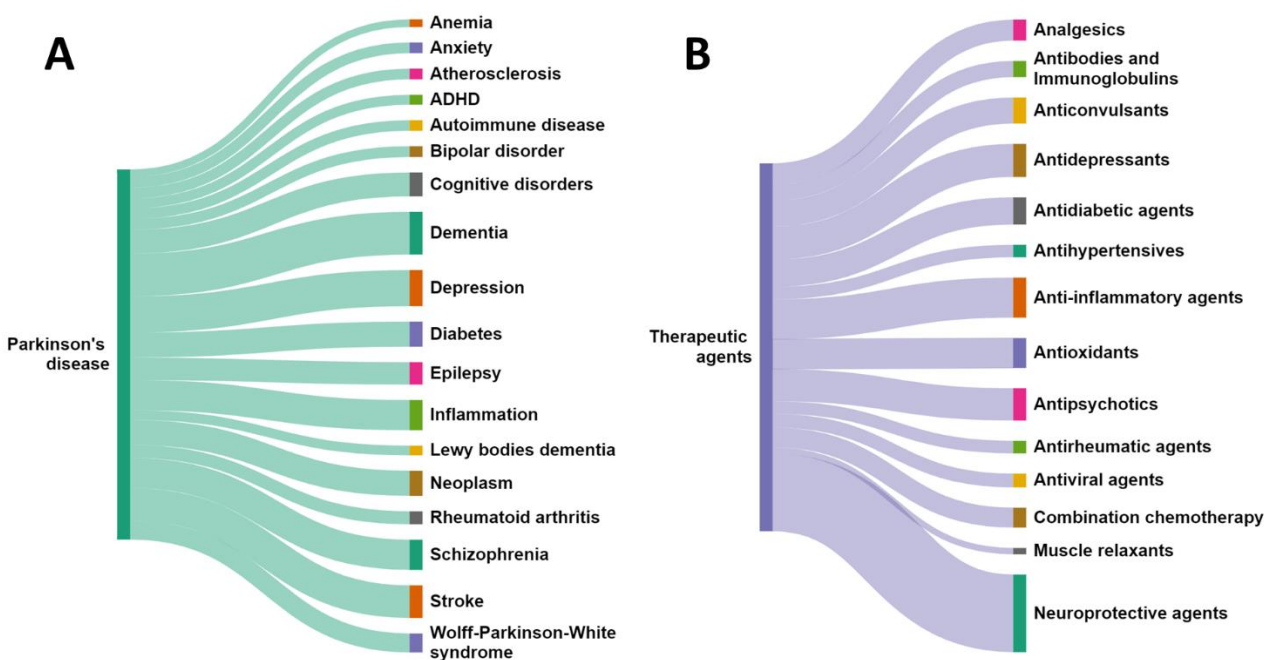


Figure 7. (A) Co-occurrence of the PD concept with other disease concepts in the CAS Content Collection documents; (B) Therapeutic agent classes explored in PD therapy as judged by their co-occurrence with the PD concept in the CAS Content Collection documents.

### ***Pathophysiological hallmarks of Parkinson's disease***

The hallmarks of PD are the key pathological attributes and clinical manifestations that characterize the condition.<sup>26, 101, 102</sup> These hallmarks encompass both the underlying molecular and cellular changes within the brain, such as dopaminergic neuron degeneration,  $\alpha$ -synuclein pathology, and neuroinflammation, as well as the observable characteristic motor and non-motor symptoms that define the clinical presentation of the disease. Understanding these hallmarks is crucial for elucidating disease mechanisms, developing diagnostic biomarkers, and identifying potential therapeutic targets for PD.

The hallmark pathological feature of PD is the progressive **degeneration of dopaminergic neurons** in the substantia nigra pars compacta, a region of the brain involved in movement control.<sup>24-26, 103, 104</sup> Dopamine is a neurotransmitter that plays a critical role in regulating motor function and coordination. This neuronal loss leads to a significant reduction in dopamine levels in the basal ganglia, impairing motor control and contributing to the development of motor symptoms such as bradykinesia, tremor, rigidity, and postural instability.

Another characteristic feature of PD is the accumulation of abnormal protein aggregates known as **Lewy bodies** within neurons of PD patients.<sup>27-29, 105, 106</sup> Lewy bodies, considered a pathological hallmark of PD, primarily consist of misfolded  $\alpha$ -synuclein protein and are found in various brain regions, including the substantia nigra and other structures involved in motor and cognitive function. The presence of Lewy bodies is thought to contribute to neuronal dysfunction and degeneration, although the exact role they play in the pathogenesis of PD is still under investigation.

**$\alpha$ -Synuclein aggregation** and deposition are central to the pathogenesis of Parkinson's disease.<sup>107-109</sup>  $\alpha$ -Synuclein is a presynaptic protein involved in regulating neurotransmitter release. In Parkinson's disease,  $\alpha$ -synuclein misfolds and aggregates into insoluble fibrils, forming Lewy bodies and Lewy neurites. This pathological accumulation of  $\alpha$ -synuclein is believed to contribute to dopaminergic neuron dysfunction and degeneration.

**Chronic inflammation** and oxidative stress are believed to play significant roles in the progression of PD.<sup>30-32, 110-112</sup> Inflammatory processes in the brain, characterized by microglial activation and increased pro-inflammatory cytokine production, can lead to neuronal damage and contribute to the degenerative cascade, exacerbating disease progression. Inflammatory mechanisms may be triggered by  $\alpha$ -synuclein pathology, oxidative stress, mitochondrial dysfunction, and other factors. **Oxidative stress**, resulting from an imbalance between reactive oxygen species (ROS) and antioxidant defenses, can damage cellular components and exacerbate neuronal dysfunction and death.<sup>23, 113-116</sup>

**Motor symptoms** are a hallmark clinical manifestation of Parkinson's disease and include bradykinesia (slowness of movement), resting tremor, rigidity (stiffness of muscles), and postural instability.<sup>117-119</sup> These motor symptoms result from the progressive loss of dopaminergic neurons and the subsequent imbalance of neurotransmitters within the basal ganglia circuitry.

Parkinson's disease is associated with a wide range of **non-motor symptoms** that can significantly impact quality of life. These include cognitive impairment, psychiatric symptoms (such as depression, anxiety, and psychosis), autonomic dysfunction (e.g., constipation, urinary problems, orthostatic hypotension), sleep disturbances, sensory symptoms (e.g., hyposmia, visual disturbances), and others.<sup>5, 120, 121</sup>

**Dysfunction of mitochondria**, the cellular organelles responsible for energy production, has been implicated in the pathophysiology of PD.<sup>33-35, 122-124</sup> Mitochondrial impairment can lead to energy deficits, increased oxidative stress, and activation of cell death pathways, contributing to neuronal degeneration. Mutations in genes associated with mitochondrial function, such as PINK1 and Parkin, have been linked to familial forms of Parkinson's disease.

