Advances in Modern Biomedicine

https://amb.cultechpub.com/amb

Cultech Publishing

Review

Neurons to Genes A Comprehensive Review of Parkinson's Disease

Jeewanjot Singh*, Subhi Sharma, Prabhjot Singh, Shafkat Hussain

School of Pharmacy, Desh Bhagat University, Mandi Gobindgarh, Punjab, India

*Correspondence author: Jeewanjot Singh, sandhujeewan7@gmail.com

Abstract

Parkinson's disease (PD) is an insidious neurodegenerative disease that is marked by loss of dopaminergic cells of the substantia nigra (SN) and aggregation of misfolded a-synuclein proteins. It is characterized by typical motor symptoms such as tremor, rigidity, bradykinesia, and postural instability, along with a wide range of non-motor manifestations including cognitive impairment, autonomic dysfunction, sleep disturbances, and mood disorders.The pathophysiology of PD is multifactorial, as it entails protein aggregation, mitochondrial dysfunction, oxidative stress, neuroinflammation, and genetics. Although significant advancements have been made in levodopa-based therapies and surgical interventions such as deep brain stimulation, these approaches primarily provide symptomatic relief and do not prevent disease progression. Emerging therapeutic strategies, including gene therapy, RNA-based therapeutics, immunotherapy, and stem cell interventions, are currently under investigation for their potential disease-modifying effects. Furthermore, patient-centered and precision medicine approaches are becoming increasingly important in PD management. This review integrates clinical, molecular, and therapeutic perspectives, with particular emphasis on challenges associated with bench-to-bedside translation. It also highlights the urgent need for reliable biomarkers, early diagnosis, and multidisciplinary disease-modifying strategies for future therapeutic interventions.

Keywords

Mitochondrial dysfunction, Neurodegeneration, Neuroinflammation, Oxidative stress, Parkinson's disease

Article History

Received: 03 March 2026
Revised: 15 June 2026
Accepted: 13 July 2026
Available Online: 27 July 2026

1. Introduction

Parkinson's Disease (PD) is a chronic and progressive neurodegenerative disease, which mainly involves movement, but has a broad spectrum of non-motor symptoms that have a very detrimental effect on the quality of life [1]. PD which is defined by bradykinesia, resting tremor, rigidity and postural instability is the second most prevalent neurodegenerative disorder after Alzheimer disease, and an increasingly worrisome global health issue [2]. The underlying pathology is characterized by the selective degeneration of dopaminergic cells in the SN pars compacta and intracellular inclusions, called Lewy bodies (LB) that are mainly made of aggregated alpha-synuclein protein [3]. Though the precise mechanism has eluded researchers, it is agreeable that multifactorial interaction of genetic predisposition and environmental exposures play a role in disease onset and progression [4]. The significance of PD extends beyond its clinical presentation, as it exerts substantial emotional, social, and economic burdens on patients, caregivers, and healthcare systems worldwide.As the world tends to age, the level of PD has been increasing at an alarming rate in the past decades. It is estimated such that more than 10 million individuals in the world are living with PD which is likely to rise to 20 million by 2040 [5]. In most low and middle-income states, late diagnosis, low access to neurologists, and insufficient treatment also contribute to the burden, and there is a sharp necessity to create better global awareness, early detection plans, and fair access to treatment. Also, PD has a high disability-adjusted life year (DALY) and healthcare price, particularly at more severe stages where motor fluctuation, cognitive, and autonomic dysfunction are more pronounced [6]. PD has had a rich medical history of existence way back to antiquity. The first clear clinical description of the symptoms similar to those of PD is dated to early Ayurvedic and Chinese medical texts, however, in 1817, the British physician James Parkinson gave a first account of it in his monograph entitled An Essay on the Shaking Palsy [7]. His work was the basis of accepting PD as a specific neurological disorder. Subsequently, the knowledge of its clinical manifestation and pathology was perfected by Jean-Martin Charcot and others [8]. The 20th and 21st centuries saw a boom of neurobiology and imaging technologies that have demonstrated the intricate interplay of molecular, cellular, and genetic changes that occur in PD that has moved the emphasis to treating the symptoms to finding disease-based interventions.

