**Review Article**

**An Integrated Review of Parkinson’s Disease: Etiology, Differential Diagnosis, Biomarkers, Emerging Therapeutic Approaches, and Translational Models**

**ABSTRACT:**

**Aims and Objectives:** This review aims to provide a comprehensive overview of risk factors, biomarkers, pathophysiology, and synthesis of experimental models of Parkinson’s Disease (PD), with an emphasis on their mechanisms and translational models. **Materials and Methods:** A narrative review methodology was employed, involving an extensive literature search using databases such as PubMed, Scopus, and Web of Science. Peer-reviewed articles published up to 2025 were included. **Results:** Pre-clinical and clinical research has provided evidence that has enabled the decoding of Parkinson’s Disease (PD) and a breakthrough in its management/treatment. Despite the underlying mechanism not being fully understood, we now have a better interpretation of its sophisticated nature. This article highlights risk factors, some of which may be considered normal ageing but need to be addressed; diagnostic biomarkers, some of which help differentiate PD from Parkinsonism, others, less invasive, identify at-risk individuals, and neuroinflammation. This article also highlights the different pathophysiology, which also helps to emphasis the heterogeneous nature. It highlights the diverse experimental PD models because no one model fully represents PD and the research work that has been reported. This may help one to understand “the missing pieces of the puzzle”, with a note that the precision medicine framework may play a crucial role in benefiting and transforming the lives of people living with Parkinson’s Disease. **Conclusions:** There is no single model that fully recapitulates all aspects of PD. However, the strategic selection or combination of models can provide valuable insights into disease mechanisms and treatment efficacy. Future directions should focus on refining models that mimic progressive and heterogeneous disease features, integrating multi-omics approaches, and validating biomarkers for clinical translation. A precision medicine framework may ultimately transform PD management by linking experimental data to patient-specific therapeutic strategies.

**Keywords:** Parkinson’s Disease (PD), Neurotoxin models, L-DOPA, abnormal involuntary Neuroinflammation

**INTRODUCTION**

Parkinson’s Disease (PD) is a chronic, progressive neurodegenerative disorder that primarily affects motor function due to the degeneration of dopaminergic neurons in the substantia nigra pars compacta. Clinically, it manifests with hallmark motor symptoms, such as rigidity, tremors, bradykinesia, and postural instability, as well as non-motor features, including cognitive decline, sleep disturbances, autonomic dysfunction, and mood disorders. These symptoms significantly impair quality of life and functional independence. Globally, PD represents a growing public health concern. It is the second most common neurodegenerative disease after Alzheimer’s and the fastest-rising neurological condition in terms of mortality, disability, and prevalence. As of 2021, over 11 million individuals were affected worldwide, a number expected to surpass 25 million by 2050 due to ageing populations and improved diagnostic capacity. The disease places a substantial burden on individuals, families, and healthcare systems, with increasing demands for long-term care, rehabilitation, and medical support services (Su *et al.,* 2025). The rising incidence and societal impact of PD highlight the urgent need for early diagnostic tools, effective disease-modifying therapies, and comprehensive care models. Current treatments primarily offer symptomatic relief, with no proven cure or intervention to halt disease progression. Consequently, PD remains a leading cause of disability among older adults, contributing significantly to years lived with disability (YLDs) and healthcare expenditures. Addressing this growing health challenge requires integrated approaches combining research, clinical innovation, public health planning, and equitable access to care globally (Dorsey *et al.,* 2018).

### ****Global Prevalence and Future Projections of Parkinson’s Disease****

As of **2021,** around **11.8 million** people globally live with PD, with an **age-standardized prevalence of 138.6 per 100,000.** This marks a dramatic increase of **155–281%** since 1990. Forecasts predict the number will rise to **25.2 million by 2050,** a **112% increase**, primarily due to **aging populations (89%)** and **population growth (20%).** Age-standardized prevalence is also expected to grow by **55%,** reaching approximately **216 per 100,000 (GBD 2019, Feigin *et al.,* 2020, Rocca 2018 &** Su *et al.,* 2025**) (Refer to fig. 1 and 2)**.

* **East Asia** leads with the highest number of cases (~2.94 million in 2019); **Oceania** has the lowest (~6,360 cases).
* Largest projected increase by 2050:
	+ **Western Sub-Saharan Africa** (+292%)
	+ **Central & Eastern Europe** (+28%)
* **Men** and individuals **aged 80+** show steeper prevalence rises, with the male-to-female ratio expected to grow from **1.46 to 1.64 (Prongsheim *et al.,* 2014 & Bloem *et al.,* 2021).**

PD is currently the fastest-growing neurological disorder worldwide, with its prevalence projected to double by 2050 due to population aging and demographic shifts. Despite extensive research, the precise mechanisms underlying PD remain incompletely understood, and current treatments are offering limited disease-modifying potential (Marras *et al.,* 2018). This review is therefore timely and necessary, aiming to provide a comprehensive synthesis of key advances in the field. The objectives are to examine global trends in PD epidemiology and burden; to critically evaluate experimental models, including pharmacological, genetic, and combined approaches, with respect to their mechanisms, translational relevance, and application in therapy development; and to explore emerging pathogenic pathways such as neuroinflammation, gene-environment interactions, and gut-brain axis dysregulation. Additionally, the review highlights progress in biomarker identification for early diagnosis and disease progression monitoring while addressing key research gaps and future directions. These include the need for standardized biomarker validation, the integration of multi-omics data, and the development of personalized, precision-medicine-based therapeutic strategies to address the growing global challenge of PD.