**Dysfunction in protein clearance mechanisms**, including autophagy and the ubiquitin-proteasome system, may contribute to the accumulation of misfolded proteins and the formation of Lewy bodies. Impaired clearance of damaged or aggregated proteins can overwhelm cellular defenses and lead to neuronal toxicity and degeneration.<sup>36-38, 125, 126</sup>

**Genetic and Environmental Factors.** While most cases of PD are sporadic, genetic factors contribute to disease susceptibility and may interact with environmental exposures.<sup>11-13</sup>

Mutations in genes such as SNCA ( $\alpha$ -synuclein), LRRK2 (leucine-rich repeat kinase 2), Parkin, PINK1, and DJ-1 are associated with familial forms of PD, providing insights into disease mechanisms. Environmental factors, including pesticides, herbicides, heavy metals, and other toxins, may increase the risk of developing PD by contributing to oxidative stress, mitochondrial dysfunction, and  $\alpha$ -synuclein aggregation.<sup>18-20</sup>

We examined the documents in the CAS Content Collection associated with the PD research from the viewpoint of their relation to the pathophysiological PD hallmarks (Figure 8A), as well their relative growth in the last five years (2019-2023) (Figure 8B). The largest portion of the PD-related documents are associated with the genetic factors for PD pathophysiology, while the mitochondrial dysfunction, along with neuroinflammation and environmental factors, exhibit the fastest and steady growth.

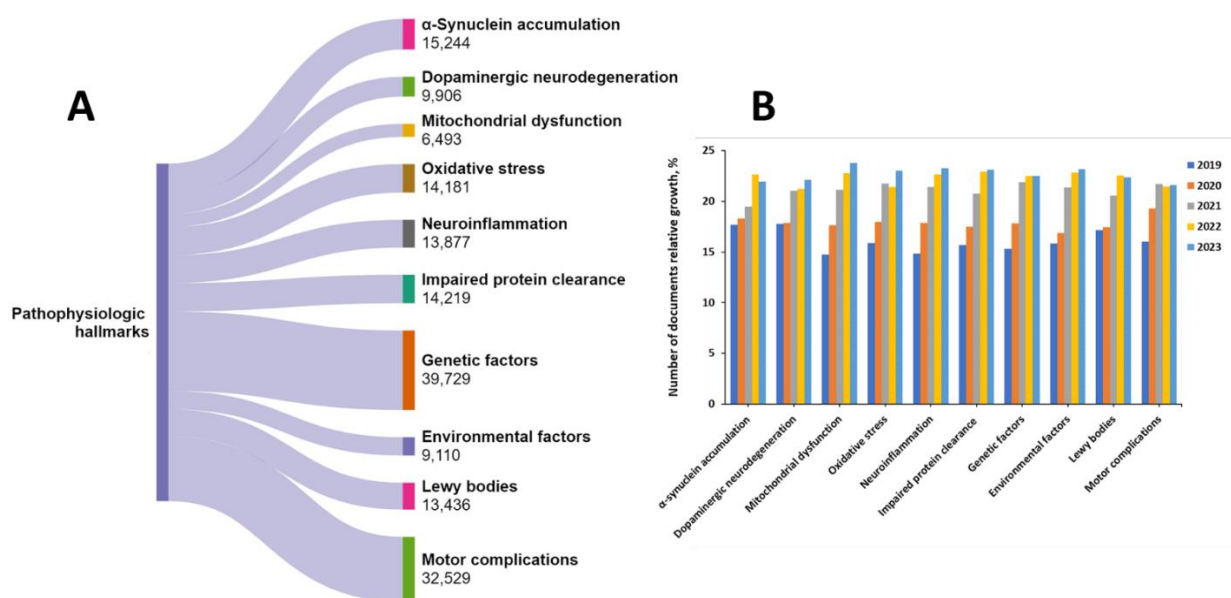


Figure 8. Pathophysiological hallmarks of PD: (A) Distribution of documents related to each hallmark within the CAS Content Collection; (B) Relative growth of the number of documents related to the PD hallmarks in the last 5-year period (2019-2023).

### **Risk factors of Parkinson's disease**

PD is a multifactorial disorder influenced by a combination of genetic, environmental, and lifestyle factors. While the exact cause of Parkinson's disease remains unclear, several risk factors have been identified that may increase an individual's likelihood of developing the condition.<sup>127-131</sup>

Advancing **age** is the most significant risk factor for PD. The incidence of PD increases with age, with the majority of cases diagnosed in individuals over the age of 60. However, PD can also occur in younger adults, known as early-onset or young-onset PD.

While most cases of Parkinson's disease are sporadic (without a known genetic cause), **genetic factors** play a role in disease susceptibility. Several genes have been implicated in both familial and sporadic forms of PD, including SNCA ( $\alpha$ -synuclein), LRRK2 (leucine-rich repeat kinase 2), Parkin (PARK2), PINK1 (PTEN-induced kinase 1), and GBA (glucocerebrosidase). Mutations or variations in these genes can increase the risk of developing Parkinson's disease.

Individuals with a **family history** of Parkinson's disease are at a higher risk of developing the condition themselves. Having a first-degree relative, such as a parent or sibling, with PD increases the risk of developing the disease compared to individuals without a family history.

Exposure to certain **environmental toxins and chemicals** has been associated with an increased risk of Parkinson's disease. Pesticides, herbicides, industrial chemicals, and heavy metals such as lead and manganese have been implicated as potential environmental risk factors for PD. Rural living and agricultural occupations, where exposure to pesticides may be more common, have been linked to a higher risk of Parkinson's disease.

Certain **lifestyle** factors, such as diet, physical activity, and caffeine consumption, have been investigated for their potential influence on Parkinson's disease risk. Some studies suggest that a diet rich in fruits, vegetables, and antioxidants may be associated with a lower risk of PD, while regular physical activity and moderate caffeine intake may also have protective effects.

We examined the documents in the CAS Content Collection associated with the PD research from the viewpoint of their relation to the PD risk factors (Figure 9A), as well their relative growth in the last five years (2019-2023) (Figure 9B). Understandably, the largest portion of the PD-related documents are associated with aging as a risk factor. Relatively small number of documents are associated with the lifestyle as a risk factor, but it clearly attracts attention in the recent years and exhibits the fastest growth.