The introduction of levodopa therapy in the 1960s revolutionized the treatment of PD and it remains the gold standard therapy to date. However, long-term levodopa administration is associated with motor complications, highlighting the limitations of current symptomatic treatments and the urgent need for more effective disease-modifying therapies. Recent advances in genetic research have identified several loci associated with PD susceptibility and progression, including mutations in *SNCA*, *LRRK2*, *PARK2*, *PINK1*, and *DJ-1* genes. These discoveries have provided important insights into disease pathophysiology and revealed potential therapeutic targets for future interventions [9]. Meanwhile, a growing awareness of mitochondrial dysfunction, oxidative stress, disrupted autophagy, and neuroinflammation has widened the molecular picture of PD and strengthened its complexity [10]. With these developments, there is no cure yet and the treatment options currently available are mostly focused on treating the symptoms of the disease instead of preventing or reversing the disease process [11]. As a result, new modalities, including gene therapy, stem cell transplantation, immunotherapy against alpha-synuclein, and RNA-based therapeutics, are of increased interest [12]. It is against this background that this comprehensive review aims to interwove knowledge across various fields including clinical neurology and molecular genetics in an attempt to be holistic in understanding PD [13]. This paper tries to explain the pathophysiological process, genetic basis, clinical developments, and treatment options of PD by following along the pathway between neurons and genes [14]. Through this, the review identifies existing gaps in knowledge and future research directions, with a focus on potential to be translational and use of personalized medicine. The review also emphasises the need to diagnose early, develop biomarkers and use sophisticated models such as induced pluripotent stem cells (iPSCs) and animal models to better reflect disease features and evaluate emerging therapies. In the end, this contribution is hoped to contribute to the current world in its quest to comprehend PD, not simply as a movement disorder, but as a multisystem disease that needs concerted research efforts and novel patient-centred approaches [15].

2. Clinical Features of PD

2.1 Cardinal Motor Symptoms

Tremor, bradykinesia, rigidity and postural instability are the hallmark motor symptoms of PD [16]. The first and most commonly known is the resting tremor commonly referred to as pill-rolling tremor, which usually begins asymmetrical. The most disabling symptom is known as bradykinesia or, in other words, slowness of movement, which causes problems with the initiation and implementation of voluntary movements [17]. The presence of rigidity which is an augmentation of the muscle tone is manifested by rigidity and may occur on both flexor and extensor muscles commonly contributing to pain and decreased range of motion [18]. Late changes include postural instability that is linked with poor balance and fall risk. These motor symptoms are caused by the progressive destruction of the dopaminergic cells in the SN which causes disruption of the signalling in the basal ganglia circuitry [19]. Their symptoms differ in severity and progression in different patients, and this affects the diagnosis, functional ability, and response to therapy. The motor features need to be recognized and characterized very early so that they can be intervened with in time and distinguish them with other movement disorders [20].

2.2 Non-Motor Symptoms (NMS)

There has been an increasing acceptance of NMS as part of the clinical picture of PD and even as a possible antecedent to the emergence of motor symptoms [21]. The severity of cognitive impairment is between mild executive dysfunction and PD dementia, which has a great impact on day-to-day functioning and the burden on the caregiver [22]. Insomnia, excessive daytime sleepiness, and sleep disturbances such as rapid eye movement (REM) sleep behavior disorder (RBD) are common NMS of PD and are frequently underreported [23]. There is widespread neurodegeneration outside dopaminergic routes, which may comprise autonomic dysfunction in the form of orthostatic hypotension, urinary incontinence, constipation, and sexual dysfunction [24]. The mood disorders such as depression, anxiety and apathy are common and may be enhanced due to the neurochemical change as well as the psychosocial effects of chronic disease [25]. NMS do not tend to be particularly associated with severity of motor symptoms, but they are good predictors of poorer quality of life. The problem of multidisciplinary approach is essential to effective management because these symptoms are frequently inadequate to the usual dopaminergic treatments. They are important in the comprehensive treatment planning and patient outcomes on PD because of their early detection [26].