**Etiology and Risk Factors (Genetic, Environment and Lifestyle and protective factors)**

The risk factors in PD are now considered manifold, and the importance of defining these factors that contribute to neurodegeneration in PD is that they provide the opportunity to develop neuroprotective therapy that interferes with neurodegeneration as a result of varying causes and hence are of value to larger PD patient populations. Some that have been attributed to otherwise healthy individuals and increase the risk of incidence of PD include constipation, hyposmia, depression, and idiopathic REM sleep disorder. In elderly populations, subtle motor disturbances that precede the full motor syndrome of PD likely serve as a risk, though this may not suffice as a formal diagnosis of parkinsonism. The above factors are based on multiple population-based and other cohort studies (Braak *et al.,* 2000). The gut has a large genomic content and metabolic complement; hence, the GI microbiota has a beneficial role as a regulator of many physiological processes, including the activity of the neurotransmitter system and immune response. This may modulate neuroinflammation and the HPA axis via intervention in recruiting local immune regulators from the periphery to the brain (Rea *et al.,* 2016). Dysbiosis, an imbalance in the gut microbial community associated with disease concerning PD, has become an intense area of research (Chen *et al.,* 2019). This imbalance could be due to the gain or loss of community members or changes in the relative abundance of microbes. The “gut-brain axis” theory, though unproven (Lionnet *et al.,* 2018), may also link dysfunction of the gut as a risk in PD. It proposes that synuclein (syn) accumulates initially in the Enteric Nervous System (ENS) and then spreads to the brain via the vagus nerve (Holmqvist *et al.,* 2014 & Ulusoy *et al.,* 2013). Calorie restriction (CR), which activates sirtuins (induces neuroprotection in epilepsy disorder, AD, PD, and stroke diseases) (Srivastava *et al.,* 2011), has been linked to reducing the incidence of several neurodegenerative disorders without incurring malnutrition. Sirtuin protein upregulation optimizes metabolism, which reduces neuronal loss in the brain, rescues blood flow, maintains cellular metabolism, inhibits inflammatory pathways, and stimulates antioxidant activity. However, it was reported by de Carvalho et al. in 2019 that sirtuin is not activated exclusively by caloric restriction but also by dietary restriction (DR), which is a moderate reduction of protein intake. There is also evidence that diet-induced obesity in humans predisposes to PD (Hu *et al.,* 2006), albeit controversial. With an unclear mechanism, it may be mediated by a GI hormone known as ghrelin, secreted from the stomach during CR to alert the brain to changes in metabolic status and promote refeeding. Studies have shown that diet-induced obesity increases the loss of dopaminergic cells in murine models of PD (Choi *et al.,* 2005).

**Risk Factors Associated with PD**(George *et al.,* 2015**)**

* Environmental toxins – Carbon disulphide, Cyanide, Methanol, Organic Solvents, Herbicides, and Pesticides.
* Head Trauma
* Increased BMI
* Activation of Microglia
* Methcathinone (Magnesium Content)
* Hypovitaminosis D
* Methamphetamine/ Amphetamine Abuse
* Post Infection States
* Apoptosis (signal-mediated)
* Generation of Reactive Oxygen Species (ROS)
* High Cholesterol
* Consumption of well water
* Mitochondrial Dysfunction
* Dysbiosis
* Increased serum or CSF expressions of Cytokines
* Comorbidities- Type 2 Diabetes
* Neuroinflammatory processes (Hirsch *et al.,*  2009)
* Liver Cytochrome P450 malfunction (Wang *et al.,* 2015)
* Those at High Risk based on Radiotracer Techniques: resulting in high sensitivity with the presence of two or more factors like PD patient relatives, family history of PD caused by unknown mutations or asymptomatic gene mutation carriers, and individual premotor symptoms such as Rem Sleep Behavior Disorder (RBD) or hyposmia (Pankaj *et al.,* 2012).

**Pathophysiological Mechanisms**

PD pathogenesis is complex, with multiple mechanisms coming to light thanks to translational scientists who have deciphered the disease. Dopaminergic degeneration is not the only cause limited to PD-related neurodegeneration as the pathology begins in the brain stem and then progresses beyond the substantia nigra (SN) to cortical and subcortical regions (Siferwf *et al.,*  2005) with depigmentation of SNpc occurring due to loss of melanin contained in nigrostriatal dopaminergic neurons upon neuronal loss (Braak *et al.,*  2003). There is also impaired dopamine release in the striatum, and classification based on phenotypic patterns of the disease for different patients may be helpful in the prediction of disease progression. For example, a comparison between tremor-dominant PD and PD with predominant Postural Instability and Gait Disturbance showed that the former was associated with slower disease progression (Lees 2012 & Foltynie *et al.,* 2002). Multiple mechanisms of PD development are supported because genetically, only < 10% of PD cases have a monogenic origin with known causal mutations affecting 15 genes, explaining only 30% monogenic (with variable penetrance, expressions and very long pre-symptomatic phases) and 3-5% sporadic cases (Espay *et al.,*  2020) and the pathways that cause non-dopamine degeneration are linked to dopaminergic degeneration with support from non-dopamine, non-motor features in genetic forms of PD which are characterized by routine motor symptoms of PD. Protein aggregation and misfolding may be referred to as the “chief instigating” process in Neurodegenerative Disorders (ND) like PD, where it leads to the formation of the primary aggregating protein known as alpha syn and amyloid-like fibrils, with evidence supporting its role in PD pathogenesis through prion-like propagation with cell to cell transmission and also induction of morphological changes which has shown to trigger mitochondrial fission (either directly or indirectly by recruiting dynamin-related protein 1, i.e., DRP 1) and prevent fusion as evidenced in cell models of PD, AD and Huntington’s Disease (HD) (Talene *et al.,* 2009, Alwena *et al.,* 2018 & Daniele *et al.,* 2020).

The crucial role of mitochondria in PD pathogenesis was first indicated by the defects of the mitochondrial respiratory chain (Schapira *et al.,*  1990 & Benner *et al.,* 2008), and other studies indicate mitochondrial defects are involved in PD pathogenesis with its damage-enhancing oxidative stress, which later on induces mitochondrial dysfunction (Schapira *et al.,*  1989 & Schapira 1994). Supporting evidence of mitochondrial dysfunction was seen in drug abusers accidentally exposed to MPTP, with later identification of genetic mutations emphasizing the role of mitochondria in sporadic PD. The effectiveness and quality of cell mitochondria are maintained by fission- the fusion process, whose rate changes in response to different energy demands of the cell (Langston *et al.,* 1983 & Chan *et al.,* 2006). If the process is impaired, morphological changes (generally fragmented, swollen, and rounded) occur, which is evident in PD. The fission process (which creates new mitochondria but also removes damaged mitochondria and facilitates apoptosis during high cellular stress levels), in cell models (Chen *et al.,* 2010), may increase the fusion process (which allows functional mitochondria to complement a dysfunctional one and sharing of components between organelles) is prevented by mutated alpha syn hence the mitochondria become prone to damage by oxidative stress and neurotoxins (Guardia *et al.,* 2014).

**Secondary Causes of Parkinsonism**

Parkinsonism refer to conditions that mimic PD but have distinct underlying causes. Drug-induced parkinsonism is one of the most common, often resulting from medications such as antipsychotics, calcium channel blockers, and antiemetics that interfere with dopamine signaling. Vascular parkinsonism arises from cerebrovascular disease, typically affecting the lower body and gait. Normal pressure hydrocephalus presents with a triad of symptoms; urinary incontinence, gait disturbance, and cognitive decline, often reversible with shunting. Exposure to toxins and certain infections can also lead to parkinsonian symptoms by damaging the basal ganglia. Additionally, autoimmune disorders and metabolic conditions such as Wilson’s disease or hypothyroidism can contribute to secondary parkinsonism, necessitating careful evaluation for appropriate management. Table 1 identifies the secondary causes of PD, which may not respond to L-Dopa depending on the response intensity and duration for the different causes and are not due to neurodegeneration (Pellicano *et al.,* 2007).

