# Unraveling Parkinson's disease: from dopaminergic dysfunction to novel therapeutic targets

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## Abstract

Parkinson's disease (PD) is a neurodegenerative disorder influenced by multiple factors and primarily defined by the gradual loss of dopaminergic neurons within the substantia nigra pars compacta. This pathological process fundamentally reduces available dopamine levels and produces core motor symptoms that include bradykinesia, resting tremor, rigidity, postural instability, and a generalized loss of balance. However, the pathology of PD appears to include far more than nigrostriatal function, as it is increasingly recognized that PD extends across the central and peripheral nervous systems through many different neurotransmitter systems/neurotransmitters, neuroinflammation, mitochondrial dysfunction, genetic mutations, abnormal protein aggregation (particularly of α-synuclein), and other factors. Thus, the complexities of PD are suggestive of more of a syndromic process rather than a single disease process with varied pathogenetic pathways that also result in varied clinical presentations. Traditionally, treatment options for PD have primarily focused on dopaminergic treatment strategies to manage the progressive symptoms, which include the lifestyle impact of diminished dopamine levels. This regimen primarily includes levodopa in addition to dopamine agonist options and an array of adjunctive therapies. While these early treatments are completely life-altering and provide considerable improvement for the first several years, their benefit eventually wanes, and they fundamentally simply do not alter disease progression. Recently, there has been a concerted effort to identify treatment options that are not simply a dopaminergic replacement treatment but can alter some aspects of the disease, including several novel approaches investigating mitochondrial health, neuroinflammation, autophagy, α-synuclein aggregation, and genetic regulation in both preclinical and early clinical studies. This review takes a critical look at the classic view of PD occurring as a result of dopaminergic dysfunction, extends into modern concepts that include abnormalities at the cellular and molecular levels, and describes new treatment strategies that fundamentally reflect the multifactorial nature of PD. However, its central aim is to direct the audience to interventions that not only relieve symptoms but also hold the promise to stop or reverse the disease, ultimately offering renewed hope to patients and physicians alike.

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## Introduction

Parkinson's disease (PD), initially characterized by James Parkinson as "Shaking Palsy" back in 1817, is the second most common neurodegenerative disorder, second only to Alzheimer's disease. PD is a progressive disorder that affects millions of people across the globe and is characterized by motor and non-motor symptoms (NMS), impacting a broad range of motor functions. Motor features include resting tremor, bradykinesia, muscle rigidity, and postural instability. Motor features are predominantly due to the loss of dopaminergic neurons in the substantia nigra in the midbrain.[1] Dopamine is the most important neurotransmitter in

motor control and is, effectively, depleted in this region, resulting in motor function characteristic of PD. Over the past few decades, however, the image of PD has become clearer; we now know that PD is a much more complex phenomenon than previously thought, as it can be classified more completely as a multisystem disorder; the pathology in PD is not just limited to the dopaminergic system and includes NMS – cognitive decline, mood disorders, sleep disturbances, dysautonomia, and gastrointestinal dysfunction – many of which are seen prior to motor function and are aligned with negative patient quality of life.[2] The presence of Lewy bodies, cytoplasmic inclusions of essentially misfolded α-synuclein, in numerous regions of the brain is evidence of the multisystem nature of PD. These inclusions are not specific to the substantia nigra and also exist in cortical, limbic, and autonomic centers, highlighting the extensive nature of neurodegeneration. The cause of PD is uncertain; it is generally conceptualized as multifactorial, with genetic and environmental contributions to disease risk. The majority of PD cases are sporadic, but familial cases occur in about 10-15%. Mutations in several genes (*SNCA*, *LRRK2*, *PARK2*, *PARK7*, and *PINK1*) are found in familial disease, and provide some insight into molecular pathways that PD may affect. These genes are implicated in processes including protein degradation, mitochondrial function, oxidative stress response, and synaptic maintenance.[3] On the environmental side, pesticide exposure, heavy metals, and rural living have all shown increases in PD risk, however, smoking and caffeine consumption appear to provide a protective effect, suggesting the presence of some yet unknown mechanism. One of the pathological hallmarks of PD is mitochondrial dysfunction. Mitochondria are powerhouses of the cell because they provide energy, regulate calcium homeostasis, and regulate a number of apoptotic pathways. Both genetic evidence and toxin-induced models (1-methyl-4-phenyl-1,2,3,6-tetrahydropyridine and rotenone) suggest that an impairment in mitochondrial complex I activity can lead to oxidative damage and neuronal death *via* increased levels of reactive oxygen species (ROS). It is important to note that oxidative stress is exceedingly more than a by-product of mitochondrial dysfunction or failure; it is an important contributor to neurodegeneration in PD. Another component of the pathophysiological process of PD is protein misfolding and aggregation, primarily involving α-synuclein.[4]