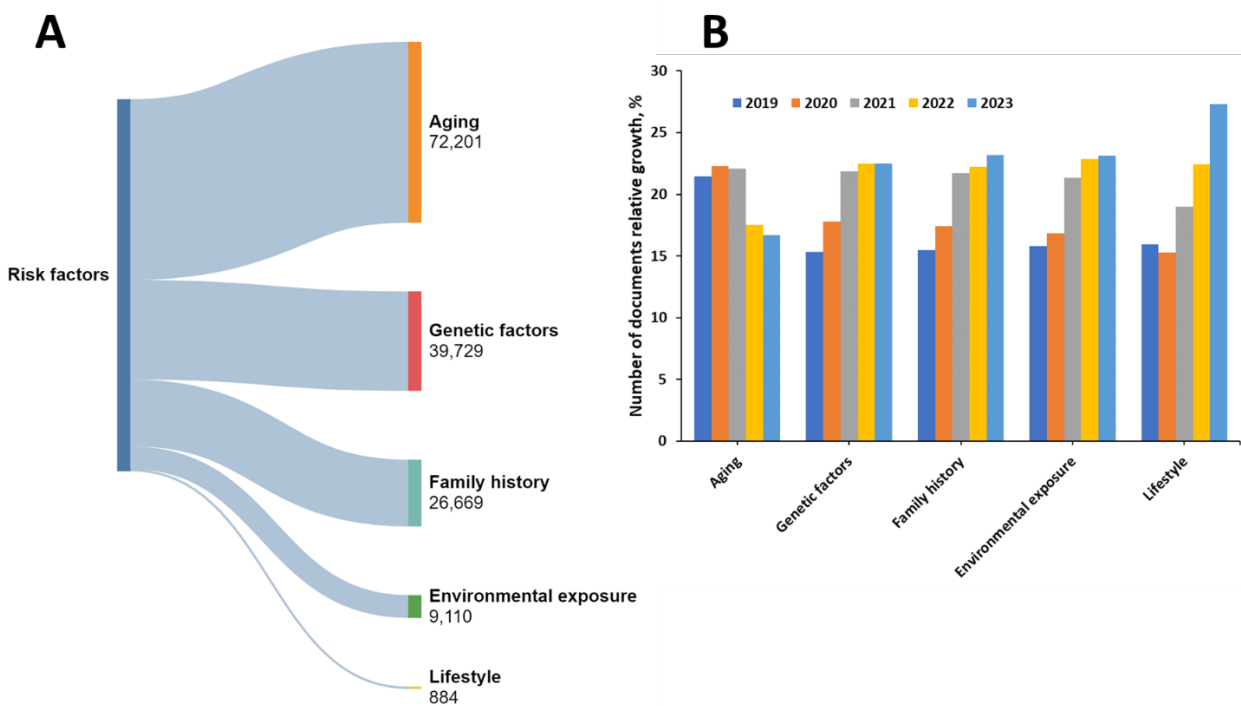


Figure 9. Risk factors for PD: (A) Distribution of documents related to each risk factor within the CAS Content Collection; (B) Relative growth of the number of documents related to the PD risk factors in the last 5-year period (2019-2023).

### ***Genetic background of the Parkinson's disease***

The genetic background of PD encompasses a complex interplay of monogenic and polygenic risk factors, gene-environment interactions, and modifiers of disease penetrance and expressivity, which all contribute to disease susceptibility. While the majority of PD cases are sporadic (without a known genetic cause), a small percentage of cases are considered familial, meaning they have a genetic component.<sup>132-136</sup> Understanding the genetic basis of PD is essential for elucidating disease mechanisms, identifying novel therapeutic targets, and developing personalized treatment approaches for affected individuals.

**Monogenic forms** of PD are caused by mutations in a single gene and are typically inherited in an autosomal dominant or recessive manner. Mutations in several genes have been implicated in familial forms of PD:

- SNCA (A-Synuclein). Mutations, duplications, or triplications in the SNCA gene lead to abnormal accumulation of  $\alpha$ -synuclein protein, forming Lewy bodies, a pathological hallmark of PD.



- LRRK2 (Leucine-Rich Repeat Kinase 2). Mutations in the LRRK2 gene are the most common cause of familial PD and are associated with both autosomal dominant and recessive inheritance patterns. LRRK2 mutations may increase the risk of developing sporadic PD as well.
- PARK2 (Parkin), PINK1 (PTEN-Induced Kinase 1), and DJ-1 (PARK7). Mutations in these genes are associated with autosomal recessive forms of PD and are involved in mitochondrial function, oxidative stress response, and protein degradation pathways.
- GBA (Glucocerebrosidase). Mutations in the GBA gene are a common genetic risk factor for PD and are associated with an increased risk of developing both familial and sporadic PD. GBA mutations are also implicated in Gaucher's disease, a lysosomal storage disorder.

**Polygenic Risk Factors.** In addition to monogenic forms, PD risk is influenced by multiple genetic variants across the genome, each contributing small effects. Genome-wide association studies (GWAS) have identified numerous common genetic variants associated with an increased risk of PD. These variants are located in or near genes involved in various pathways, including  $\alpha$ -synuclein aggregation, lysosomal function, immune response, and synaptic transmission.

**Gene-Environment Interactions.** While genetics play a significant role in PD risk, environmental factors also contribute to disease susceptibility, and gene-environment interactions may modulate risk. Environmental exposures, such as pesticides, herbicides, heavy metals, and traumatic brain injury, may interact with genetic factors to increase the risk of developing PD.

**Incomplete Penetrance and Variable Expressivity.** Not all individuals with pathogenic mutations in PD-associated genes develop the disease, indicating incomplete penetrance. Variable expressivity refers to the wide range of clinical features and disease severity observed among individuals with the same genetic mutation.

We examined the documents in the CAS Content Collection associated with the PD research from the viewpoint of their relation to genes implicated in familial forms of PD (Figure 10A), as well their relative growth in the last five years (2019-2023) (Figure 10B). PARK2, PINK1, and GBA are those with highest relative growth in the recent years.

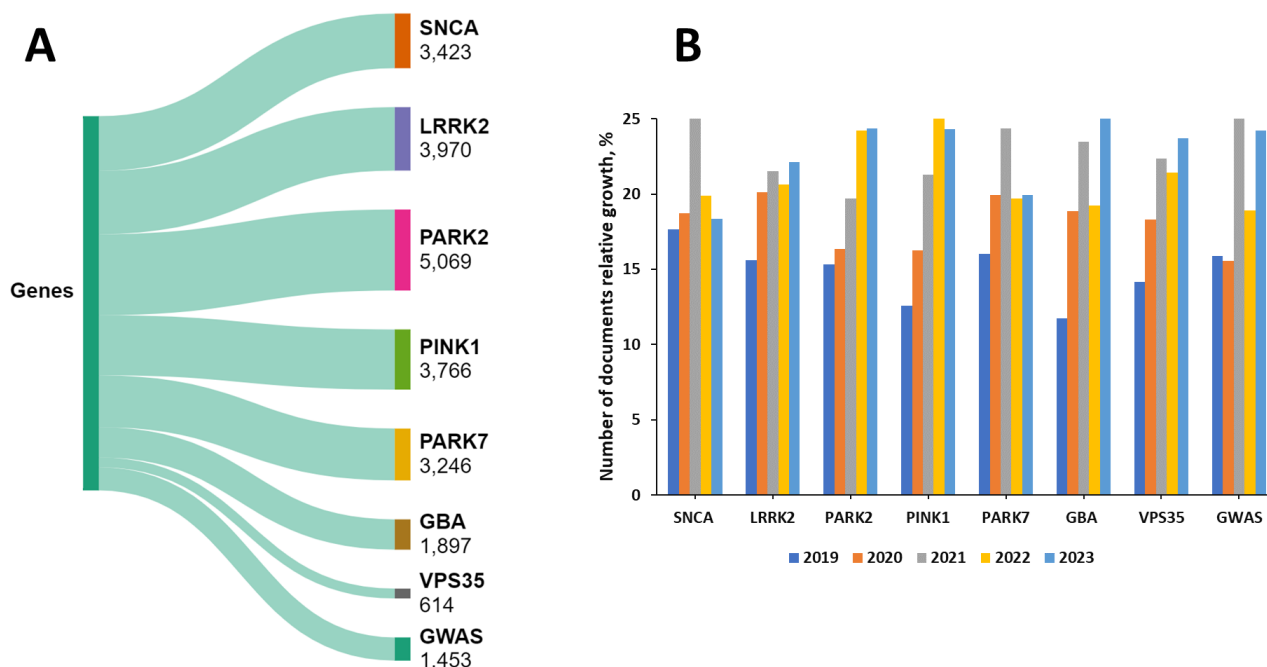


Figure 10. Major genes implicated in familial forms of PD: (A) Distribution of documents related to these genes within the CAS Content Collection; (B) Relative growth of the number of documents related to the genes in the last 5-year period (2019-2023).