**Differential Diagnosis of Parkinson’s Disease**

Parkinson-plus syndromes are a group of neurodegenerative disorders that share clinical features with Parkinson’s disease but have additional distinguishing characteristics and typically respond poorly to levodopa therapy. These include MSA, characterized by prominent autonomic dysfunction; PSP, marked by early postural instability and vertical gaze palsy; CBD, which presents with asymmetric rigidity and cortical signs; and DLB, where cognitive decline and visual hallucinations appear early (Refer to Table 2).

**Diagnostic Challenges in Early-Onset Parkinsonism**

The Diagnosis and Progression of PD includes the use of biomarkers that are not necessarily limited to dopaminergic tracers, as a study reported that the most disabling features of advanced PD do not have a significant dopaminergic basis. However, the reduction in uptake of all markers of DA activity has been highly associated with PD. Other reports, either interventional or observational studies and involved testing for DA metabolites, amino acids, and various forms of alpha syn in blood and CSF fluid and also the possibility of using microRNA (mRNA) analysis, have listed specific biomarkers for PD in ClinicalTrials.gov. Biomarkers or Biological markers, whether “wet” or “dry,” are identified as indicators of normal biological processes, pathogenic processes, or pharmacologic responses to therapeutic intervention, which comprise objectively measured and evaluated characteristics. Biomarkers may serve as pragmatic clinical indicators confirming diseases with wet biomarkers focusing on disease-specific biofluid profiles like spinal fluid, serum, or tissue-based indicators and dry biomarkers referring to non-invasive procedures like electrophysiological and neuroimaging measures. Biomarkers also play a diagnostic role in the prodromal phase of the disease as it enables neuroprotective approaches to be tested in sporadic cases of PD because of difficulties arising in performing clinical trials in familial PD. Biomarkers may also reflect both the underlying severity of the disease and its response to therapeutic intervention more efficiently, especially in clinical trials, compared to rating scales such as the UPDRS, which is used to measure the quality of life, which has been reported to be subjective, has low interrater consistency, is susceptible to placebo effect and reflects non-equivalent difference between subjective points hence is non-linear (Lee *et al.,*  2021). Another role of biomarkers is that they help to stratify and select patient populations more likely to benefit from specific treatments to speed up their development, especially for novel chemical entities, as New Drug Development (NDD) is a long, expensive, and challenging process, overcome regulatory hurdles by prioritizing the development of repurposed drugs because the drugs already in the market for other therapeutic indications have known safety human profiles and ultimately change the lives of patients and their caregivers. Ideally, an in vivo biomarker should exclusively reflect the progression of the disease and the uptake of the imaging tracer used should not be affected by age, disease related compensatory mechanisms or pharmacological treatments yet realistically this may not be the case and Table 3 represents the types of biomarkers available with main classification including neuroimaging, which measures the function of specific neuronal population known to degenerate in PD and has been reported to provide a valuable adjunct to clinical measures especially in assessment of neuroprotective agents and provides an objective measure that changes (approximately 10% per year in PD as compared to 1% in control subjects) with disease progression, albeit dispute that there is a possibility of drugs having a regulatory action on the imaging measure (McFarthing *et al.,* 2020, Koller *et al.,* 2004 & Miranda *et al.,* 2012), and another classification being Biochemical and molecular biomarkers which have made it possible to differentiate PD from other ND disorders such as AD and MSA from healthy controls as they are detected and quantified by highly sensitive assays (refer to Table 4).

**Biomarkers in Parkinson’s Disease**

CSF biomarkers such as α-synuclein, tau proteins, and neurofilament light chain reflect underlying neurodegenerative processes and help differentiate PD from other parkinsonian syndromes. Blood-based biomarkers, including inflammatory cytokines and metabolic markers, offer a less invasive alternative and provide insights into systemic involvement in PD pathophysiology. Genetic and epigenetic markers, such as mutations in SNCA, LRRK2, and epigenetic modifications, aid in identifying at-risk individuals and understanding disease mechanisms. Neuroimaging biomarkers, including DAT-SPECT and PET scans targeting neuroinflammation or synaptic density, enhance diagnostic accuracy and allow tracking of disease progression at the molecular and functional levels (Refer to Table 5).

**FDA-Approved Drugs for Treating Parkinson’s Disease**

To reduce “OFF episodes” from long-term L-Dopa use, FDA-approved options include inhaled L-Dopa (Inbrija), Opicapone (Ogentys), and sublingual Apomorphine (Kynmobi). In early-onset PD, continuous drug delivery (e.g., P2B001, *Mucuna pruriens*, apomorphine pumps) helps preserve motor function and reduce dyskinesia. Advanced PD treatments involve cholinesterase inhibitors like Rivastigmine and Atomoxetine for cognitive decline. Sleep and mood disorders are managed using CBT, light therapy, or rTMS. Non-pharmacologic approaches like speech therapy for dysphagia and cognitive lifestyle enhancement also play key roles (refer to table 6).

**New Therapeutic Mechanisms in Drug Development**

Gene therapy is being explored to enhance dopamine synthesis or promote neuroprotection through vectors delivering genes such as GAD or GBA1. Neurotrophic factors like GDNF and BDNF aim to support the survival and function of dopaminergic neurons. Therapies targeting alpha-synuclein, either by preventing its aggregation or enhancing its clearance using immunotherapies or antisense oligonucleotides are also gaining prominence. Mitochondrial-targeting agents such as ursodeoxycholic acid (UDCA) and coenzyme Q10 are being studied for their ability to improve mitochondrial function and reduce oxidative stress. Similarly, autophagy enhancers like ambroxol and rapamycin aim to boost the clearance of misfolded proteins. Anti-inflammatory strategies are being developed to counteract neuroinflammation, including the use of NSAIDs, NLRP3 inflammasome inhibitors, and microglial modulators. Calcium channel blockers like isradipine are being tested for their role in modulating neuronal calcium influx, while iron chelators such as deferiprone aim to reduce iron-induced oxidative damage. Finally, regenerative approaches such as dopaminergic cell replacement using stem cell-derived neurons, and neuroimmunophilin ligands that support neuronal survival, represent promising directions for disease-modifying therapy (refer to table 7).