Physiologically, α-synuclein is thought to serve a role in regulating synaptic vesicles. When misfolded, the α-synuclein monomer can aggregate into insoluble fibrils known as Lewy bodies and Lewy neurites. The aggregates are thought to enter the neuron and cause damage by inhibiting synaptic operations, suppressing mitochondrial functioning, causing oxidative stress, and inducing the proinflammatory pathway. Interestingly, emerging evidence suggests that misfolded α-synuclein can spread to other areas of the brain in a prion-like manner by also spreading pathology through synaptically related networks, which may explain the stereotypical progression of cognition and motor symptoms from the brainstem to cortical structures.[5] Neuroinflammation is a contributor to the pathogenesis of PD. Observations in PD patient brains show activated results in microglia and increased levels of inflammatory cytokines, which demonstrate a chronic inflammatory state.[6] Although inflammation may initially be a protective response to neuronal damage, continued inflammation can exacerbate and create a vicious cycle of neurotoxicity and additional loss of neurons. There is also a growing interest in the gut-brain axis and potential involvement of the microbiome in modulating neuroinflammation and α-synuclein aggregation. Alteration of gut flora and the presence of α-synuclein in the enteric nervous system, well before the appearance of motor symptoms, suggest that gut involvement is an important component of disease initiation. As a clinical entity, PD is heterogeneous, multi-faceted in terms of clinical presentation, in age at onset, symptoms, rate of symptom progression, therapy responsiveness, differing comorbidities, and sometimes, those who are considered idiopathic may have symptomatic representations of genetic.[7] This heterogeneity of the condition also reflects variants in pathophysiology that create significant challenges for diagnosis and treatment. To date, there is no definitive test to diagnose PD; we primarily make clinical diagnoses based on the presence of cardinal motor symptoms and the response to dopaminergic therapy. Neuroimaging may have a limited role as a dopamine transporter scan will provide supporting evidence of loss of dopaminergic function, but neither identify with confidence PD *vs.* another disorder nor provide definitive evidence of a physiologic loss befitting of a diagnosis of PD. Lacking adequate identification procedures, we cannot yet identify a biomarker applicable for diagnosis, early detection, or tracking disease progression. Certainly, the lack of an accurate and reliable diagnostic process creates delays in definitive diagnosis, and potentially negates early interventions as well as further separates the time phenotypically from clinical presentation to pathways of therapies, promoting disease-modifying therapies.[8] Currently, the mainstay treatment for PD is taking replacement therapy for the required therapeutic content of dopamine. At this point, all dopamine is pharmacological, and the steps taken toward emphasizing symptomatic treatment are considered to be best with levodopa, the dopamine precursor. Yet chronic levodopa therapy has drawbacks, including the development of dyskinesias and motor fluctuations. There are also several other pharmacological options, including dopamine agonists, monoamine oxidase-B inhibitors, and catechol-O-methyl transferase inhibitors, but they often have limited effect, and the effect can be further narrowed by intolerable side effects of their own.[9]