### ***Biomarkers for Parkinson's disease***

Biomarkers for PD are objective measures that can be used to detect, diagnose, monitor disease progression, assess treatment response, and predict outcomes in affected individuals. Identifying reliable biomarkers is crucial for improving early diagnosis, developing disease-modifying therapies, and advancing personalized medicine approaches in PD.<sup>137-148</sup> Overall, while several promising biomarkers for Parkinson's disease have been identified, further validation and standardization are needed to establish their clinical utility in diagnosis, prognosis, and therapeutic development. Integration of multiple biomarkers from different modalities may enhance diagnostic accuracy, improve patient stratification, and facilitate personalized treatment approaches in PD.

**Clinical biomarkers:** (i) Motor symptoms such as bradykinesia, rigidity, tremor, and postural instability are hallmark clinical manifestations of PD and are used in diagnosis and monitoring disease progression; (ii) Non-motor symptoms, including cognitive impairment, psychiatric symptoms, autonomic dysfunction, and sleep disturbances, may serve as biomarkers for PD severity and progression.<sup>145, 147, 149-154</sup>

**Neuroimaging biomarkers:** (i) Dopamine transporter (DAT) imaging with single-photon emission computed tomography (SPECT) or positron emission tomography (PET) can assess presynaptic dopaminergic function and differentiate PD from other parkinsonian syndromes; (ii) Functional MRI (fMRI) can evaluate changes in brain activity and connectivity patterns associated with PD, providing insights into disease pathophysiology and compensatory mechanisms; (iii) Structural MRI techniques, such as volumetric analysis and diffusion tensor imaging (DTI), can detect changes in brain morphology, white matter integrity, and gray matter density associated with PD. <sup>45, 145, 155-157</sup>

**Cerebrospinal fluid (CSF) biomarkers:** (i) Measurement of  $\alpha$ -Synuclein levels or specific  $\alpha$ -synuclein species (e.g., oligomeric forms) in CSF may reflect underlying pathology and serve as a diagnostic or prognostic biomarker for PD; (ii) Elevated levels of Tau and phosphorylated Tau (p-Tau) in CSF have been reported in PD patients and may indicate neurodegeneration and tau pathology. <sup>151, 153, 158-160</sup>

**Blood-based biomarkers:** (i) Blood-based assays for  $\alpha$ -Synuclein levels and post-translational modifications are under investigation as potential biomarkers for PD. However, blood-based  $\alpha$ -synuclein assays have been challenging due to low concentrations and high variability; (ii) Biomarkers of neuroinflammation, such as cytokines, chemokines, and inflammatory mediators, have been proposed as potential indicators of disease activity and progression in PD. <sup>153, 157, 159, 161</sup>

**Genetic biomarkers:** (i) Genetic variants associated with PD risk identified through genome-wide association studies (GWAS) and next-generation sequencing may serve as genetic biomarkers for disease susceptibility and progression; (ii) Pathogenic monogenic mutations in genes such as SNCA, LRRK2, PARK2, and GBA are associated with familial forms of PD and may serve as biomarkers for genetic testing and personalized risk assessment. <sup>147, 161-163</sup>

**Peripheral biomarkers:** (i) Olfactory dysfunction, commonly observed in PD patients, may serve as a peripheral biomarker for early disease detection and monitoring; (ii) Alterations in gut microbiota composition and metabolites have been reported in PD patients and may represent peripheral biomarkers of disease risk and progression. <sup>164, 165</sup>

### ***Therapeutic classes considered for treating Parkinson's disease***

Several drug classes have been explored for treating PD, leveraging their potential neuroprotective, symptomatic, or disease-modifying effects. Some of these drugs are well identified in treating other diseases. Drug repurposing offers a promising strategy for identifying new treatments for PD by leveraging existing drugs with known safety profiles and mechanisms of action. The occurrence of certain drug class concepts within the PD research area in the documents of the CAS Content Collection are illustrated in Figure 7B.

– Tricyclic **antidepressants** and selective serotonin reuptake inhibitors (SSRIs) have been investigated for their potential to alleviate depression and anxiety symptoms in PD patients.

Certain antidepressants may also modulate neurotransmitter systems implicated in PD pathophysiology, such as dopamine and serotonin.

- **Antihypertensives:** Calcium channel blockers, such as isradipine, have been studied for their potential neuroprotective effects in PD. These agents may exert neuroprotective effects by blocking calcium influx, reducing oxidative stress, and preserving dopaminergic function.

- Nonsteroidal **anti-inflammatory drugs** (NSAIDs), corticosteroids, and other anti-inflammatory agents have been investigated for their potential to mitigate neuroinflammation and oxidative stress in PD. Chronic neuroinflammation is thought to contribute to neurodegeneration in PD, and anti-inflammatory drugs may have neuroprotective effects.

- **Glucagon-Like Peptide-1 (GLP-1) Receptor Agonists**, originally developed for the treatment of type 2 diabetes, have shown promise for their neuroprotective effects in PD. Drugs such as exenatide and liraglutide may promote neuronal survival, enhance dopamine release, and reduce inflammation in the brain.

- Some **antiviral drugs**, including amantadine and favipiravir, have been repurposed for the treatment of PD. Amantadine is used to alleviate dyskinesias and motor fluctuations in PD patients, while favipiravir has shown potential neuroprotective effects in preclinical models of PD.

- Dantrolene, a **muscle relaxant** used to treat muscle spasticity, has been investigated for its potential neuroprotective effects in PD. It may modulate calcium release from intracellular stores and protect against neurotoxicity.

- **Antioxidants**, including coenzyme Q10, vitamin E, and N-acetylcysteine, have been studied for their potential to reduce oxidative stress and mitochondrial dysfunction in PD. These agents may have neuroprotective effects and could potentially slow disease progression.

- **Bisphosphonates**, commonly used to treat osteoporosis and bone-related conditions, have been investigated for their potential neuroprotective effects in PD. Some studies suggest that bisphosphonates may reduce neuroinflammation and protect against dopaminergic cell loss in PD models.

Specific drugs considered for repurposing to treat PD are presented further in the paper, in the drug repurposing section.