**Preclinical and Clinical Studies in Parkinson’s Disease**

The basis for using animal models for PD for investigating symptomatic treatment occurred after Carlsson *et al.,* 1957, discovered that administration of Reserpine or Haloperidol to rodents and rabbits led to transient parkinsonian-like state symptoms, which the administration of L-Dopa later on reversed. This opened up a new era in pre-clinical studies (Biglan *et al.,* 2007). For a better understanding of any disease process, including etiology and pathophysiology, experimental models are required to replicate the disease, bearing in mind the vast diversity in pathophysiology and prognosis in different diseases, which requires customization and specification to be established accordingly in animal modelling (Khan *et al.,* 2023). Animal models for neurodegeneration can be validated by demonstrating that they show similarities in the progressive nature of the disease and the defining pathological feature, for example, with motor parameters like Bradykinesia and non-motor parameters referring to centrophobism-like behaviour, e.g., anxiety and depression determined in the assay for locomotor activity. On the other hand, animal models for testing neuroprotective agents in PD should provide a time window for drug application and prompt reproducible nigral lesions with stable loss of DA neurons without spontaneous recovery (Pavese *et al.,* 2009). Animal models also require diversification because no one animal model for PD mimics the full pathology and clinical symptomatology of the illness due to complex PD etiology with interindividual variations in environmental and genetic risk factors reflecting the heterogeneity of PD, which is observed in both idiopathic and monogenic cases. Diversification and different PD induction forms essentially play a role in deciding what type of outcomes are expected, which modulates the pathology closely and is relevant in the investigation. Apart from diversification, there is a need for experimental models to deepen the understanding of PD as a multi-faceted disease, expand treatment options, and explore and discover potential therapy, as it is challenging to evaluate disease-modifying medications because very few animal models mimic the features of neuronal GSH content and chronic oxidative stress and age-related progression. The ideal PD model should show a high measure of Firstly, Face Validity, with features like noticeable biochemistry and neuropathology-related techniques, i.e., birth stage presence of a complement of dopaminergic neurons with adulthood progression of specific and gradual depletion of DA neurons (>50% of the total amount in nigrostriatal tract) with the accompanying altered downstream chemistry and Lewy Body deposition and similar symptoms such as the expected behavioural phenotypes like akinesia and rigidity. Secondly, Construct Validity, which is identical pathogenesis to the disease like neuroinflammation, Complex I inhibition, underlying oxidative stress or Proteasome inhibition, and Lastly, Predictive Validity, which is the ability to positively identify agents that are clinically effective since the closer the similarity of the model is to PD, the higher the predictive value for clinical trials and suffice to say for success in demonstrating neuroprotection in humans, confirmation is assured through the predictive power of animal models. Model systems, which represent specific PD attributes like electrical activity, changes in behaviour, and changes at the cellular or molecular levels, serve as a contributing factor to limitations of existing PD model pathology as they develop the disease pathology transiently for study purposes, unlike the duration of actual PD development in humans. The facilitation of species-specific differences should be understood to better interpret behavioural observation and pathophysiology in experimental designs. Table 8 summarizes the species-specific characteristics of the three animals commonly used in modeling human disease, including PD, i.e., rodents, non-human primates (NHPs), and non-mammalian species (NMS).

**Animal Models in Parkinson’s Disease**

The 6-hydroxydopamine (6-OHDA) model is widely used in rodents and produces selective dopaminergic neuron loss, making it ideal for motor dysfunction studies, though it lacks progressive α-synuclein pathology. The MPTP model, used in mice and non-human primates, induces dopaminergic degeneration and motor symptoms, closely mimicking several PD features but without Lewy body formation. The rotenone model replicates mitochondrial dysfunction and α-synuclein aggregation and offers progressive neurodegeneration, although it is highly toxic and shows variability. Paraquat induces oxidative stress and some dopaminergic loss, but results are inconsistent and often lack α-synuclein pathology. Combined treatment enhances dopaminergic toxicity and mimics environmental exposure, though outcomes depend on dose and timing. The reserpine model depletes central monoamines and causes reversible PD-like symptoms without neuron loss, making it suitable for screening anti-parkinsonian drugs. Haloperidol induces parkinsonian symptoms via dopamine D2 receptor blockade and is used to model drug-induced parkinsonism rather than idiopathic PD (refer to table 9 & 10).

**Comparative Overview of Pharmacological/Neurotoxin Models of Parkinson’s Disease**

Neuromelanin to activate microglia and trigger inflammation, leading to dopaminergic neuron loss. Used in rodents, these models replicate PD-related inflammation but lack full disease features and widespread pathology. Genetic Models involve mutations or deletions in PD-related genes (e.g., SNCA, LRRK2, PINK1, DJ-1). They model α-syn aggregation, mitochondrial dysfunction, or oxidative stress. Useful for studying familial PD, but often lack complete PD pathology or motor symptoms. AIMs Models in rats simulate L-DOPA-induced dyskinesia. They assess abnormal involuntary movements to test anti-dyskinetic drugs. While validated, they focus on motor symptoms and not broader PD features. Combined Models pair genetic mutations with neurotoxins like MPTP to better mimic PD’s complexity. They show enhanced neurodegeneration and are valuable for studying gene–environment interactions, though technically demanding (refer to table 10).

**Future Directions and Gaps in Research**

Advancing precision medicine in PD holds significant potential to revolutionize patient care. Current therapies are largely symptomatic and "one-size-fits-all", but precision approaches aim to customize treatment based on individual genetic, molecular, and clinical profiles. This shift requires a better understanding of patient subtypes, including early-onset vs. late-onset PD and familial vs. sporadic forms. A major future direction is the integration of multi-omics data, genomics, transcriptomics, proteomics, metabolomics, and epigenomics, which can provide a comprehensive understanding of PD pathogenesis. Combining these data layers can uncover new pathogenic mechanisms, reveal novel therapeutic targets, and improve patient stratification in clinical trials. However, a key challenge remains in harmonizing and interpreting such complex datasets across diverse populations and platforms. Another significant gap lies in biomarker standardization and validation. Despite extensive research, very few biomarkers for PD have been validated for clinical use. This includes molecular biomarkers (e.g., α-synuclein, DJ-1 in CSF), neuroimaging markers (e.g., DAT-SPECT, PET), and physiological indicators (e.g., wearable sensor-based gait and tremor patterns). Standardizing sample collection, assay techniques, and analytical methods across centers is critical to ensure reproducibility and clinical applicability. Finally, the development of personalized therapeutics is still in its infancy. There is a need to design and test targeted treatments based on an individual’s genetic makeup, molecular signatures, and disease progression rate. This includes gene therapy (e.g., for SNCA and LRRK2 mutations), neuroprotective strategies, and repurposed drugs identified via patient-derived iPSC models and high-throughput screening platforms. Such personalized approaches require well-characterized cohorts, advanced computational modelling, and robust regulatory frameworks to move from bench to bedside effectively.

**CONCLUSION**

In conclusion, Pre-clinical and clinical research has significantly advanced our understanding of Parkinson’s Disease (PD), although its underlying mechanisms remain partially unclear. Key areas such as risk factors, diagnostic biomarkers, and neuroinflammation contribute to early detection and differentiation from other Parkinsonian disorders. The heterogeneous nature of PD is reflected in its complex pathophysiology and diverse clinical manifestations. While no single experimental model can replicate all aspects of the disease, the strategic use of neurotoxin, genetic, and inflammogen-based models offers valuable insights. Future research should focus on refining these models, integrating multi-omics approaches, and validating reliable biomarkers. Ultimately, the adoption of a precision medicine framework may revolutionize PD management by enabling personalized, targeted therapeutic strategies.