## Pathophysiology

PD pathophysiology is complex and multifactorial. Genetics, molecular processes, and environmental influences conspire to lead to progressive neurodegeneration. Central to the pathological process is the death of dopaminergic neurons in the substantia nigra pars compacta and the associated reduction in dopamine levels in the striatum (the major input structure of the basal ganglia). Dopamine signaling in the striatum coordinately influences neuronal firing rates in basal ganglia circuitry that ultimately modulates voluntary movement. The result of this disequilibrium is thalamocortical inhibition of motor pathways, resulting in the clinical motor features of PD. Another pathology associated with PD is Lewy bodies, misconstrued intracytoplasmic inclusions, which are primarily composed of misfolded α-synuclein. α-synuclein is a presynaptic neuronal protein associated with the regulation of synaptic vesicles.[10] In a diseased state, it aggregates into insoluble fibrils, which disrupt cellular homeostasis. Cell-to-cell transfer of misfolded α-synuclein, in a prion-like manner, likely facilitates disease progression in the central nervous system. This concept, called Braak staging, describes the progression of Lewy pathology based on its movement from the lower brainstem and olfactory bulb into cortical areas, which relate to the sequential emergence of non-motor and motor symptoms. Mitochondrial dysfunction plays a significant role in the pathogenesis of this disease. Decreased function of the mitochondrial respiratory chain, including complex I, has been demonstrated in sporadic and genetic forms of the disease and leads to increased oxidative stress, creating ROS, which results in neuronal injury. The mutations in *PINK1* and *PARKIN*, both associated with mitochondrial quality control and the removal of damaged organelles by autophagy, illustrate how maintaining mitochondrial homeostasis is necessary for the prevention of the disease. Neuroinflammation contributes to the

neurodegenerative cascade of PD.[11] In *post-mortem* studies of patients with PD, activated microglia and increased pro-inflammatory cytokines were found in both the substantia nigra and cerebrospinal fluid. While acute inflammation may benefit neuronal health, chronic inflammation is detrimental and can facilitate neurodegenerative processes by promoting neuronal death through the consequences of toxic mediator release. Disruption of the organism's protein degradation, notably through the action of the ubiquitin-proteasome system or autophagy-lysosomal pathway, is an additional factor that contributes to cellular stress and enhances the severity of PD. Mutations associated with PD, such as in *LRRK2* and *GBA*, are also associated with loss of lysosomal function and represent secondary risk factors. As damaged proteins and organelles accumulate, regulatory processes involving apoptosis and eventually necrosis are triggered, and the unnecessary demise of cells progresses. In addition, an emerging body of literature implicating the gut-brain axis further reinforces the notion that alterations in the gastrointestinal tract can play a powerful role in potentially initiating or propagating neurodegenerative processes in PD.[12]

## Current therapeutic approaches

The cornerstone of PD management remains symptomatic relief, particularly targeting motor symptoms arising from dopaminergic neuronal degeneration. Levodopa, introduced over half a century ago, continues to be the gold standard for symptomatic therapy. When administered with peripheral decarboxylase inhibitors like carbidopa or benderizine, levodopa effectively crosses the blood-brain barrier and is converted into dopamine, replenishing depleted stores. While highly effective in the early stages, chronic levodopa use is often marred by the emergence of motor complications such as wearing-off phenomena and dyskinesias, necessitating adjunctive therapies or altered dosing strategies. Dopamine agonists like pramipexole, ropinirole, and retigabine are often used in the early stages or in combination with levodopa in advanced disease. They act directly on dopamine receptors and offer the advantage of a lower risk of dyskinesia early in treatment, but may cause impulse control disorders and hallucinations in susceptible individuals. Enzyme inhibitors such as MAO-B inhibitors (*e.g.*, rasagiline, selegiline) and COMT inhibitors (*e.g.*, entacapone, opicapone) are employed to enhance the efficacy and duration of levodopa's effect by inhibiting its metabolism. For advanced PD cases, continuous dopaminergic stimulation through infusion therapies like levodopa-carbidopa intestinal gel or subcutaneous apomorphine is increasingly used to manage severe motor fluctuations.[13] Invasive options such as deep brain stimulation (DBS) targeting the subthalamic nucleus or globus pallidus interna provide substantial motor improvement and reduced medication dependence in carefully selected patients. NMS are addressed with targeted pharmacotherapy. Depression and anxiety are treated with antidepressants, while cognitive impairment may benefit from cholinesterase inhibitors. Management of autonomic dysfunction, including orthostatic hypotension, constipation, and urinary incontinence, often requires multi-drug regimens and lifestyle interventions. Rehabilitative therapies such as physical therapy, occupational therapy, and speech-language therapy form essential components of multidisciplinary care. Exercise regimens, particularly those involving aerobic and resistance training, have demonstrated benefits in maintaining motor function and potentially slowing disease progression. The evolving integration of wearable technology and telemedicine also holds promise for individualized monitoring and therapy optimization.[14]