## Clinical trial research

Clinical trials currently researching the treatment of Parkinson's disease are explored in this section to gain an overall view of the current state of clinical development. Around 1000 clinical trials have been registered on [clinicaltrials.gov](https://clinicaltrials.gov) over the last 10 years for the treatment of Parkinson's disease, showing lower numbers but continued growth of clinical development for treatments of this debilitating disease. Figure 11. shows an increasing oscillating curve through 2018, with continued upward growth onwards, starting at just a few clinical trials in 2003, and raising to around 150 clinical trials in 2023.

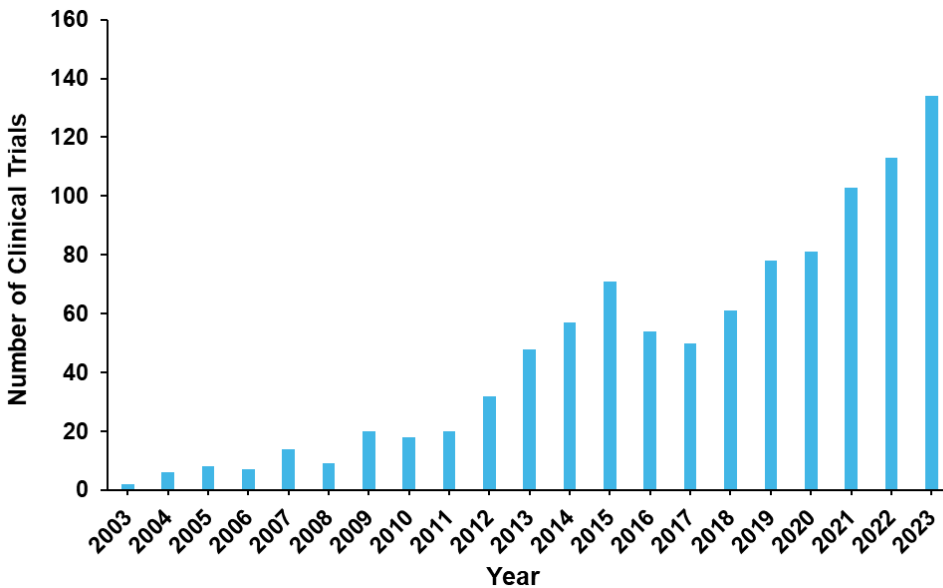


Figure 11. Number of Parkinson's disease therapeutic clinical trials by year.

Analysis of Parkinson's disease therapeutic clinical trials, reveals that around 64% of all trials are not phased, these trials include interventions without FDA-defined phases such as medical devices or behavior interventions (Figure 12A). The phase that contains the next largest group of trials is Phase I and Phase II studies, researching the safety and efficacy of newer anti- Huntington's disease agents. This indicates efforts being placed on researching newer anti-Parkinson agents and testing their safety and efficacy. Over half of all clinical trials in the past 10 years have been completed (Figure 12B). The status with the next largest group of trials is the recruiting status which is encouraging as new clinical trials are created and carried out to research the treatment of Parkinson's disease, offering hope to patients worldwide.

**A**

Early Phase I	Phase I	Phase I/II	Phase II	Phase II/III	Phase III	Phase IV	NA
2%	10%	3%	13%	1%	5%	4%	64%

**B**

Not yet recruiting	Recruiting	Active	Completed	Withdrawn/Terminated/Suspended
7%	24%	7%	52%	10%

Figure 12. Percentage of Parkinson's disease clinical trials in various: (A) phases; (B) statuses.

Representative clinical trials examining Parkinson's disease therapeutics are highlighted in Table 1. These are examined in further detail below to showcase a variety of interventions, drug classes and mechanism of actions, sponsors, locations, statuses, and phases.

Table 1. Highlighted Parkinson's disease clinical trials

Status	Intervention	Drug class/mechanism of action	Sponsor, location	Phase	NCT Number
Not yet recruiting	MitoCell	MitoCell is an autologous stem cell product. It improves the brain microenvironment by modulating the immune response, and secreting more BDNF and SDF-1 neurotrophic factors protecting and repairing damaged dopamine neurons and stimulating regeneration. <sup>166</sup>	Taiwan Mitochondrion Applied Technology	Phase I	NCT05094011
Recruiting	NouvNeu001	NouvNeu001 is a chemically induced human dopaminergic neuron precursor derived from induced pluripotent stem cells. Following transplantation, the cells differentiate into new dopaminergic neurons that establish connections with existing neurons and increase dopamine release. <sup>167</sup>	iRegene Therapeutics	Phase I/ II	NCT06167681
Enrolling by invitation	Tavapadon	Tavapadon is a dopamine D1/D5 receptor partial agonist designed activate at levels that maximize motor benefits without receptor overexcitation and desensitization. <sup>168</sup>	Cerevel Therapeutics	Phase III	NCT04760769
Active	ABBV-951	ABBV-951 is carbidopa and levodopa prodrugs delivered subcutaneously. Levodopa is converted into dopamine and carbidopa makes more levodopa available for transport to the brain. <sup>169</sup>	AbbVie	Phase III	NCT04750226
Active	Bydureon	Bydureon is an extended-release formulation of exenatide, a GLP-1 receptor agonist that supports dopamine neuron function and reduces inflammation. <sup>170</sup>	University College, London	Phase III	NCT04232969
Active	MSK-DA01	MSK-DA01 is a cell therapy derived from pluripotent stem cells that are human embryonic stem cells. Once transplanted, they can reform affected neural networks restore motor and non-motor function to patients. <sup>171</sup>	BlueRock Therapeutics	Phase I	NCT04802733
Active	Prasinezumab	Prasinezumab is a humanized IgG1 monoclonal antibody directed against aggregated $\alpha$ -synuclein. <sup>172</sup>	Hoffmann-La Roche	Phase II	NCT04777331
Completed	Buntanetap	Buntanetap suppresses APP, tau, and $\alpha$ -synuclein protein synthesis reducing nerve cell death and neurodegeneration. <sup>173</sup>	Annovis Bio	Phase II	NCT05357989

Completed	Nilotinib	Nilotinib is a tyrosine kinase inhibitor with the highest affinity to inhibit Abelson and discoidin domain receptors. It reduces the level of brain $\alpha$ -synuclein and reduces inflammation. <sup>174</sup>	Northwestern University	Phase III	NCT03205488
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## ***Current Treatment and Management of Parkinson's disease***

The treatment and management of PD aims to alleviate symptoms, improve quality of life, and slow disease progression. Treatment strategies typically involve a combination of medications, lifestyle modifications, rehabilitative therapies, and surgical interventions. The specific treatment plan is tailored to each individual based on their symptoms, disease stage, and overall health. Overall, the management of PD is multidisciplinary and requires a collaborative approach involving healthcare professionals, patients, and caregivers. By addressing motor and non-motor symptoms, optimizing medication regimens, promoting healthy lifestyle habits, and providing supportive care, it is possible to enhance quality of life and functional independence for individuals living with PD.<sup>39, 175-179</sup>