2.3 Staging and Progression of the Disease

Clinical stages of the PD are assessable through motor based and neuropathological staging systems [27]. The Hoehn and Yahr Scale is a common clinical instrument that has five stages of motor disability with the first one (Stage 1) being unilateral disability and the last one (Stage 5) being wheelchair or bed bound [28]. This staging aids in the monitoring of disease progress and informing the treatment decision. The Braak staging system, in turn, concentrates on the pathological diffusion of alpha-synuclein aggregates in the brain [29]. It suggests a six steps model, the first two stages (Stages 1 and 2) occur in the olfactory bulb, dorsal motor nucleus of the vagus, SN (Stages 3 and 4), and finally in the cortical areas (Stages 5 and 6). The model confirms the hypothesis that pathology of PD can have its inception in peripheral systems and climb up to the brain. The fusion of the clinical and pathological staging offers a better idea of how the disease develops and could help classify patients to qualify them into clinical trials [30].

2.4 Differential Diagnosis

It is important to distinguish the PD in comparison to other PD syndromes to make appropriate diagnosis and treatment plan. A number of disorders can imitate PD, but differ in pathology, progression and response to treatment, which are referred to as atypical PD. These are multiple system atrophy (MSA), progressive supranuclear palsy (PSP), corticobasal degeneration (CBD) and Dementia with LB [31]. Unusual characteristics can include the early postural instability, slow response to levodopa, early cognitive impairment, supranuclear gaze palsy or autonomic failure, which can be indicative of alternative diagnoses. There are also essential tremor, vascular PD and drug induced PD that enter the differential and should be carefully clinically evaluated. Diagnosis may be assisted by neuroimaging, especially DAT scans which show dopaminergic deficiencies [32]. Nevertheless, PD is not confirmed by only one test; diagnosis is mainly clinical. Early and precise differentiation is imperative, because the course of the disease, prognosis and treatment vary widely. Continuous efforts are being made to improve biomarkers and imaging modalities to enhance the diagnostic accuracy of PD. Figure 1 shows the neuropathology of PD.

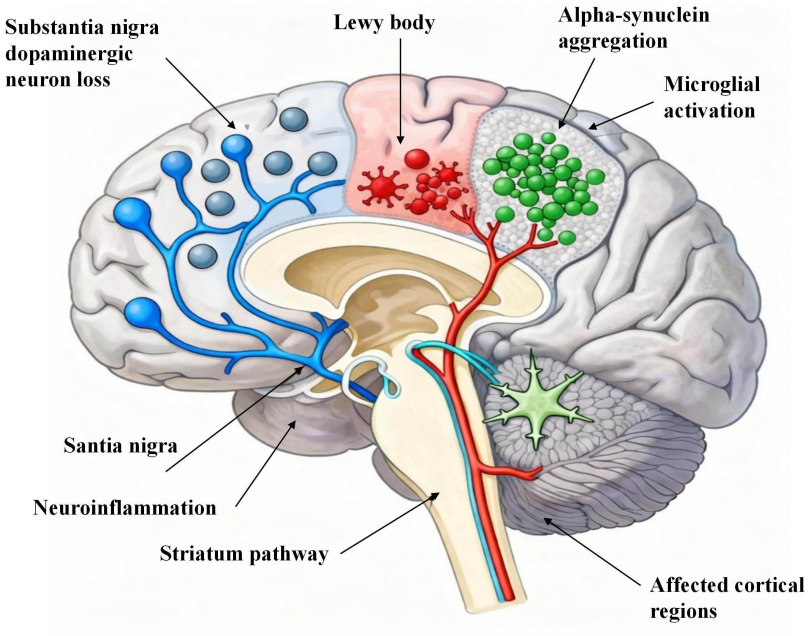

Figure 1. Neuropathology of PD.

3. Molecular Pathophysiology of PD

3.1 Substantia Nigra-Loss of Dopaminergic Neurons

One of the major pathological features of PD is the progressive loss of dopaminergic neurons in the substantia nigra pars compacta (SN), which disrupts the nigrostriatal pathway and dopamine-mediated motor control [33]. The resulting dopamine deficiency leads to dysfunction of basal ganglia circuits and contributes to the cardinal motor symptoms of PD, including bradykinesia, rigidity, tremor, and postural instability [34]. Although the exact mechanisms underlying neuronal vulnerability remain unclear, mitochondrial dysfunction, oxidative stress, and α-synuclein pathology are considered important contributors to dopaminergic neurodegeneration [35].

