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REVIEW

Updates on Parkinson's Disease

Hong Bai[1], Wenhui Ma[2], Lei Zhu[1], Yaling Lu[3], Jiaojiao Fan[4], Mengjia Chen[1], Cong Huang[2]

[1]Department of Neurology, No. 926 Hospital, Joint Logistics Support Force of PLA, Kaiyuan, Yunnan, 661699, People's Republic of China; [2]Department of Radiology, No. 926 Hospital, Joint Logistics Support Force of PLA, Kaiyuan, Yunnan, 661699, People's Republic of China; [3]Department of Health Management, No. 926 Hospital, Joint Logistics Support Force of PLA, Kaiyuan, Yunnan, 661699, People's Republic of China; [4]Department of Outpatient, No. 926 Hospital, Joint Logistics Support Force of PLA, Kaiyuan, Yunnan, 661699, People's Republic of China

Correspondence: Cong Huang, Department of Radiology, No. 926 Hospital, Joint Logistics Support Force of PLA, Kaiyuan, Yunnan, 661699, People's Republic of China, Email magichc401@163.com

Abstract: Parkinson's disease (PD) represents a progressive neurodegenerative disorder with escalating global burden, with mechanistic studies revealing α-synuclein propagation through gut-brain axis, mitochondrial defects, and neuroinflammatory cascades driven by genetic-environmental interplay. Recent advancements in diagnostic paradigms have successfully combined α-synuclein seed amplification assays with multimodal neuroimaging techniques, achieving an impressive diagnostic accuracy of 92% during the prodromal stages of disease. Phase II trials highlight disease-modifying potential of α-synuclein-targeting immunotherapies (40% reduction in motor decline) and LRRK2 kinase inhibitors showing blood-brain barrier penetration. Neuromodulation advances feature closed-loop deep brain stimulation systems with 63% superior symptom control versus conventional approaches. Current challenges center on biomarker validation across ethnic cohorts (30% variability in α-synuclein thresholds) and non-motor symptom management. Emerging solutions leverage single-cell spatial transcriptomics identifying dopaminergic neuron vulnerability signatures, coupled with wearable-enabled digital phenotyping achieving 89% prediction accuracy for motor fluctuations. This synthesis underscores the critical transition from symptomatic care to precision-targeted interventions of PD pathogenesis.

Keywords: Parkinson's disease, α-synuclein propagation, biomarkers, disease-modifying therapies, gene-environment interaction, mitochondrial dysfunction, deep brain stimulation, precision medicine

Introduction

Parkinson's disease (PD) ranks as the second most prevalent neurodegenerative disorder, marked by the gradual loss of dopaminergic neurons in the substantia nigra and the buildup of misfolded α-synuclein aggregates, known as Lewy bodies, in both the central and peripheral nervous systems.[1] With over 6 million people affected worldwide, PD presents significant socioeconomic challenges, especially as the global population ages.[2] Traditionally, research has concentrated on the motor symptoms of the disease, such as bradykinesia, rigidity, and resting tremor. However, recent advancements in molecular biology and neuroimaging techniques have shed light on the intricate nature of non-motor symptoms, including cognitive decline and autonomic dysfunction, as well as the varied progression of the disease.[3]

The past decade has brought significant advancements in our understanding of PD pathogenesis, highlighting the roles of genetic factors such as mutations in the LRRK2 and GBA genes, environmental influences like pesticide exposure, and the dysregulation of the gut-brain axis.[4–6] In 2023, the International PD and Movement Disorder Society introduced new criteria for biomarker-guided stratification, which focuses on innovative techniques like α-synuclein seed amplification assays (αS-SAA, highly sensitive detection technique for enrichment of pathological α-synuclein aggregates in vitro) and dopamine transporter imaging (DAT).[7] Such advancements align with evolving efforts to refine diagnostic frameworks, including updates to operational definitions for Parkinson's disease dementia.[8]

Additionally, Novel therapies targeting α-synuclein transmission, neuroinflammation, and mitochondrial dysfunction, such as the monoclonal antibody prasinezumab—are revolutionizing the therapeutic landscape.[9] These approaches, which aim to delay disease progression unlike traditional dopamine replacement strategies, complement recent updates in managing motor fluctuations.[10] This review will systematically address epidemiology, risk factors, pathogenesis,

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biomarkers, diagnostics, and emerging therapies, integrating recent findings to outline future directions for personalized management of Parkinson's disease.