### **Medications**

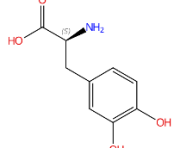
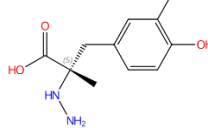
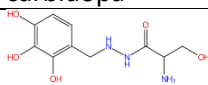
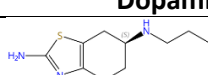
- **Levodopa (L-dopa)** is the most effective medication for managing motor symptoms of PD. It is converted into dopamine in the brain, replenishing dopamine levels and improving motor function. Levodopa is combined with carbidopa or benserazide, which prevent the peripheral conversion of levodopa to dopamine outside the brain, reducing peripheral side effects such as nausea. Common brand names include Sinemet, Madopar, and Stalevo.
- **Dopamine Agonists** mimic the action of dopamine in the brain and can be used as monotherapy or in combination with levodopa. They stimulate dopamine receptors and help alleviate motor symptoms. Examples include pramipexole (Mirapex), ropinirole (Requip), rotigotine (Neupro), and apomorphine (Apokyn).
- **Monoamine Oxidase Type B (MAO-B) Inhibitors** block the enzyme monoamine oxidase type B, which metabolizes dopamine in the brain, thereby increasing dopamine levels. They can be used as monotherapy in early PD or as adjunctive therapy with levodopa. Examples include selegiline (Eldepryl, Zelapar) and rasagiline (Azilect).
- **Catechol-O-Methyltransferase (COMT) Inhibitors** prolong the effects of levodopa by inhibiting its breakdown, reducing motor fluctuations. They are often used in combination with levodopa/carbidopa. Examples include entacapone (Comtan), tolcapone (Tasmar), and opicapone (Ongentys).

- **Anticholinergic drugs** may be used to manage tremors and dystonia in some PD patients. They work by blocking the action of acetylcholine, a neurotransmitter involved in motor control. Examples include trihexyphenidyl (Artane) and bntropine (Cogentin).
- **Amantadine** can provide relief from dyskinesias (involuntary movements) and may also have modest benefits for other PD symptoms. Its exact mechanism of action in PD is not fully understood but may involve dopamine release and NMDA receptor antagonism. Commonly used as an adjunctive therapy in advanced PD.

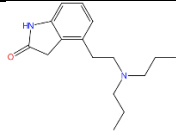
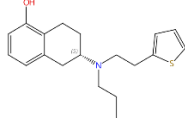
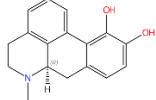
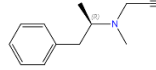
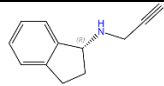
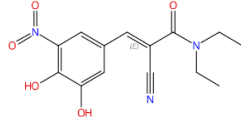
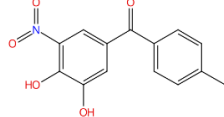
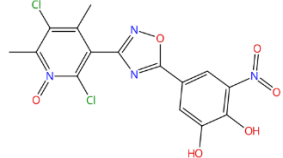
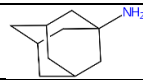
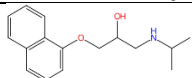
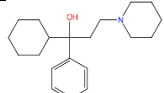
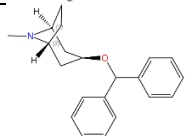
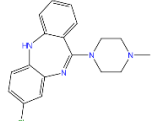
Although levodopa is the most effective medication available for treating the motor symptoms of PD, in certain instances, other medications such as MAO-B Inhibitors, amantadine, anticholinergics,  $\beta$ -blockers, or dopamine agonists may be introduced initially to avoid levodopa-related motor complications. Modifying the levodopa dosing regimen or combining it with other medications, such as MAO-B Inhibitors, catechol-O-methyltransferase inhibitors, or dopamine agonists may help managing motor fluctuations. Reducing or withdrawing dopaminergic medication, particularly dopamine agonists, may help manage impulse control disorders.<sup>180</sup> Along these lines, using levodopa and dopamine agonists for motor symptoms at all stages of PD has been proven beneficial. Dopamine agonists and drugs that block dopamine metabolism are effective for motor fluctuations. Regarding non-motor symptoms, clozapine has been found effective for hallucinations, cholinesterase inhibitors may improve symptoms of dementia, and antidepressants and pramipexole may improve depression.<sup>180</sup>

Table 2 summarizes common PD medication for treating motor symptoms, with their chemical structures, indications, and an exemplary clinical trial.

Table 2. Treatment of motor symptoms of Parkinson disease<sup>180</sup>

Drug Name	CAS RN	Structure	Indication	NCT Number
<b>Levodopa (+ peripheral dopa decarboxylase inhibitor)</b>				
Levodopa	59-92-7		All motor symptoms	NCT06236230
Levodopa-carbidopa	59-92-7; 28860-95-9	 carbidopa	All motor symptoms	NCT05471609
Levodopa-benserazide	59-92-7; 322-35-0	 benserazide	All motor symptoms	NCT03097211
<b>Dopamine agonists</b>				
Pramipexole	104632-26-0		All motor symptoms	NCT00321854

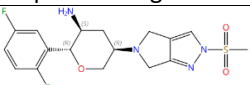
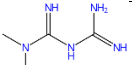
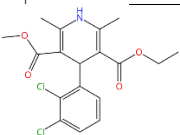
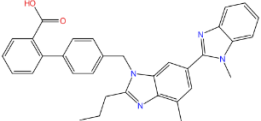
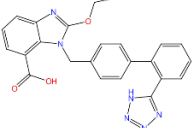
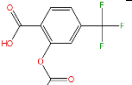
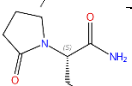


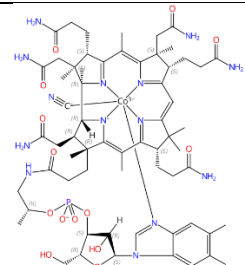
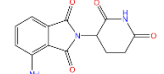
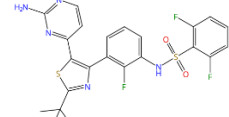
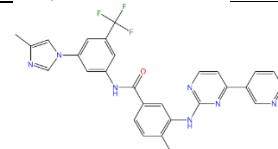
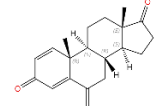
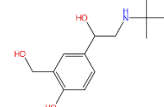
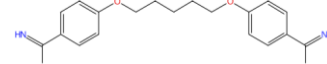
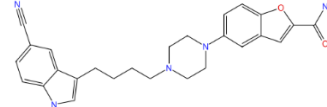
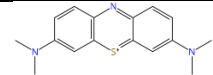
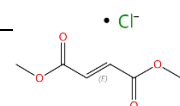
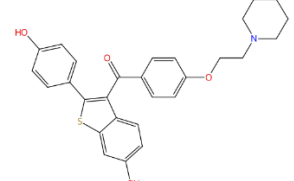
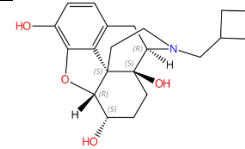
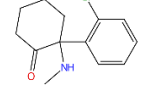
Ropinirole	91374-21-9		All motor symptoms	NCT01536574
Rotigotine	99755-59-6		All motor symptoms	NCT06247410
Apomorphine	58-00-4		All motor symptoms	NCT04887467
<b>MAO-B Inhibitors</b>				
Selegiline	14611-51-9		Early, mild symptoms and motor fluctuations	NCT00640159
Rasagiline	136236-51-6		Early, mild symptoms and motor fluctuations	NCT00203060
<b>COMT Inhibitors</b>				
Entacapone	130929-57-6		Motor fluctuations	NCT00247247
Tolcapone	134308-13-7		Motor fluctuations	NCT00906828
Opicapone	923287-50-7		Motor fluctuations	NCT02071810
<b>Antidyskinetic</b>				
Amantadine	768-94-5		Gait dysfunction and dyskinesia	NCT00632762
<b>β-Blockers</b>				
Propranolol	525-66-6		Tremor	NCT03832712
<b>Anticholinergic</b>				
Trihexyphenidyl	144-11-6		Tremor	n/a
Benzotropine	86-13-5		Tremor	n/a
<b>Neuroleptic</b>				
Clozapine	5786-21-0		Tremor and dyskinesia	NCT00004826