3.2 Aggregation of LB and Alpha-Synuclein

LB are a pathological hallmark of PD and mainly consist of misfolded α-synuclein aggregates [36]. Abnormal post-translational modifications of α-synuclein promote fibril formation, resulting in toxic protein accumulation that disrupts mitochondrial function, protein clearance pathways, and synaptic activity. These pathological aggregates contribute to neuronal dysfunction and degeneration in PD [36-38].

3.3 Microglial Activation and Neuroinflammation

Neuroinflammation plays an important role in PD progression through chronic activation of microglia, the resident immune cells of the CNS. Activated microglia release pro-inflammatory cytokines, ROS, and nitric oxide, promoting oxidative stress and neuronal damage. α-synuclein aggregates can further stimulate microglial activation, creating a cycle of inflammation and neurodegeneration [39-41] (Table 1).

Table 1. Major molecular mechanisms associated with mitochondrial dysfunction and oxidative stress in PD.

Aspect	Description	Effect on Neurons	Result Outcome	References
Mitochondrial Dysfunction	Decreased Complex I activity in the electron transport chain reduces ATP production and increases ROS formation.	Energy failure in dopaminergic neurons.	Neuronal death due to energy loss	[42]
Genetic Mutations	Mutations in PINK1, Parkin, and DJ-1 impair mitophagy (removal of damaged mitochondria).	Accumulation of dysfunctional mitochondria and elevated ROS.	Progressive oxidative damage	[43]
Oxidative Stress	Overproduction of ROS overwhelms antioxidant defenses.	Lipid peroxidation, protein oxidation, DNA damage.	Impaired neuronal function and survival	[44]
Iron & Dopamine Metabolism	Iron overload and dopamine oxidation in the substantia nigra trigger Fenton reaction, producing more ROS.	Promotes oxidative stress and mitochondrial damage.	Worsens neuronal degeneration	[45]
Vicious Cycle	Mitochondrial dysfunction ↑ ROS → ROS further damages mitochondria.	Continuous feedback loop of oxidative injury.	Accelerated neuron loss	[46]
Cellular Consequences	ROS and mitochondrial failure activate apoptotic pathways and α-synuclein aggregation.	Dopaminergic neuron death.	Onset of PD motor symptoms	[47]
Clinical Impact	Dopamine deficiency due to neuronal loss.	Impaired movement control.	Characteristic motor symptoms of PD	[48]
Therapeutic Targets	Antioxidants, mitochondrial protective agents, and iron chelators under study.	Reduce oxidative damage and improve mitochondrial health.	Potential neuroprotective therapy	[49]

4. PD Genetics

PD has a complex etiology involving interactions between genetic susceptibility and environmental factors. Although most cases are sporadic, approximately 5%-10% are associated with genetic mutations. Genes such as *SNCA*, *LRRK2*, *PARK2*, *PINK1*, and *DJ-1* have provided important insights into mechanisms involving α-synuclein aggregation, mitochondrial dysfunction, and impaired cellular clearance pathways. Understanding these genetic mechanisms has contributed to the development of targeted and personalized therapeutic approaches [50-52].

4.1 Monogenic Forms of PD

Monogenic forms of PD originate because of inherited mutations in a single gene and follow Mendelian inheritance patterns. They are uncommon forms of PD that provide important insights into the molecular basis of familial and sporadic PD [53]. Monogenic forms account for approximately 5%-10% of PD cases and are commonly associated with early-onset disease. The major genes involved include *SNCA* (alpha-synuclein), *LRRK2*, *PARK2* (Parkin), *PINK1*, and

DJ-1. These mutations affect cellular processes such as mitochondrial quality control, protein degradation, and oxidative stress regulation [54]. They have also contributed to understanding shared mechanisms between familial and idiopathic PD, including mitochondrial dysfunction and impaired autophagy. However, not all monogenic forms exhibit Lewy body pathology, highlighting the biological heterogeneity of PD [55].