Epidemiology

PD is becoming an increasingly significant global health issue, with its prevalence rising by 15% over the last decade, largely due to aging populations and advancements in diagnostic methods.[2] Currently, it is estimated that more than 10 million people around the world are living with PD, with annual incidence rates varying between 8 and 18 cases per 100,000 person-years.[11] The incidence of PD increases markedly after the age of 60, reaching its highest point between 85 and 89 years. Additionally, early-onset PD, which is diagnosed before the age of 50, represents about 5% to 10% of all cases and is often associated with specific genetic mutations, such as those found in the PARK2 and PINK1 genes.[4]

Geographic disparities in the prevalence of PD are notable, with higher rates observed in North America and Europe, where the prevalence ranges from 1.5% to 2.0% among individuals over 65 years old.[12] In contrast, the prevalence is significantly lower in Asia, at 0.3% to 1.0%, and in Africa, where it ranges from 0.1% to 0.8%.[12] These differences may be influenced by various factors, including environmental exposures, genetic susceptibility, and access to healthcare. Additionally, there are marked sex differences in PD risk, with males being 1.5 times more likely to develop the disease than females.[13] This disparity may be linked to the neuroprotective effects of estrogen in females and differences in exposure to occupational toxins. Longitudinal studies have also shown that the rates of PD diagnosis are increasing more rapidly in industrialized regions. This trend appears to be associated with urbanization-related factors, such as increased air pollution and a decline in physical activity levels.[14]

Recent data highlight the impact of COVID-19 on the epidemiology of PD, revealing that post-pandemic cohorts exhibit a higher incidence of prodromal symptoms, such as hyposmia and REM sleep behavior disorder, alongside delayed clinical diagnoses resulting from disruptions in healthcare services.[15] These trends emphasize the critical need for population-based screening programs that incorporate genetic, environmental, and biomarker data. Such initiatives are essential for improving risk stratification and alleviating the overall burden of the disease.

Risk Factors

The above global epidemiological profile is closely related to genetic susceptibility (eg, geographical differences in GBA mutation frequencies) and environmental exposures (eg, regional distribution of agricultural chemical use), and specific risk factors can be dissected from the following dimensions.

PD develops through intricate interactions among genetic predisposition, environmental factors, and lifestyle choices. Around 15% to 20% of individuals with PD indicate a family history of the condition, with certain genetic mutations, such as those in the LRRK2, GBA, and SNCA genes, exhibiting either autosomal dominant or recessive inheritance patterns.[4,16] Additionally, genome-wide association studies have uncovered 90 risk loci associated with PD, including GCH1 and VPS13C, which play crucial roles in dopamine production and the functioning of lysosomes.[17]

Environmental triggers are crucial, especially in the case of sporadic PD. Research indicates that long-term exposure to certain pesticides, such as rotenone and paraquat, can increase the risk of developing PD by 2.5 times. This heightened risk is linked to the inhibition of mitochondrial complex I and the aggregation of α-synuclein, a protein associated with PD.[5,18] Additionally, new studies suggest that air pollution, particularly fine particulate matter measuring less than 2.5 micrometers, contributes to the loss of dopaminergic neurons.[14] This occurs through mechanisms involving systemic inflammation and oxidative stress. On a more positive note, habits like smoking and consuming caffeine seem to offer some protective benefits against PD. These activities can lower the risk of developing the disease by 30% to 40%, likely due to their effects on nicotinic receptors and the antagonism of adenosine A2A receptors.[19,20]

Lifestyle factors and comorbidities play a significant role in modifying risk levels. For instance, individuals who have experienced a traumatic brain injury have a 50% higher incidence of Parkinson's disease (PD).[21,22] Additionally, factors like physical inactivity and metabolic syndrome can worsen neuroinflammation and contribute to the pathology associated with α-synuclein.[23] Recent research has shed light on the gut-brain axis, revealing that dysbiosis, characterized by a decrease in Prevotella abundance, is linked to the misfolding of α-synuclein and its propagation via the vagus nerve.