## Emerging molecular targets

While symptomatic management has significantly improved quality of life in PD, it does not address the underlying neurodegenerative processes. Thus, research is increasingly focused on identifying and targeting molecular mechanisms that contribute to disease pathogenesis, with the goal of developing disease-modifying therapies. A central hallmark of PD pathology is the misfolding and aggregation of α-synuclein into Lewy bodies. Consequently, therapeutic efforts targeting α-synuclein have gained momentum. Immunotherapeutic approaches, both passive (monoclonal antibodies) and active (vaccination strategies), aim to enhance the clearance of pathogenic α-synuclein species.[15] Agents such as prasinezumab have shown promise in early trials, though further research is needed to validate long-term benefits. Genetic mutations associated with PD, particularly those in *LRRK2* and *GBA*, have opened new avenues for targeted treatment. Inhibitors of *LRRK2* kinase activity are under development, seeking to counteract the effects of gain-of-function mutations that contribute to neuronal toxicity. Similarly, therapies aiming to enhance glucocerebrosidase activity in *GBA* mutation carriers are being pursued to restore lysosomal function and reduce α-synuclein accumulation. Mitochondrial dysfunction, another key feature of PD pathogenesis, has prompted interest in agents that support mitochondrial health or reduce oxidative stress. Coenzyme Q10, creatine, and newer compounds, such as ursodeoxycholic acid, are under investigation for their neuroprotective properties. Additionally, modulation of neuroinflammation *via* microglial inhibitors or anti-inflammatory cytokines is being explored to mitigate the neurodegenerative cascade.[16] Novel neurotrophic factors, such as glial cell line-derived neurotrophic factor, are also under evaluation for their ability to support dopaminergic neuron survival. Despite some setbacks in clinical trials due to delivery challenges and variability in response, ongoing research seeks to refine administration methods and identify responsive subpopulations. Emerging evidence suggests that targeting the gut-brain axis, particularly through modulation of gut microbiota, may influence neurodegenerative processes. Probiotics, antibiotics, and dietary interventions are being studied for their potential to alter disease trajectory. These novel strategies represent a shift toward personalized medicine and offer hope for modifying the course of PD.[17]

## Role of non-motor symptoms

NMS in PD are often under-recognized yet have a profound impact on patients' quality of life. These symptoms frequently precede the onset of motor signs and persist throughout the disease course. The recognition and management of NMS are now central to comprehensive PD care. Cognitive impairment in PD ranges from mild executive dysfunction to PD dementia (PDD). These symptoms may be attributed to Lewy body deposition in cortical regions and cholinergic deficits. Cholinesterase inhibitors such as rivastigmine have demonstrated modest efficacy in PDD. Depression and anxiety are common and may emerge independently of disease stage. These mood disorders are managed with selective serotonin reuptake inhibitor, serotonin-norepinephrine reuptake inhibitor, and cognitive-behavioural therapy, although antidepressant response can be variable.[18] Psychosis, especially visual hallucinations and delusions, often emerges in later stages and is exacerbated by dopaminergic therapy. Management typically involves medication adjustment and the cautious use of antipsychotics such as clozapine or quetiapine. Pimavanserin, a selective serotonin inverse agonist, has also shown efficacy without worsening motor symptoms. Autonomic dysfunction is another major NMS domain, encompassing orthostatic

hypotension, constipation, urinary incontinence, erectile dysfunction, and sweating abnormalities. These symptoms reflect widespread neurodegeneration affecting peripheral autonomic pathways. Management includes both pharmacological and non-pharmacological strategies, ranging from midodrine and droxidopa for hypotension to dietary fiber and laxatives for constipation. Sleep disturbances, particularly REM sleep behavior disorder (RBD), excessive daytime sleepiness, and insomnia, are common and may significantly impair daily functioning.[19] RBD often precedes motor onset and may serve as a biomarker for prodromal PD. Treatment includes melatonin and clonazepam, although response may vary. Fatigue, pain, and sensory complaints further add to the burden of PD. These symptoms are often multifactorial and require an individualized, interdisciplinary approach. Regular screening for NMS using validated tools such as the Non-Motor Symptoms Questionnaire is essential for early identification and appropriate intervention. Recognition of NMS as intrinsic to the disease process rather than secondary complications has transformed PD management. Future research is increasingly focused on elucidating the pathophysiological mechanisms of NMS and integrating its treatment into standard care algorithms.[20] Figure 1 shows the role of NMS in PD.