**ABBREVIATIONS**

**PD** – Parkinson’s Disease, **EOPD** – Early-Onset Parkinson’s Disease, **DA** – Dopaminergic, **SNpc** – Substantia Nigra pars compacta, **L-Dopa** – Levodopa, **FDA** – Food and Drug Administration, **COMT** – Catechol-O-Methyl Transferase, **SC** – Subcutaneous, **CBT** – Cognitive Behavioral Therapy, **CBT-I** – Cognitive Behavioral Therapy for Insomnia, **rTMS** – Repetitive Transcranial Magnetic Stimulation, **DLPFC** – Dorsolateral Prefrontal Cortex, **NE** – Norepinephrine, **ROS** – Reactive Oxygen Species, **IL-1β** – Interleukin-1 beta, **TNF-α** – Tumor Necrosis Factor-alpha, **LPS** – Lipopolysaccharide, **ATP** – Adenosine Triphosphate, **GFAP** – Glial Fibrillary Acidic Protein, **GDNF** – Glial Cell Line-Derived Neurotrophic Factor, **MPO** – Myeloperoxidase, **6-OHDA** – 6-Hydroxydopamine, **MPTP** – 1-Methyl-4-phenyl-1,2,3,6-tetrahydropyridine, **Th1 / Th17** – T-helper Cell Type 1 / Type 17, **CSF** – Cerebrospinal Fluid

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Fig. 1 Global burden of Disease



Fig. 2: Global prevalence of PD

Table 1: Secondary Causes of Parkinsonism

|  |  |  |  |  |
| --- | --- | --- | --- | --- |
| **S. No** | **Cause** | **Mechanism / Pathology** | **Clinical Features** | **Treatment / Management** |
| 1 | Normal Pressure Hydrocephalus (NPH) (Recette *et al.,*  2004) | - Mechanical disruption of basal ganglia- Ventricular enlargement from CSF resistance- Histopathology: tau-positive neurons, tufted astrocytes, sometimes Lewy bodies | - Urinary incontinence- Ataxia- Dementia- Parkinsonian features | - Shunt surgery to restore CSF flow and reduce pressure |
| 2 | Vascular Parkinsonism (VP) (Starr *et al.,*  2014) | - Subcortical infarcts- Bilateral white matter ischemia- Disruption of thalamocortical and basal ganglia pathways | - Lower body parkinsonism- Gait disturbance- Poor L-Dopa response | - L-Dopa- Antiplatelets (e.g., Aspirin, Clopidogrel) |
| 3 | Drug-Induced Parkinsonism (DIP) (Hayes 2019 & Avorn *et al.,*  1995) | - Postsynaptic D2 dopamine receptor blockade- May mimic PD but is symmetrical- No Lewy bodies in SNpc | - Bradykinesia- Rigidity- Masked face- Tremor | - Discontinue offending drug- Switch to safer antipsychotics (e.g., Clozapine)- Benztropine, Trihexyphenidyl- Amantadine, ECT in refractory cases |
| 4 | Toxin-Induced Parkinsonism (TIP) (Bondon *et al.,*  2011 & Racette *et al.,*  2014) | - Manganese toxicity affecting globus pallidus and SNpr- Iron accumulation disrupting SNpc homeostasis | - Cogwheel rigidity- Bradykinesia- Behavioral changes (early), dyskinesia (late) | - Avoid exposure- L-Dopa partially effective- Supportive care |
| 5 | Chronic Traumatic Encephalopathy (CTE) (Kwakye *et al.,*  2015) | - Repeated trauma → neuronal loss, diffuse axonal injury, plaques | - Parkinsonian signs- Mood/behavioral changes- Common in boxers, rugby players | - Supportive care- Prevention via protective sports protocols |
| 6 | Brain Tumors(Shrimanker *et al.,*  2023 & Adhiyaman *et al.,*  2003) | - Compression or infiltration of basal ganglia/SNpc- Edema decreasing perfusion | - Parkinsonism with resting tremor- Associated with supratentorial tumors (e.g., meningioma) | - Surgical excision of tumor- Symptom resolution post-op |
| 7 | Juvenile Parkinsonism (JP) (Krauss *et al.,*  1995) | - Mutations in PARKIN, PINK1, PARK7- Autosomal recessive- Strong family history | - Onset <21 years- Bradykinesia- Rigidity- Male predominance (4:1) | - Genetic counseling- L-Dopa for symptom relief |

Table 2: Differential Diagnosis of Parkinson's Disease

|  |  |  |  |
| --- | --- | --- | --- |
| No. | **Condition** | **Key Features / Distinguishing Criteria** | **Notes** |
| 1 | Lewy Body Disease (LBD) (Starr *et al.,*  2014 & Kwakye *et al.,*  2015) | Parkinsonism + cognitive fluctuations, visual hallucinations, REM sleep disorder | Lewy bodies in striatum and cortical neurons; highly sensitive to neuroleptics |
| 2 | Multiple System Atrophy (MSA) (Kwakye *et al.,*  2015 | Autonomic dysfunction, cerebellar ataxia, early postural instability | Poor levodopa response; features extrapyramidal, cerebellar, and autonomic signs |
| 3 | Progressive Supranuclear Palsy (PSP) | Vertical gaze palsy (especially downward), early falls, axial rigidity | Tauopathy; poor levodopa response; neurofibrillary tangles and mitochondrial dysfunction |
| 4 | Corticobasal Degeneration (CBD) | Asymmetric rigidity, apraxia, myoclonus, alien limb phenomenon | Cortical atrophy, tau pathology; poor dopaminergic response |
| 5 | Benign Essential Tremor  | Action/intention tremor, head involvement | No rigidity or bradykinesia; improved with alcohol |
| 6 | Alzheimer’s Disease (Thomsen *et al.,*  2010) | Dementia dominates; parkinsonism may co-exist | Overlapping oxidative stress pathology with PD |
| 7 | Progressive Pallidal Atrophy | Chorea, dystonia, myoclonus, seizures | Rare; affects globus pallidus |
| 8 | Shy-Drager Syndrome (MSA variant) | Parkinsonism + severe autonomic dysfunction | Syncope, incontinence, cardiac arrhythmia |
| 9 | Basal Ganglia Tremor (BGT) (Perl *et al.,* 1998 & Helmich *et al.,* 2012) | Tremor post-stroke; variable frequencies | Often postural/kinetic; linked to thalamic or basal ganglia lesions |
| 10 | Olfactory Dysfunction | Often absent in MSA, PSP, CBD | Useful diagnostic tool; correlates with locus coeruleus, nucleus basalis degeneration |
| 11 | Creutzfeldt-Jakob Disease (CJD) (Park 2016) | Rapidly progressive dementia, myoclonus | Prion disease; fatal within 1 year |
| 12 | Subdural Hematoma (Sitammagari *et al.,* 2024) | Sudden onset Parkinsonism post head injury | Resolves post hematoma evacuation |
| 13 | Post-Traumatic Brain Injury PD | Parkinsonism years after TBI | Risk ratio ~1.48; linked to neurodegeneration |
| 14 | Metabolic Disorders | Hypoparathyroidism, thyroid issues, nutritional deficiencies | Reversible with correction |
| 15 | Olivopontocerebellar Atrophy (OPCA) (Balabandian *et al.,* 2023) | Parkinsonism + postural instability, reflex myoclonus | Difficult to differentiate from PD; shows triad of PD but with severe imbalance |
| 16 | Wilson’s Disease | Copper accumulation; hepatic, neurological signs | Young onset; treatable with chelation |
| 17 | SWEDD (Scans Without Evidence of DA Deficit) (Rodriguez *et al.,* 1994) | PD-like symptoms but no dopaminergic deficit on imaging | Includes misdiagnosed cases: essential tremor, psychogenic illness, ataxias, etc. |