Furthermore, gene-environment interactions, such as the increased sensitivity of GBA mutation carriers to pesticide exposure, underscore the importance of developing personalized frameworks for risk assessment.[24]

Disease Mechanisms and Pathology

PD is characterized by the degeneration of dopaminergic neurons in the substantia nigra pars compacta, accompanied by Lewy bodies—intraneuronal aggregates primarily composed of misfolded α-synuclein.[1] Braak's staging theory describes the pathological spread of α-synuclein, originating in the olfactory bulb and enteric nervous system, then propagating through neural networks via tunneling nanotubes and exosomes, ultimately affecting the midbrain and cortex.[1,25]

This aggregation process is intertwined with multiple cellular dysfunctions: mitochondrial impairment (due to PINK1/Parkin mutations) elevates reactive oxygen species, while lysosomal dysfunction (eg, GBA mutations) hinders α-synuclein clearance.[24,26] Neuroinflammation, synaptic dysfunction, and iron dysregulation further promote aggregation, with emerging roles for lipid metabolism and gut-brain axis interactions.[23,27–30] These interconnected pathways highlight PD's multisystem nature (Table 1).

Biomarker Studies

Significant advancements have been achieved in biomarker studies for PD, spanning central, peripheral, digital, and microbiome dimensions (Table 2).

Central Biomarkers: Advancing Pathological Specificity

Recent advances in biomarker research have significantly transformed the early detection and monitoring of PD. For instance, αS-SAA conducted on cerebrospinal fluid (CSF) show impressive results, demonstrating 90% sensitivity and 95% specificity in identifying pathological α-synuclein aggregates. This capability allows for the effective stratification of patients into distinct molecular subtypes, enhancing personalized treatment approaches.[31] Additionally, DAT continues to be regarded as the gold standard for visualizing presynaptic dopaminergic deficits.[3] In this context, reduced striatal binding observed through DAT imaging has been found to correlate closely with the severity of motor symptoms, providing valuable insights into disease progression and patient management.

Peripheral Biomarkers: Non-Invasive Diagnostic Innovations

Peripheral biomarkers are increasingly recognized for their non-invasive characteristics. For instance, plasma neurofilament light chain (NfL) levels can effectively distinguish PD from atypical parkinsonian disorders, achieving an area

Table 1 Summary of Key Pathogenic Mechanisms in PD

Core Mechanisms	Key Drivers/Molecules	Pathological Associations	References
α-synuclein aggregation and propagation	Misfolded α-synuclein, tunneling nanotubes, exosomes	Follows Braak staging; spreads from olfactory bulb/enteric nervous system to midbrain and cortex, forming Lewy bodies	[1,25]
Mitochondrial dysfunction	PINK1/Parkin mutations	Increases reactive oxygen species (ROS); enhances vulnerability of dopaminergic neurons	[24,26]
Lysosomal dysfunction	GBA gene mutations	Impairs α-synuclein clearance, exacerbating aggregation	[24]
Neuroinflammation	Microglial activation, proinflammatory cytokines	Promotes α-synuclein aggregation and accelerates neuronal degeneration	[27]
Gut-brain axis dysfunction	Gut dysbiosis (reduced Prevotella), vagus nerve	Misfolded α-synuclein in the gut propagates to the central nervous system via the vagus nerve	[23,24]
Gene-environment interactions	LRRK2/GBA mutations + pesticide exposure	Mutant carriers show increased sensitivity to environmental toxins, amplifying risk	[4,5,24]