4.2 *SNCA*

SNCA encodes the alpha-synuclein presynaptic neuronal protein involved in synaptic function and neurotransmitter release [56]. Mutations in *SNCA* cause autosomal dominant PD and were the first genetic alterations linked with familial PD. Mutations such as *A53T*, *E46K*, and *SNCA* multiplications promote alpha-synuclein overproduction or misfolding, leading to aggregation into LB and neuronal toxicity. These aggregates impair mitochondrial function, autophagy, and protein degradation pathways, contributing to neurodegeneration [57]. Alpha-synuclein pathology is also a central feature of sporadic PD, indicating a shared mechanism in disease progression [58].

4.3 *LRRK2*

LRRK2 is the most common genetic cause of autosomal dominant PD and is also associated with some sporadic cases. The G2019S mutation increases *LRRK2* kinase activity, contributing to neurotoxicity [59]. *LRRK2* regulates cellular processes including vesicle trafficking, autophagy, mitochondrial dynamics, and immune signaling. Mutations can result in impaired protein clearance and increased oxidative stress, contributing to dopaminergic neuronal degeneration. *LRRK2*-associated PD often shows clinical features similar to idiopathic PD [60].

4.4 *PARK2*

Parkin is an E3 ubiquitin ligase encoded by the *PARK2* gene and plays an important role in the removal of damaged proteins and mitochondria. PARK2 mutations cause autosomal recessive juvenile PD, commonly with early onset [61]. Loss of Parkin function disrupts mitophagy through impaired mitochondrial quality control, leading to oxidative stress and neuronal dysfunction. Parkin works closely with PINK1 to regulate mitochondrial clearance, and *PARK2*-associated PD may lack Lewy body pathology, indicating differences from idiopathic PD [62,63].

4.5 *PINK1* and *DJ-1*

PINK1 and *DJ-1* are associated with early-onset PD and contribute to mitochondrial protection and oxidative stress regulation [64]. *PINK1* encodes a mitochondrial kinase that detects damaged mitochondria and recruits Parkin to initiate mitophagy. Mutations in *PINK1* impair mitochondrial quality control and increase oxidative stress [65]. *DJ-1* functions as an antioxidant protein involved in protecting cells against oxidative damage and maintaining mitochondrial stability. Dysfunction of these pathways contributes to dopaminergic neuronal degeneration and highlights the importance of mitochondrial homeostasis in PD [66].

5. Molecular Pathobiology of PD

PD is a multifactorial neurodegenerative disorder involving progressive dopaminergic neuronal loss and multiple interconnected pathological mechanisms [67]. Major molecular processes include α-synuclein aggregation, mitochondrial dysfunction, impaired autophagy and ubiquitin–proteasome pathways, neuroinflammation, and oxidative stress [68]. These mechanisms interact in a self-amplifying cycle, where mitochondrial impairment and oxidative damage further promote protein aggregation and neuronal dysfunction. Genetic susceptibility and environmental factors may contribute to these pathological changes, providing important targets for disease-modifying therapeutic approaches [69].

5.1 Protein Misfolding and Aggregation

Protein misfolding and aggregation, particularly involving α-synuclein, are major pathological features of PD [70]. Under normal conditions, α-synuclein is a presynaptic protein involved in vesicle transport and synaptic function. However, genetic alterations, oxidative stress, and cellular dysfunction promote abnormal α-synuclein aggregation into toxic fibrils and LB. These aggregates disrupt mitochondrial function, autophagy, and cellular homeostasis, contributing to neuronal dysfunction and degeneration [71]. Misfolded α-synuclein may also propagate between cells, facilitating disease progression [72]. Impaired protein quality control systems, including chaperone-mediated pathways and the proteasome, further enhance the accumulation of toxic proteins [73].

5.2 Mitochondrial Dysfunction

Mitochondrial dysfunction is a key mechanism involved in both familial and sporadic PD. Mitochondria maintain cellular energy production, calcium regulation, and apoptotic control [74]. Impaired mitochondrial function results in reduced ATP production, increased ROS generation, and activation of apoptotic pathways, making dopaminergic neurons particularly vulnerable [75]. Mutations in *PINK1*, *PARK2* (Parkin), and *DJ-1* disrupt mitochondrial quality

control and mitophagy [76]. In addition, mitochondrial complex-I inhibitors such as rotenone and paraquat induce PD-like pathology in experimental models. Mitochondrial impairment further promotes oxidative stress and α-synuclein aggregation, creating a cycle of neurodegeneration [77].