Table 3: Emerging Biomarkers for Early Diagnosis and Progression

|  |  |  |  |  |
| --- | --- | --- | --- | --- |
| **Type** | **Technique/Marker** | **Purpose** | **Key Advantages** | **Limitations (esp. in EOPD)** |
| Pre-synaptic Imaging | FD PET (6-[¹⁸F]-fluoro-L-dopa) | Assesses DA synthesis via AADC activity | Correlates with disease severity; widely studied | May underestimate denervation; compensatory AADC upregulation in EOPD |
| FMT PET (6-[¹⁸F]-fluoro-m-tyrosine) | Similar to FD; not affected by COMT | Less metabolism interference | Less available; does not assess DA turnover |
| DAT Imaging (SPECT/PET) | Measures DA transporter density (DAT) | Early PD sensitivity; correlates with clinical severity | Downregulated in EOPD; affected by age & medications |
| DTBZ PET ([¹¹C]-Dihydrotetrabenazine) | Measures VMAT2 density (monoamine vesicular transport) | Stable against pharmacologic change; reflects DA terminal density | May be influenced by DA vesicular/cytosolic balance |
| Post-synaptic Imaging | D2/D3 Receptor Ligands (e.g., RAC, IBZM, FLB-457) | Assesses striatal and extrastriatal DA receptor binding | Reflects synaptic DA changes; indicates receptor regulation | Binding influenced by endogenous DA, disease stage, and therapy |
| D1 Receptor Ligands ([¹¹C]-SCH23390) | Evaluates D1 receptor integrity | Useful in differentiating PD from atypical parkinsonism (e.g., MSA) | May be normal in early PD |
| Neuroinflammation Marker | [¹¹C]-PK11195 PET | Detects activated microglia (neuroinflammation) | In vivo evidence of inflammation in PD brain regions | Low resolution; limited use in progression tracking |

Table 4: Functional and Structural Neuroimaging

|  |  |  |  |
| --- | --- | --- | --- |
| **Technique** | **Marker/Feature** | **Purpose** | **Remarks** |
| MRI (Iron-sensitive) | Swallow-tail sign (Nigrosome 1), QSM, R2\*, SWI | Early PD detection | Loss of dorsolateral nigral hyperintensity; ↑ Nigral iron in PD |
| DTI | Fractional Anisotropy (FA) | Microstructural changes | ↓ FA in SN in EOPD; correlates with motor symptoms (UPDRS) |
| Multimodal MRI (3T) | FA, R2\*, Mean diffusivity (MD), T1, T2\* | Combined structural-functional imaging | FA↓ & R2\*↑ in SN, thalamus; 95% accuracy for PD vs controls |
| Transcranial Ultrasound | Midbrain echogenicity | Iron deposition detection | Hyperechogenicity present in PD; not useful for progression tracking |

Table 5: Biochemical and Molecular Biomarkers

|  |  |  |  |
| --- | --- | --- | --- |
| Marker | Sample | Finding in PD | Remarks |
| α-Synuclein (Lee *et al.,* 2021, Lohle *et al.,* 2010, Salamon *et al.,* 2019 & Imberdis *et al.,* 2019) | CSF, plasma | ↓ in CSF, ↑ oligomers in plasma | Oligomer/total α-syn ratio: 85–90% specificity for PD |
| DJ-1 | CSF | ↓ in CSF | Helps distinguish EOPD from controls; not reliable for progression |
| Aβ42 | CSF | ↓ especially in PD with cognitive decline | Shared marker with AD; ↓ levels linked to dementia |
| Total Tau | CSF | ↓ or variable | Elevated in AD; low in PD |
| EGF | Plasma | ↓ levels | Predicts cognitive decline risk |
| Tyrosine Hydroxylase (TH) | Tissue | Inhibited by α-syn → ↓ DA synthesis | Marker of dopaminergic neuron loss in models |
| Oxidative Stress Markers |
| Uric Acid | Plasma, CSF | ↓ levels | Higher levels = slower progression; identified by HPLC/EC array |
| 8-OHdG, MDA, CoQ10 | Blood, urine | ↑ in PD | Assayed via ELISA; also influenced by aging/lifestyle |
| Inflammatory Markers |
| IL-6, IL-10, IL-12 | Blood/CSF | ↑ cytokine levels | Reflects chronic neuroinflammation in PD |
| Omics-Based Biomarkers |
| Transcriptomics | Microarray, qRT-PCR | 4-gene panel (e.g., ALDH1A1, PSMA2) | Sensitivity & specificity > 80% for PD |
| Proteomics | MALDI-TOF MS, 2D Electrophoresis | 5-protein panels from serum | 85% sensitivity, 70% specificity |
| Metabolomics | Mass Spec, HPLC | Metabolic fingerprint of PD | Separates PD (incl. LRRK2 subtype) from controls |
| Genomics | GWAS, gene panels | Early PD gene expression changes | Distinguishes idiopathic vs genetic PD |