Table 2 Summary of Biomarker Types and Characteristics in PD

Biomarker Categories	Specific Biomarkers	Sample Type	Key Features/Diagnostic Value	References
Central Biomarkers	α-synuclein seed amplification assay (αS-SAA)	Cerebrospinal fluid (CSF)	90% sensitivity and 95% specificity; enables stratification of molecular subtypes; useful for prodromal diagnosis	[31]
	Dopamine transporter imaging (DAT)	Imaging (PET/SPECT)	Gold standard; reduced striatal binding correlates with motor symptom severity; assesses presynaptic dopaminergic deficits	[3]
Peripheral Biomarkers	Plasma neurofilament light chain (NfL)	Plasma	Distinguishes PD from atypical parkinsonian disorders (AUC=0.88)	[32]
	Salivary oligomeric α-synuclein	Saliva	82% diagnostic accuracy in prodromal cohorts	[33]
	Skin biopsy with real-time quaking-induced conversion (RT-QuIC)	Skin tissue	Detects phosphorylated α-synuclein in cutaneous nerves; 95% concordance with CSF findings	[34]
Digital and Microbiome Biomarkers	Wearable sensors/voice analysis	Motor/voice data	Objectively measures bradykinesia, tremor frequency, etc.; outperforms UPDRS for long-term monitoring	[35]
	Gut microbiota (reduced Roseburia, increased Akkermansia)	Feces	Indicates rapid disease progression	[23]

under the curve (AUC) of 0.88. Additionally, salivary oligomeric α-synuclein demonstrates an impressive diagnostic accuracy of 82% in identifying individuals within prodromal cohorts.[32,33] Furthermore, innovative methods like real-time quaking-induced conversion (RT-QuIC, is an ultrasensitive diagnostic technique that detects misfolded proteins by amplifying their aggregation in vitro using shaking) applied to skin biopsies have shown the capability to detect phosphorylated α-synuclein in cutaneous nerves, yielding a remarkable 95% concordance with findings from cerebrospinal fluid (CSF) analyses.[34]

Digital and Microbiome Biomarkers: Bridging Technology and Biology

Digital biomarkers that utilize wearable sensors and voice analysis algorithms provide an objective means to measure bradykinesia, tremor frequency, and speech patterns, showing superior performance compared to traditional assessments like the Unified Parkinson's Disease Rating Scale (UPDRS) for long-term monitoring.[35] Furthermore, profiling the gut microbiome has identified a decrease in Roseburia and an increase in Akkermansia as indicators of rapid disease progression.[23]

However, despite these advancements, there are ongoing challenges in standardizing pre-analytical variables, such as sample collection protocols, and in validating these biomarkers across diverse ethnic populations. The 2023 Parkinson's Progression Markers Initiative (PPMI) emphasizes the promise of integrating multiple modalities, such as combining αS-SAA with MRI neuromelanin imaging, to improve predictive capabilities.[36]

Diagnostic Criteria

The diagnosis of PD has shifted from relying solely on clinical features to a framework supported by biomarkers. According to the 2023 International Parkinson and Movement Disorder Society (MDS) criteria, there are now two levels of diagnosis: clinically established PD, which requires the presence of bradykinesia along with at least one supportive motor feature, and probable PD, which is supported by biomarker evidence such as abnormal DAT imaging or the αS-SAA.[7] Importantly, the updated criteria also acknowledge the significance of non-motor prodromal markers, including REM sleep behavior disorder (RBD) and hyposmia, as key diagnostic indicators when they are present alongside dopaminergic dysfunction.[37]

Key updates in the field include several significant advancements. Firstly, the integration of biomarkers has introduced reduced striatal DAT binding (≤65% age-adjusted uptake) or CSF αS-SAA positivity as critical "exclusionary red flags" for atypical parkinsonism.[3,31] Secondly, for prodromal diagnosis, a probability threshold of 80% or higher, as

recommended by the MDS research criteria, is now suggested for identifying preclinical Parkinson's disease (PD). This approach combines factors such as genetic risk, olfactory loss, and hyperechogenicity of the substantia nigra.[38] Thirdly, genetic stratification has become more refined, allowing LRRK2 or GBA mutation carriers who present with isolated REM sleep behavior disorder (RBD) or asymmetric tremor to qualify for early therapeutic trials, even if they do not exhibit overt motor symptoms.[4] Additionally, emerging technologies, including digital gait analysis and transcranial sonography, are being utilized as supportive tools in diagnosis. Notably, the misdiagnosis rates have decreased to between 10% and 15% in specialized centers, compared to the historical rate of 25%.[35,39] However, challenges remain, particularly in standardizing biomarker thresholds across different ethnic populations and in differentiating PD from conditions that mimic it, such as vascular parkinsonism.[40]

Therapeutics

The therapeutic measures for PD show amultidimensional developmental trend, covering aspects such as pharmacological interventions, gene and cell therapies, non-pharmacological interventions, and management of non-motor symptoms (Table 3).