## Challenges and future directions

Despite considerable advancements in understanding and managing PD, several challenges remain. One of the most pressing limitations is the lack of a definitive disease-modifying therapy. Current treatments primarily offer symptomatic relief, and no intervention has yet been proven to halt or reverse neurodegeneration. This gap underscores the need for continued investment in basic and translational research. Another major challenge lies in the heterogeneity of the disease. Parkinson's is now understood as a syndrome with multiple subtypes, influenced by genetic, environmental, and pathological variability. This diversity complicates diagnosis, prognosis, and therapeutic response, highlighting the need for precision medicine approaches that tailor treatment to individual profiles. Diagnostic limitations, especially in early or atypical presentations, impede timely intervention. Biomarker development (whether through imaging, cerebrospinal fluid analysis, or blood-based tests) holds promise for improving diagnostic accuracy and tracking disease progression. However, translating these tools into routine clinical practice remains a work in progress.[21] The management of NMS and long-term complications continues to challenge clinicians. Motor fluctuations, dyskinesias, and neuropsychiatric issues are often difficult to balance, especially as the disease progresses. Integration of multidisciplinary care and the development of patient-specific treatment algorithms are essential for addressing these complexities. Access to advanced therapies like DBS and infusion systems remains uneven, particularly in low-resource settings. The cost of treatment, need for specialized care teams, and long-term follow-up requirements limit their widespread adoption. Expanding telemedicine, increasing provider education, and supporting caregiver networks can help bridge this gap. Looking ahead, future directions in PD research include expanding clinical trials targeting α-synuclein, *LRRK2*, *GBA*, and mitochondrial pathways. Cell and gene therapies are poised to redefine disease management if safety, delivery, and efficacy challenges can be overcome. Real-time monitoring through wearable sensors, machine learning algorithms, and patient-reported outcomes will enable personalized and adaptive care models. Ultimately, unraveling PD requires a multifaceted approach, integrating pathophysiological