Table 6: The **new and emerging treatment strategies in PD**

|  |  |  |
| --- | --- | --- |
| **Category** | **Aim / Description** | **Examples / Strategies** |
| **Drugs for “OFF Episodes” (Lee *et al.,* 2021)** | Improve symptom control during periods when L-Dopa is less effective. | Inbrija (inhaled L-Dopa), Opicapone (Ogentys), Kynmobi (sublingual Apomorphine), CVT-301, Camicinal, Safinamide |
| **Targeting Motor Symptoms in EOPD** | Use alternatives or continuous delivery to minimize dyskinesia. | P2B001 (Rasagiline + Pramipexole), Mucuna pruriens, Melatonin, continuous delivery of Apomorphine, Ropinirole, Rotigotine, L-Dopa + Entacapone |
| **Drugs for Advanced PD** | Address symptoms unresponsive to L-Dopa. | Rivastigmine (for gait, balance, speech deficits) |
| **Cognitive Impairment Treatment** | Enhance norepinephrine signaling and cognitive reserve. | Atomoxetine, cognitive reserve assessment (education, occupation, activities) |
| **Dysphagia Treatment** | Non-invasive support for swallowing. | High-effort speech and respiratory exercises |
| **Sleep Disturbances Treatment** | Improve sleep quality through pharmacologic and behavioural approaches. | CBT-I, light therapy, Quetiapine, benzodiazepines (short-term use) |
| **Mood Disorders Treatment** | Improve mood and motor symptoms using neuromodulation. | rTMS to motor cortex and DLPFC |
| **Surgical Approaches** | Treat motor and non-motor symptoms in advanced PD. | DBS (STN, GPi), VIM-DBS, Focused Ultrasound (FUS), LCIG, Apomorphine SC infusion |
| **Exercise Therapy** | Non-pharmacological intervention to improve QoL and reduce hospitalizations. | Treadmill, dance, self-directed community exercise, inpatient multidisciplinary programs, occupational and physiotherapy |

Table 7: Emerging Therapeutic Strategies in Parkinson’s Disease

|  |  |  |  |
| --- | --- | --- | --- |
| **Therapeutic Strategy** | **Mechanism of Action** | **Examples / Agents** | **Clinical Stage / Notes** |
| Gene Therapy (Voss *et al.,* 2008 & Tardiff *et al.,* 2022) | Delivery of genes to restore dopamine synthesis or protect neurons | - AAV2-GAD (inhibitory modulation of STN)- AAV2-AADC (dopamine synthesis enzyme)- GDNF, NRTN gene delivery | Phase I/II trials Mixed results; invasive delivery limits use |
| Cell-Based Therapy | Transplantation of dopaminergic neurons to restore striatal function | - Fetal mesencephalic tissue- iPSC-derived DA neurons- hESC-derived neurons | Advanced preclinical to early clinical trials Long-term safety under evaluation |
| Neurotrophic Factors | Promote survival and regeneration of DA neurons | - GDNF- Neurturin (NRTN)- CDNF | Limited BBB penetration Intracerebral infusion required |
| Neuroimmunophilins | Protect neurons via immunophilin ligands without immunosuppression | - GPI-1046- V-10367 (non-immunosuppressive) | Preclinical/early trials Show anti-apoptotic properties |
| Receptor Antagonists/Modulators | Reduce excitotoxicity and inflammation | - NMDA receptor antagonists (e.g., amantadine)- Adenosine A2A antagonists (e.g., istradefylline) | Approved as adjuncts Target non-dopaminergic symptoms |
| Iron Chelators / Calcium Modulators | Reduce oxidative stress from metal accumulation / regulate Ca²⁺ overload | - Deferiprone (iron chelator)- Isradipine (L-type Ca²⁺ blocker) | Deferiprone in trials Isradipine failed in Phase III |
| Alpha-Synuclein Targeting | Reduce aggregation and propagation of α-synuclein | - Immunotherapy (e.g., Prasinezumab)- Anti-aggregating molecules | Phase II ongoing Focus on disease modification |
| Anti-inflammatory Agents | Suppress chronic neuroinflammation in PD | - NSAIDs- Minocycline- NLRP3 inflammasome inhibitors | Experimental Biomarker-guided therapy under investigation |
| Mitochondrial Support / Antioxidants | Improve energy metabolism, reduce ROS production | - Coenzyme Q10- Creatine- MitoQ | Trials show limited efficacy alone Potential in combination therapy |
| Signal Pathway Modulators | Modulate intracellular pathways (e.g., PI3K/Akt, mTOR, MAPK) | - Rasagiline (MAO-B + neuroprotective)- Rapamycin (mTOR modulator) | Preclinical to early-phase trials |

Table 8: Species-Specific Characteristics of Animal Models Used in PD

|  |  |  |  |
| --- | --- | --- | --- |
| Aspect (Biglan *et al.,* 2007, Khan *et al.,* 2023 & Konnova *et al.,* 2018) | Rodents *(Rats, Mice)* | Non-Human Primates (NHP) *(Macaques, Marmosets, Squirrel monkeys, Baboons, African green monkey)* | Non-Mammalian Species (NMS) *(C. elegans, Drosophila, Zebrafish)* |
| Relation to PD | Widely used due to correlation between motor deficits and DA neuronal loss in SNpc | Provide anatomical/genetic similarity to humans; valuable for understanding PD mechanisms | Ideal for studying genetic, cellular, and network changes from DA loss |
| Features | Easy lab maintenance; supports transgenic models; behavioral & pharmacological studies feasible | Used mainly for preclinical trials; large, long-lived, high cost and ethical constraints | Exhibit clear neuropathology; support high-throughput, genetic studies; short life cycle |
| Advantages | Correlate nigrostriatal loss to motor symptoms; allow modeling of familial and sporadic PD | Show complex motor symptoms (chorea/dystonia), human-like sleep; presence of Lewy Bodies (LBs); rating scales applicable | Cost-effective; easy genetic manipulation; accurate DA neuron quantification (C. elegans); oxidative stress and α-syn pathology (Drosophila); conserved PD genes (Zebrafish) |
| Disadvantages | Pharmacological models may lack molecular PD accuracy; LBs absent in genetic models | Resource-intensive; limited by ethical concerns | Low translational value; face validity limited due to species-specific symptom representation |
| Motor Symptom Tests | Pole test, open field, rotarod, stepping test, grip strength | Tower test (akinesia), hourglass test (rigidity), dyskinesia studies in macaques | C. elegans: basal slowing, coiling; Drosophila: climbing assay; Zebrafish: reduced swimming post-toxin |
| Non-Motor Symptom Tests | Tail suspension/forced swim test (depression), grooming/nesting (anxiety/apathy), activity monitoring | Pre-diagnostic markers (e.g., sleep/social behavior) in macaques | Limited, but some models show stress-related behavioral changes |
| Research Usage | ~23,000 PD studies since 1990 | ~10% of PD animal studies | Small fraction of PD studies; high-throughput applications |
| Drug Testing Applications | Evaluate L-Dopa, MAO-B inhibitors, COMT inhibitors, decarboxylase inhibitors | Test therapeutic response to pharmacological and gene-based therapies | L-Dopa and DA agonists reverse behavioral phenotypes in C. elegans/Drosophila; high-throughput screening possible |