Table 3 Summary of Therapeutic Strategies and Clinical Progress in PD

Therapeutic Categories	Specific Methods/Drugs	Target/Mechanism of Action	Clinical Phase/Effect	References
Pharmacological - Symptomatic	Levodopa	Dopamine replacement	First-line therapy; long-term use may cause dyskinesias and "on-off" fluctuations	[41]
	COMT inhibitors/MAO-B inhibitors	Prolong levodopa half-life	Adjuvant therapy; reduce symptom fluctuations	[41]
Pharmacological - Disease-Modifying	α-synuclein-targeting monoclonal antibodies (eg, prasinezumab)	Inhibit α-synuclein aggregation/propagation	Phase II trial; 40% reduction in motor decline	[9,10]
	LRRK2 kinase inhibitors (eg, DNL151)	Inhibit LRRK2 activity (for mutation carriers)	Phase II trial; blood-brain barrier penetration; reduced kinase activity	[42]
Gene and Cell-Based Therapies	AAV2-GAD gene therapy	Enhance GABAergic signaling in the subthalamic nucleus	Clinical trials; improve motor control	[43]
	Stem cell-derived dopaminergic neuron transplantation	Replace degenerated dopaminergic neurons	Phase I/II trials (effective in non-human primates; ongoing human validation)	[44]
Non-Pharmacological - Neuromodulation	Closed-loop deep brain stimulation (DBS)	Target subthalamic nucleus; real-time response to biomarkers	63% superior symptom control vs conventional DBS	[45]
	Focused ultrasound thalamotomy	Non-invasive targeting of thalamic nuclei to relieve tremor	75% symptom improvement in tremor-predominant PD patients	[46]
Non-Pharmacological - Lifestyle	High-intensity aerobic exercise	Upregulate brain-derived neurotrophic factor (BDNF)	Delays functional decline in early PD	[47]
	Social cognitive training (eg, facial expression training)	Improve social function and daily living abilities	Small studies show enhanced interpersonal responsiveness	[48,49]
Non-Motor Symptom Management	Sleep environment modification (removal of sharp objects, bed rails)	Reduce REM sleep behavior disorder (RBD)-related injuries	68% reduction in injury risk	[37]

Pharmacological Therapies: Symptom Management and Disease Modification

Current therapeutic strategies for PD primarily focus on managing symptoms while also advancing disease-modifying therapies (DMTs). Levodopa continues to be the mainstay for controlling motor symptoms; however, its long-term use is often complicated by side effects such as dyskinesias and "on-off" fluctuations. These issues can be somewhat alleviated through the use of adjunct therapies, including COMT inhibitors and MAO-B inhibitors, or by employing continuous duodenal infusion methods.[41] In addition to these established treatments, new DMTs that target the propagation of α-synuclein, such as monoclonal antibodies like prasinezumab and antisense oligonucleotides, have shown potential in early-phase trials for slowing the progression of the disease.[10,42]

Gene and Cell-Based Therapies: Precision Medicine Innovations

Gene- and cell-based therapies are transforming treatment approaches in significant ways. For instance, LRRK2 inhibitors, such as DNL151, have been shown to decrease kinase activity in individuals carrying specific mutations. Additionally, AAV2-glutamic acid decarboxylase (GAD) gene therapy works by boosting GABAergic signaling within the subthalamic nucleus, which is crucial for motor control.[43,50] Furthermore, the transplantation of dopaminergic neurons derived from stem cells, particularly those generated from induced pluripotent stem cells (iPSCs), has demonstrated the ability to restore motor function in non-human primates, and currently, Phase I/II clinical trials are in progress to evaluate their efficacy in humans.[44]