5.3 Autophagy-Lysosomal Pathway and Ubiquitin-Proteasome System

The autophagy-lysosomal pathway and ubiquitin–proteasome system (UPS) are essential mechanisms responsible for the removal of damaged proteins and organelles [79]. In PD, dysfunction of these pathways leads to the accumulation of toxic proteins, including α-synuclein, and impaired mitochondrial clearance. Mutations in *PARK2*, *PINK1*, and *GBA* disrupt protein degradation and lysosomal function, contributing to disease progression [80]. Impaired proteostasis further promotes oxidative stress and neuronal damage, emphasizing the importance of maintaining cellular protein homeostasis in PD [81].

5.4 Neuro inflammation and Immune Response

Neuroinflammation contributes significantly to PD progression through chronic activation of microglia and immune responses [82]. Activated microglia release inflammatory mediators, ROS, and nitric oxide, which promote neuronal damage and enhance α-synuclein pathology. Aggregated α-synuclein can further activate microglia, creating a continuous cycle of inflammation and neurodegeneration. Alterations in peripheral immune responses and inflammatory pathways may also contribute to PD progression [83,84].

5.5 Metabolism and Oxidative Damage of Dopamine

Dopaminergic neurons of the substantia nigra are highly vulnerable to oxidative damage due to dopamine metabolism, which generates ROS [85]. Excessive ROS production causes lipid peroxidation, protein modification, and DNA damage when antioxidant defenses become insufficient. Dopamine-derived metabolites may also promote α-synuclein aggregation, while neuromelanin-associated metal accumulation further enhances oxidative stress. These processes contribute to selective neuronal vulnerability and PD progression [86,87]. Figure 2 illustrates the mechanisms involved in oxidative damage and neurodegeneration in PD.

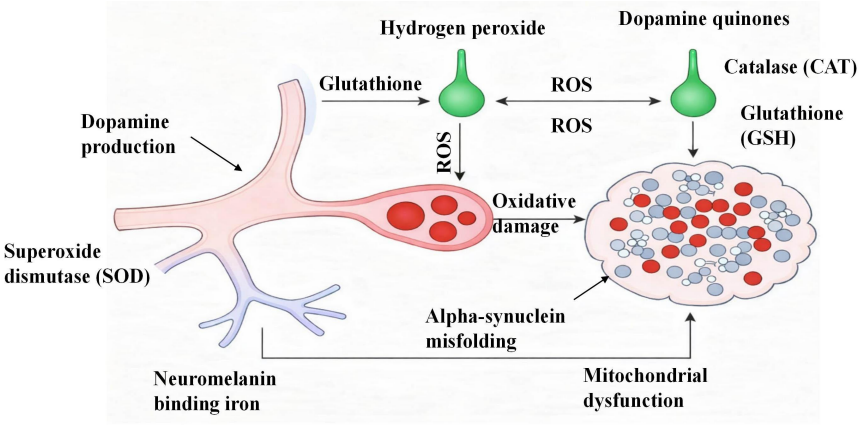

Figure 2. Mechanisms of oxidative damage and neurodegeneration in PD.

6. Biomarkers in PD

6.1 Biomarkers Imaging

The use of imaging biomarkers is very instrumental in the diagnosis and management of PD, especially in differentiating it with other movement disorders. Dopamine transporter single photon emission computed tomography (DAT-SPECT) and positron emission tomography (PET) are two of the most common imaging methods [88]. DAT-SPECT uses radioligands to visualize DAT density within the striatum.

In PD, DAT binding is greatly decreased particularly in the putamen, which is an indication of loss of presynaptic dopaminergic neurons loss. The method is particularly effective in distinguishing PD and essential tremor or drug-induced PD with the latter having normal levels of DAT.