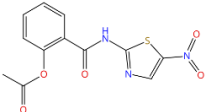
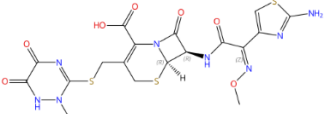
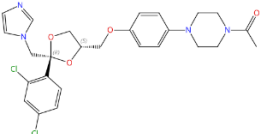

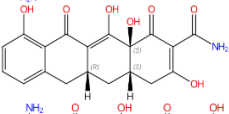
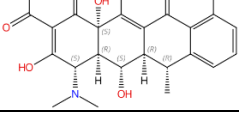
## Drug repurposing

Since there is no cure for PD, drug repurposing studies have been intensely searching to identify existing drugs that could be repositioned to treat PD. As the pharmaceutical development process is both time-consuming and costly, drug repurposing provides a chance to accelerate it by exploring the PD-related effects of agents approved for other disorders. These drugs have established safety profiles, pharmacokinetic description, formulations, dosages, and manufacturing procedures. Recently, *in silico* pharmacology has been widely applied and various computer applications including machine learning and artificial intelligence approaches have been explored in identifying potential drugs for repurposing to PD. Drug repurposing has already been attempted in PD with various methodologies applied and several clinical trials are currently evaluating drug-repurposing candidates for PD. Exemplary drugs for PD repurposing are summarized in Table 3.

Table 3. Exemplary drugs commonly considered for repurposing to PD <sup>181-210</sup>

Drug	CAS RN	Structure	Original therapeutic indication
Exenatide	141758-74-9	Protein/Peptide Sequence Sequence Length: 39	Type II diabetes
Semaglutide	910463-68-2	Protein/Peptide Sequence Sequence Length: 34	Type II diabetes
Omarigliptin	1226781-44-7		Type II diabetes
Metformin	657-24-9		Type II diabetes
Felodipine	72509-76-3		Hypertension
Telmisartan	144701-48-4		Hypertension
Candesartan	139481-59-7		Hypertension, heart failure
Triflusal	322-79-2		Thromboembolic prophylaxis
Levetiracetam	102767-28-2		Epilepsy

Vitamin B12	68-19-9		Vitamin B12 deficiencies
Pomalidomide	19171-19-8		Multiple myeloma
Dabrafenib	1195765-45-7		Metastatic melanoma
Nilotinib	641571-10-0		Chronic myelogenous leukemia
Exemestane	107868-30-4		Breast cancer, postmenopausal
Salbutamol	18559-94-9		Bronchospasm, chronic bronchopulmonary disorders
Pentamidine	100-33-4		<i>Pneumocystis carinii</i> pneumonia
Vilazodone	163521-12-8		Antidepressant
Methylene blue	61-73-4		Acquired methemoglobinemia
Dimethyl fumarate	624-49-7		Multiple sclerosis
Raloxifene	84449-90-1		Osteoporosis, postmenopausal
Nalbuphine	20594-83-6		Analgesic
Ketamine	6740-88-1		General anesthetic

Nitazoxanide	55981-09-4		Gastrointestinal infection
Ceftriaxone	73384-59-5		Bacterial infections (antibiotic)
Ketoconazole	65277-42-1		Fungal infections
Kanamycin	59-01-8		Bacterial infections (antibiotic)
Incyclinide CMT-3	15866-90-7		Reduced antibiotic activity
Doxycycline	564-25-0		Bacterial infections (broad-spectrum antibiotic)

## Surgical interventions

**Deep Brain Stimulation (DBS)** involves implanting electrodes into specific brain regions and delivering electrical impulses to modulate abnormal neuronal activity. It can help improve motor symptoms and reduce medication-related complications in certain patients. **Duopa pump therapy** includes a gel formulation of levodopa and carbidopa (Duopa) that is delivered continuously through a pump system directly into the small intestine. It can provide more stable levodopa levels and improve motor fluctuations in advanced PD. **Exablate Neuro** uses focused ultrasound to target and ablate the globus pallidus to treat mobility symptoms, tremor, rigidity, and dyskinesia in both tremor-dominant and advanced Parkinson's disease patients.<sup>53</sup>

## Rehabilitative therapies

**Physical therapy** can help improve mobility, balance, flexibility, and strength in PD patients. It may also include exercises to address gait abnormalities and freezing of gait. **Occupational therapy** can assist PD patients in developing strategies to perform daily activities more independently and safely, as well as recommend assistive devices and modifications to the home environment. **Speech therapy** can help PD patients to address speech and swallowing difficulties, improve vocal projection, and teach techniques to enhance communication.

## Lifestyle modifications

**Regular exercise**, including aerobic activities, strength training, and balance exercises, can help improve motor function, mobility, and overall well-being in PD patients. **Healthy diet** rich in fruits, vegetables, whole grains, and lean proteins may support overall health and help manage constipation, a common non-motor symptom of PD. **Stress management** techniques such as mindfulness, relaxation exercises, and stress reduction strategies may help alleviate anxiety and improve coping mechanisms.

## *Drug delivery systems*

While there is currently no cure for PD, there are medications that can help to manage the symptoms. However, these medications can have limitations, such as short-lived effects and difficulty crossing the blood-brain barrier. The blood-brain barrier is a highly selective barrier that protects the brain from harmful substances in the bloodstream. Unfortunately, it also prevents many drugs from reaching the brain, where they are needed to treat PD. Drug delivery systems are being developed to overcome these limitations. Drug delivery systems are designed to deliver drugs to specific sites in the body, including the brain. For PD, drug delivery systems are being investigated as a way to (i) improve the delivery of drugs to the brain; (ii) reduce harmful side effects; (iii) provide sustained release of medication.

Pharmaceutical nanotechnologies enables novel approaches to drug delivery.<sup>211, 212</sup> Nanoparticles, as drug carriers, impart certain advantages concerning improved efficacy as well as reduced adverse drug reactions. Pharmaceutical nanoparticles allow overcoming pharmacological limitations such as low solubility, rapid biodegradation, low bioavailability, adverse effects, and low permeability through biological barriers. The main challenges in developing PD drug formulations include crossing through the blood-brain barrier and controlled drug release to prevent concentration fluctuations.