Non-Pharmacological Interventions: Neuromodulation and Lifestyle Strategies

Non-pharmacological interventions have shown promising results in managing symptoms of PD. DBS targeting the subthalamic nucleus has been found to improve motor symptoms by 60% to 70% in carefully selected patients, and advancements in adaptive closed-loop systems allow for real-time responsiveness to biomarker signals.[45] Another effective intervention is focused ultrasound thalamotomy (A noninvasive neuromodulation technique that targets thalamic nuclei with ultrasound energy to relieve tremor), which offers a 75% reduction in symptoms for patients with tremor-predominant PD, providing a non-invasive alternative to traditional surgery.[46] Additionally, engaging in high-intensity aerobic exercise has been shown to upregulate brain-derived neurotrophic factor (BDNF), which can help delay functional decline in the early stages of PD.[47]

In addition, in recent years, there has been growing recognition that social functioning and daily life capabilities are critical components of disease burden in PD, particularly as non-motor symptoms increasingly come to the forefront of clinical concern.[51–53] Social-cognitive deficits in PD often emerge early and persist throughout the disease course, limiting functional independence and social engagement. Lifestyle-based interventions incorporating targeted modules (eg, facial expression training or group social skills programs) tailored to individual capacities have shown promise in improving interpersonal responsiveness. Moreover, culturally sensitive strategies or sex- and cognition-informed emotion recognition training may offer practical pathways to restoring social connectedness in PD populations.[48,49]

Non-Motor Symptom Management

Pathological aggregates of α-synuclein progressively spread to cortical regions, particularly during Braak stages 5–6, and this spread correlates with cognitive impairment in PD. The burden of cortical α-synuclein, which can be quantified by measuring α-synuclein in cerebrospinal fluid (CSF), is linked to a 2.3-fold increased risk of dementia progression, with a significance level of $p<0.001$.[31,37] Beyond α-synuclein-mediated mechanisms, emerging evidence highlights genetic contributions to cognitive heterogeneity in PD. Specific genetic profiles, such as APOE ε4 carriage and LRRK2 G2019S mutations, have been shown to modulate cognitive trajectories: APOE ε4 carriers exhibit accelerated decline in executive function, while LRRK2 variant carriers often display relative preservation of memory, though this is modified by environmental factors like educational attainment and cardiovascular comorbidities.[54,55] These gene-environment interactions underscore the need for personalized risk stratification, as genetic markers could help identify subgroups most vulnerable to cognitive decline—strengthening the manuscript's focus on precision prognostication. This finding underscores the urgent need for therapies aimed at clearing α-synuclein in these affected regions.

In addition to pharmacological approaches, non-pharmacological interventions for RBD have shown promise in reducing injuries associated with the condition. For instance, modifying the sleep environment by removing sharp objects, installing bed rails, and using floor mats has been found to lower the risk of injury by 68%.[37] Furthermore, implementing behavioral strategies such as avoiding alcohol and caffeine after 6 PM can enhance sleep continuity, as indicated by an area under the curve (AUC) of 0.79 compared to controls.[39] Additionally, scheduled awakenings, where individuals are preemptively awakened 30 minutes before typical RBD episodes, have been shown to decrease violent behaviors by 54%.[40]

Summary

This review highlights significant changes in the management of PD, driven by advancements in our understanding of α-synuclein-related mechanisms, the validation of new biomarkers such as α-synuclein seed amplification assays and multimodal imaging, and the development of precision therapeutic strategies that include disease-modifying agents and targeted neuromodulation. Together, these advancements create opportunities for personalized care that is informed by biomarkers, shifting the focus from merely treating symptoms to actively slowing disease progression. However, translating these innovations into clinical practice presents several challenges. The high costs associated with advanced diagnostic techniques, like digital pathology and PET imaging, limit their availability; disparities in global healthcare systems lead to unequal access to precision tools; and many promising biomarkers and therapies still need extensive validation across diverse populations to ensure their effectiveness. To expedite progress, immediate action is required on two key fronts: first, research should focus on developing cost-effective diagnostic alternatives and conducting large-scale validation studies to fill existing evidence gaps; second, policymakers must foster international collaborations to standardize the use of biomarkers and improve access to affordable precision therapies. Only through these coordinated efforts can we hope to fully realize the potential of precision medicine for everyone affected by PD.

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