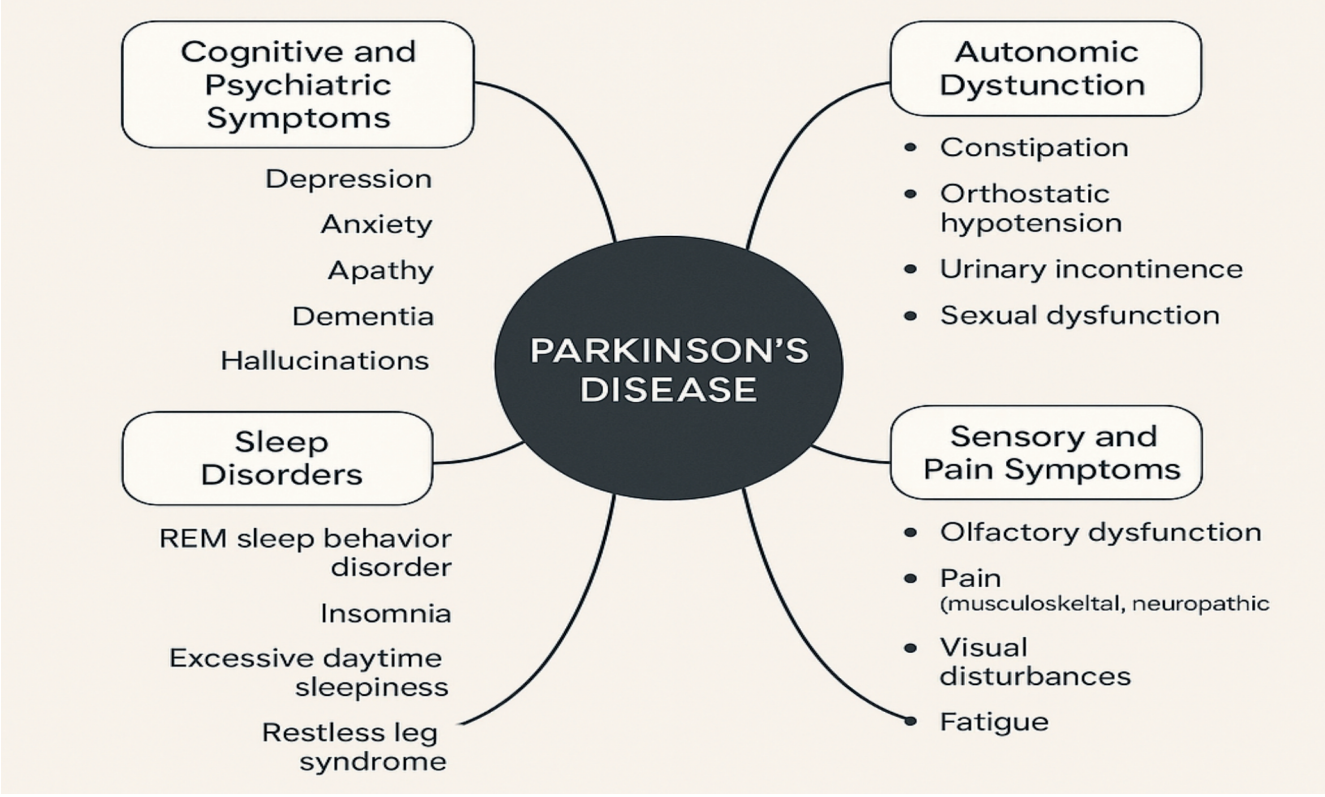


**Figure 1.** Role of non-motor symptoms in Parkinson's disease.

insights, innovative therapies, and comprehensive patient-centered care. Collaboration among clinicians, researchers, patients, and advocacy groups is essential to translating scientific discoveries into tangible clinical benefits.[22] This review aims to explore the evolution of PD from a traditionally dopaminergic-centric disorder to a complex multisystem disease. We examine its molecular and clinical heterogeneity, summarize emerging therapeutic targets beyond dopamine replacement, and emphasize the need for precision medicine approaches tailored to subtypes of PD.

## Discussion

PD represents a complex, multifactorial neurodegenerative syndrome rather than a single disorder, reflecting the convergence of diverse pathological processes. While traditionally framed around dopaminergic neuron loss, PD encompasses a broader pathophysiological landscape including α-synuclein aggregation, mitochondrial dysfunction, neuroinflammation, and proteotoxic failure. These mechanisms are not independent but rather form interconnected pathways, contributing to progressive neuronal loss.[23] Across the previous sections, we have discussed how misfolded α-synuclein disrupts synaptic transmission and mitochondrial function, with evidence suggesting its propagation through the nervous system in a prion-like manner.[24] Mitochondrial deficits, particularly in complex I of the respiratory chain, exacerbate oxidative stress and contribute to neuronal apoptosis.[25] Genetic mutations in genes such as *SNCA*, *LRRK2*, *PINK1*, and *GBA* further illustrate hereditary susceptibility and disruption of intracellular homeostasis. Importantly, chronic neuroinflammation mediated by activated microglia and elevated pro-inflammatory cytokines not only accompanies but may drive disease progression.[26] These overlapping mechanisms underscore why dopamine-centric therapies, although effective initially, fail to halt disease progression. Levodopa remains the cornerstone of symptomatic relief but is associated with long-term complications like dyskinesias and motor fluctuations.[27] Adjunctive pharmacotherapies and advanced strategies like DBS offer improved symptom control, yet the absence of disease-modifying options remains a major therapeutic gap.[28]

Recent research pivots toward disease modification, with novel approaches targeting α-synuclein aggregation, *LRRK2* inhibition, lysosomal enhancement in *GBA* mutation carriers, and mitochondrial support.[29] Immunotherapeutic strategies and gene therapy trials show early promise but face hurdles in delivery, efficacy, and patient stratification. Targeting neuroinflammation and gut-brain axis alterations also opens new avenues for intervention, particularly in early or prodromal PD.[30] A crucial advancement lies in recognizing PD heterogeneity. Subtyping based on clinical features (*e.g.*, malignant *vs*. non-malignant), prodromal markers like REM RBD, and genetic or neurophysiological profiles allows tailored interventions. Such stratification is essential not only for clinical management but for designing robust clinical trials.[31] Looking forward, the development of reliable biomarkers for early diagnosis and disease monitoring is vital. Integration of digital health technologies, artificial intelligence, and wearable biosensors may revolutionize personalized care and enable real-time tracking of disease progression. Moreover, rehabilitation strategies and multidisciplinary care models continue to play a foundational role in maintaining quality of life.[32,33] In summary, unraveling PD requires a shift from a singular focus on dopamine to a systems-level understanding that embraces its complexity (Table 1).[34-51] Bridging mechanistic insights with translational therapies, advancing biomarker discovery, and personalizing treatment through subtype identification are imperative to transform PD care from symptomatic relief to true disease modification.