Pharmaceutical nanoparticles can be prepared from various materials offering variable physicochemical characteristic. Some of the most successful polymeric materials used include gelatin, hyaluronic acid, alginate, chitosan, polylactic-co-glycolic acid (PLGA), polylactide, polyethylene glycol (PEG), and polycaprolactone.<sup>213</sup> For instance, polymeric nanoparticles has been developed based on PEG– polycaprolactone, encapsulating Ginkgolide B, which is believed to act as a neuroprotectant and treat PD.<sup>214</sup> PLGA nanoparticles loaded with L-DOPA have been reported to increase motor function in PD patients.<sup>215</sup> PLGA-PEG nanoparticles were engineered as carriers of coumarin, a potent drug inhibitor of monoamine oxidase B, which could cross the intestinal and brain membranes, allowing the successful transport of coumarin to the brain.<sup>216</sup>

Lipid nanoparticles have certain advantages that make them attractive to be used as nanocarriers in PD, mainly their composition based that is physiologically tolerable and their high bioavailability.<sup>211, 217</sup> Liposomes loaded with dopamine hydrochloride and functionalized with transferrin exhibited outstanding stability and improved ability to cross the blood-brain

barrier.<sup>218</sup> Semaglutide loaded liposomes demonstrated high stability, bioavailability, passage through the blood-brain barrier, and avoids toxic accumulation due to a half-life of approximately one week.<sup>219</sup> Nalbuphine loaded solid lipid nanoparticles allowed oral/nasal administration and greater dosage control.<sup>220</sup>

## Current research and future directions on Parkinson's disease

Research into PD is an active and evolving field, with ongoing efforts focused on understanding disease mechanisms, identifying biomarkers, developing new treatments, and improving patient care. Ongoing research efforts in PD aim to deepen our understanding of disease mechanisms, advance precision medicine approaches, and develop new therapeutic strategies to improve outcomes for individuals living with PD. Collaboration among researchers, clinicians, patients, advocacy organizations, and industry partners is essential to accelerate progress and translate scientific discoveries into meaningful benefits for patients and families affected by PD.

**Disease mechanisms and pathogenesis.** (i) Investigating the underlying mechanisms of PD pathology, including protein aggregation, mitochondrial dysfunction, neuroinflammation, and oxidative stress; (ii) Studying the role of genetic factors, environmental exposures, and epigenetic modifications in disease susceptibility and progression; (iii) Exploring the interplay between different cell types in the brain, including neurons, glial cells, and immune cells, in the development and progression of PD.

**Biomarkers for early detection and diagnosis.** (i) Identifying reliable biomarkers, such as imaging markers, fluid biomarkers (e.g., cerebrospinal fluid proteins), and genetic markers, for early detection and accurate diagnosis of PD; (ii) Developing non-invasive and accessible biomarkers that can be used in clinical practice to aid in disease monitoring, prognosis, and treatment response assessment.

**Neuroprotective and disease-modifying therapies.** (i) Developing neuroprotective and disease-modifying therapies aimed at slowing or halting the progression of PD; (ii) Investigating novel pharmacological agents, gene therapies, and biologics targeting specific pathways implicated in PD pathology, such as  $\alpha$ -synuclein aggregation, mitochondrial dysfunction, and neuroinflammation; (iii) Repurposing existing drugs or compounds with potential neuroprotective effects for PD treatment.

**Precision medicine and personalized therapies.** (i) Advancing precision medicine approaches to tailor treatment strategies based on individual patient characteristics, including genetic profiles, biomarker profiles, and clinical phenotypes; (ii) Using omics technologies, including genomics, transcriptomics, proteomics, and metabolomics, to identify patient subtypes and predict treatment response.

**Non-motor symptoms and quality of life.** (i) Investigating the underlying mechanisms of non-motor symptoms in PD, such as cognitive impairment, psychiatric symptoms, autonomic dysfunction, and sleep disturbances; (ii) Developing targeted interventions and supportive care

strategies to address non-motor symptoms and improve quality of life for PD patients and their caregivers.

**Advanced therapies and surgical interventions.** (i) Advancing surgical interventions, such as deep brain stimulation (DBS), focused ultrasound, and gene therapy, for the management of motor complications and non-motor symptoms in PD; (ii) Exploring novel targets and techniques for neuromodulation and neurostimulation to improve treatment outcomes and reduce adverse effects.

**Digital health and technology innovations.** (i) Harnessing digital health technologies, including wearable devices, smartphone applications, and remote monitoring systems, for continuous monitoring of PD symptoms, motor fluctuations, and medication adherence; (ii) Integrating artificial intelligence (AI) and machine learning algorithms to analyze large-scale data sets and identify patterns in disease progression, treatment response, and patient outcomes.

**Clinical trials and translational research.** (i) Conducting well-designed clinical trials to evaluate the safety and efficacy of new therapies, including disease-modifying treatments, symptomatic therapies, and supportive interventions; (ii) Facilitating translational research to bridge the gap between basic science discoveries and clinical applications, accelerating the development of innovative treatments and improving patient care.

## Outlook, roadblocks, and perspectives

Continued research efforts hold promise for developing novel treatments, identifying biomarkers for early diagnosis, and understanding disease mechanisms. Personalized treatment approaches based on genetic, biomarker, and clinical profiles may improve outcomes and tailor therapy to individual patient needs. Integration of digital health technologies, wearable devices, and artificial intelligence (AI) could revolutionize disease monitoring, management, and therapeutic interventions.

Emphasis on patient-centered care, shared decision-making, and holistic approaches to treatment may enhance quality of life and well-being for PD patients and their caregivers. Collaboration among researchers, clinicians, patients, advocacy groups, and industry partners is essential for accelerating progress, translating scientific discoveries into clinical applications, and addressing unmet needs. Empowering patients and caregivers through education, support services, and advocacy initiatives can raise awareness, reduce stigma, and drive policy changes to improve access to care and resources.

Despite significant research efforts, there are currently no disease-modifying therapies available to slow or halt the progression of PD. Developing effective neuroprotective treatments remains a major challenge. Non-motor symptoms of PD, including cognitive impairment, psychiatric symptoms, autonomic dysfunction, and sleep disturbances, can be challenging to manage and may have a significant impact on quality of life. There is variability in treatment response among PD patients, and individualized approaches to therapy are needed to optimize

outcomes. Identifying predictors of treatment response and refining precision medicine strategies are ongoing challenges. Disparities in access to specialized care, support services, and research opportunities exist among PD patients, particularly in underserved communities and rural areas. Addressing these disparities is crucial for ensuring equitable care delivery and improving outcomes.

In summary, while there are reasons for optimism regarding advancements in PD research, personalized care approaches, and technological innovations, significant challenges and roadblocks remain. Overcoming these challenges will require sustained efforts, collaboration, and a multifaceted approach to improving the outlook and quality of life for individuals affected by Parkinson's disease.

## Notes

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## Author Contribution

R.T. and J.M.S: Conceptualization, investigation, methodology, data acquisition, writing, editing. Q.A.Z.: Conceptualization, investigation, methodology, validation, data and resource acquisition. All authors have approved the submitted final version.

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