Table 9: Utility of Different PD experimental Models in Biomarker and Drug Discovery

|  |  |  |  |
| --- | --- | --- | --- |
| **Feature** | **6-OHDA** | **MPTP** | **Reserpine** |
| Discovery | Prototype PD model; intracerebral injection in rats | Discovered after accidental exposure caused parkinsonism in humans (1982) | One of the earliest PD models; Carlsson *et al.,*  1957 demonstrated L-DOPA efficacy |
| Mechanism | Analog of DA/NE, induces oxidative stress and mitochondrial dysfunction via direct brain injection | Crosses BBB → converted by MAO-B to MPP+ → inhibits mitochondrial complex I → DA neuron death | Inhibits VMAT2 → depletes monoamines (DA, NA, 5HT) → akinesia and rigidity |
| Targeted Regions | SNpc, Striatum, Medial Forebrain Bundle | SNpc, striatum, putamen, caudate (esp. in NHP) | SNpc (~85% DA loss), striatum (>95% DA loss), entopeduncular nucleus |
| Animals Used | Rats (most common), mice, cats, dogs, NHP | Mice (C57BL/6), NHP | Rats |
| Route of Administration | Intracerebral only (unilateral or bilateral) | Systemic: IP, IV, SC (mice); Intracarotid (NHP) | SC (systemic); Intracerebral for validation |
| Use/Application | L-DOPA-induced dyskinesia, DBS, neuroprotection, gene therapy studies | DA neuron degeneration, α-syn, gut-brain axis, non-motor symptoms, dyskinesia | Screening for dopaminergic/non-dopaminergic agents for symptomatic relief |
| Doses Administered | Full lesion: 8 µg (MFB/SNpc); Partial: ~6 µg → 70% DA loss | Mouse: 25–40 mg/kg (acute/subacute); NHP: 0.2–2 mg/kg | 4–5 mg/kg SC; may combine with AMPT |
| Face Validity | Moderate (especially in partial lesions) | High (esp. in NHP – mimics clinical PD signs) | Good: akinesia, rigidity resemble PD symptoms |
| Construct Validity | High – mimics oxidative stress and mitochondrial dysfunction | High – mitochondrial dysfunction, ROS, α-syn pathology | Low – no DA neuron degeneration |
| Predictive Validity | Moderate – used for neuroprotective drug screening | High – all clinical DA drugs effective in NHP | Strong – predictive of symptomatic drug efficacy |
| Advantages | Stable, site-specific DA loss; mimics biochemical and motor signs of PD; full lesion is reproducible | Systemic administration; bilateral damage (mouse); strong primate model; α-syn aggregation possible | Simple, low cost, robust for short-term symptomatic drug screening |

Table 10: Comparative Overview of Parkinson’s Disease (PD) Animal Model

|  |  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- | --- |
| **Model** (Anthony 2009, Tardiff *et al.,* 2022 & Gold *et al.,* 2002) | **Mechanism of Induction** | **Animals Used** | **Uses** | **Route of Administration** | **Targeted Areas** | **Advantages** |
| Haloperidol | DA D2 receptor blockade → altered BG signaling → rigidity, catalepsy | Rodents (rats, mice) | Evaluate non-DA drugs (e.g., mGlu4 modulators), screen antiparkinsonian agents | IP | Striatum | Simple, useful for motor disability & drug screening |
| Proteasomal Inhibitor (e.g., PSI, Epoxomicin, Lactacystin) | Proteasomal inhibition → α-syn aggregation, DA neuron loss, motor disability | Rodents, Primates | Study neuroprotection, α-syn pathology | SC, Oral (not IP) | SN, striatum, raphe, LC, DMNV | Progressive, mimics α-syn pathology, neuroprotective studies |
| Preformed Fibril (PFF) | Direct brain seeding → α-syn aggregation → LB pathology, neuron loss | Rodents (rats, mice) Primates (macaques, marmosets) | Study syn propagation, LB formation, pathogenesis, therapy screening | Intra-striatal | Striatum, nigrostriatal pathway | Mimics progressive PD, α-syn pathology in NHPs |
| Rotenone (Agrochemical) | Mitochondrial dysfunction, ROS → DA neuron loss, α-syn inclusion | Rats | Test neuroprotection, inflammation, LB pathology | IP, IV, SC, stereotaxic | SNpC, striatum, LC, cortex, OB | Mimics pathology & behavior; supports drug efficacy |
| Paraquat (PQ) | Redox stress via glutathione/thioredoxin; enters via AA transporter | Rodents, frogs | Study oxidative stress, early-stage PD | Systemic injections | SNpC, midbrain, striatum | Useful in early PD studies, synergistic with other toxins |
| PQ + Maneb | PQ: ROS, Complex I; Maneb: Complex III inhibition | Rats, mice (Wistar, C57B1/6) | Study neuroprotection, gene-environment interaction | IP | SNpC, striatum | Synergistic toxicity, motor/non-motor PD-like signs |
| Glial Activation (Neuroinflammatory / Inflammogen) Models | LPS induces inflammatory cascade via microglia: cytokines, iNOS, peroxynitrite. Neuromelanin triggers microglial activation and neurodegeneration. | Rodents (Rats, Mice) | Mimics inflammation in PD, evaluates anti-inflammatory strategies | Unilateral stereotaxic injection, multiple small doses, continuous infusion | Nigrostriatal pathway | Mimics activated microglia + DA neuron degeneration; Useful for studying neuroinflammation |
| Genetic Models | Overexpression, knockout or mutation of PD genes. α-syn, LRRK2, PRKN, DJ-1, PINK1. Viral vectors used. | Rodents, Drosophila, NHPs | Study gene function, mechanisms of PD pathology, therapeutic testing | Transgenesis, viral vector-mediated delivery | SNpc, striatum, cortex, hippocampus, olfactory bulb | Recapitulates genetic PD aspects; enables study of specific gene mutations |
| Abnormal Involuntary Movement (AIMs) Model | AIMs Rating Scale scores forelimb, axial, and orolingual dyskinesia post L-DOPA | Rats | Detect anti-dyskinetic drug effects, study L-DOPA-induced dyskinesia | Behavioral induction and scoring post-lesion and L-DOPA administration | Contralateral side to lesion (forelimb, oral muscles) | Can distinguish anti-akinetic vs anti-dyskinetic; Validated in primates |
| Combined Genetic + Pharmacological Models | KO or overexpression of genes (e.g., PINK1, DJ-1, PRKN, Nurr-1) with toxins like MPTP or 6-OHDA | Mice, Rats | Explores interplay between genes and environment; models more realistic PD pathology | Gene editing, viral KO, plus neurotoxin administration | SNpc, striatum | Mimics complex PD etiology; reveals synergistic pathology |