**Table 1.** Representative table of key past studies (2000-2024) related to "Unraveling Parkinson's disease: from dopaminergic dysfunction to novel therapeutic targets". These studies span major focus areas including dopaminergic therapies, genetic research, neuroinflammation, and emerging novel treatments.

| Year | Study titles | Authors | Focus area | Key findings |
|---|---|---|---|---|
| 2000 (34) | Levodopa therapy and motor fluctuations in PD | Katzenschlager *et al.* | Dopaminergic therapy | Long-term use improves motor symptoms but leads to dyskinesia and fluctuations |
| 2003 (35) | Deep brain stimulation of the STN in PD | Deuschl *et al.* | Surgical therapy (DBS) | Demonstrated significant motor improvements in advanced PD |
| 2004 (36) | α-synuclein and Lewy body formation | Spillantini *et al.* | Protein aggregation | Identified alpha-synuclein as a key component in Lewy body pathology |
| 2005 (37) | Mutations in the *LRRK2* gene | Zimprich *et al.* | Genetic factors | Linked LRRK2 mutations to familial and sporadic PD |
| 2007 (38) | Non-motor symptoms in PD | Chaudhuri *et al.* | Non-motor symptoms | Highlighted the prevalence and impact of non-motor symptoms on quality of life |
| 2008 (39) | Neuroinflammation in PD | Hirsch and Hunot | Neuroinflammation | Identified microglial activation as a key player in PD progression |
| 2009 (40) | Braak staging and gut-brain hypothesis | Braak *et al.* | Gut-brain axis | Proposed PD pathology may begin in the gut before reaching the brain |
| 2010 (41) | Stem cell therapy for neurorestoration | Lindvall and Kokaia | Regenerative medicine | Discussed potential of stem cells in repairing dopaminergic neurons |

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**Table 1.** Continued from previous page.

| Year | Study titles | Authors | Focus area | Key findings |
|---|---|---|---|---|
| 2011 (42) | *AAV2-GDNF* gene therapy trials | Bankiewicz *et al.* | Gene therapy | Early trials showed safety but limited functional improvement |
| 2012 (43) | Personalized medicine in Parkinson's disease | Marras *et al.* | Precision medicine | Advocated for patient-specific approaches in PD treatment |
| 2013 (44) | Advanced neuroimaging in early PD | Bohnen *et al.* | Imaging and biomarkers | Improved detection of early PD through dopaminergic imaging |
| 2015 (45) | Microbiome analysis in PD patients | Scheperjans *et al.* | Gut-brain axis | Found altered gut microbiota profiles in PD patients |
| 2016 (46) | Wearable sensor-based PD monitoring | Patel *et al.* | Digital health | Enabled remote symptom monitoring via smart devices |
| 2017 (47) | *GBA* mutations and PD pathology | Sidransky *et al.* | Genetic/lysosomal dysfunction | Established GBA mutations as risk factors for earlier-onset PD |
| 2019 (48) | Therapeutic alpha-synuclein vaccine trials | Schneider *et al.* | Immunotherapy | Explored vaccine safety; further efficacy studies required |
| 2020 (49) | Dual pathway treatment strategies | Connolly and Lang | Combination therapy | Recommended combining dopaminergic and non-dopaminergic therapies |
| 2021 (50) | AI algorithms for early PD detection | Arora *et al.* | Artificial Intelligence | Machine learning tools identified subtle motor changes predictive of PD |
| 2022 (51) | Telemedicine in Parkinson's care | Dorsey *et al.* | Telehealth | Increased access and continuity of care for rural patients |

PD, Parkinson's disease; STN, subthalamic nucleus; AI, artificial intelligence.

## Conclusions

A comprehensive and holistic approach that integrates pharmacologic, surgical, rehabilitative, and supportive treatments remains indispensable for addressing the full range of PD; recent advances in biomarkers, imaging, and genomics will pave the way for clinicians to eventually provide better personalized and targeted care. With further studies and collaboration through scientific and clinical disciplines, the hope of moving PD from an unavoidable progressive disorder to living with a manageable condition is becoming a realized possibility.

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