PET imaging has a more accurate way of quantification and is able to apply diverse radiotracers to evaluate various brain functioning. As an example, 8F-DOPA PET measures the production of dopamine, and 11C-raclopride PET determines the binding of dopamine receptor. More recent PET tracers can additionally measure glucose metabolism, neuroinflammation and synaptic density, making it no longer solely useful in the dopaminergic process. PET and DAT-SPECT have drawbacks such as high cost, low availability and radiation exposure despite their diagnostic worth. They are not generally used as a screening tool but can be useful in the assurance of diagnosis especially in atypical or early

stage cases and are often used in research and in clinical trials that are aimed at modifying the disease [89]. A comparison of blood and CSF biomarkers is presented in Table 2.

Table 2. Blood biomarkers and CSF-comparison.

Aspect	Blood Biomarkers	CSF (Cerebrospinal Fluid) Biomarkers
Collection Method	Collected from plasma or serum through simple venipuncture	Collected through lumbar puncture (invasive)
Invasiveness	Non-invasive	Invasive
Ease of Collection	Easy, suitable for large-scale screening and long-term monitoring	Difficult, requires clinical setup
Specificity to Brain Pathology	Less specific (reflects systemic changes)	Highly specific (direct reflection of CNS pathology)
Key Biomarkers	α-synuclein, *DJ-1*, Neurofilament light chain (NfL), Inflammatory cytokines, Oxidative stress markers	Total & phosphorylated α-synuclein, Tau proteins, Dopamine metabolites, NfL
Reflects	General body changes, oxidative stress	Brain biochemical alterations (dopaminergic neuron loss, α-synuclein aggregation)
Diagnostic Sensitivity	Moderate	High
Monitoring Frequency	Can be collected repeatedly	Limited repeat collection due to invasiveness
Current Research Focus	Standardizing plasma-based assays for clinical use	Used as reference standard for diagnosis
Overall Use	Convenient, but less specific	Accurate, but invasive

6.2 Genetic Screening and Predictive Testing

Genetic screening in PD has become an important method of risk identification and disease pathophysiology [90,91]. The monogenic mutations are responsible of about 5%-10% of PD cases, especially the *SNCA*, *LRRK2*, *PARK2*, *PINK1* and *DJ-1* genes. The most frequent among them are *LRRK2* and *GBA* mutations observed in the late-onset familial and few sporadic cases. A clinical diagnosis of PD, at-risk family members, or participation in gene-targeted clinical trials can be confirmed through genetic screening as a tool to confirm a clinical diagnosis in early-onset PD [92]. Furthermore, due to the development of direct-to-consumer genetic testing, and mass biobanking initiatives, polygenic risk scores (PRS) are now being created to predict the total genetic risk of a person, which is an attempt to estimate the sum of multiple small-effect variants.

Nevertheless, predictive testing of asymptomatic persons is still ethically and clinically complicated. Although identification of a PD-related mutation may carry information on risk, penetrance is often incomplete, particularly in the case of *LRRK2* mutations - that is, not all carriers of the mutation develop the disease. This restricts the usefulness of genetic testing of general populations in prediction. There is also the psychological effect, possibility of insurance discrimination, and absence of curative treatment which must be taken into consideration. As such, genetic testing must also be accompanied by genetic counselling, especially when not in the context of research. Genetic screening can be utilized in personalized medicine in PD as more gene-specific therapies are created, as this screening method would be used to prevent and treat disease [93].

6.3 Problems in Diagnosis during Early Stages

PD remains a major clinical challenge, particularly with respect to early diagnosis, despite advances in imaging techniques and biomarker research [94]. The diagnosis of PD is primarily based on the identification of characteristic motor symptoms, including bradykinesia, tremor, and rigidity. However, these symptoms typically appear only after approximately 60%-70% of dopaminergic neurons have already been lost, limiting the opportunity for effective neuroprotective intervention.

NMS such as constipation, REM sleep behavior disorder (RBD), hyposmia, depression, and fatigue may precede motor manifestations by several years or even decades. However, these symptoms are often nonspecific and can also occur in other neurological or systemic disorders, thereby limiting their diagnostic specificity.

Clinical heterogeneity further complicates diagnosis. Several atypical parkinsonian syndromes, including MSA and PSP, may mimic idiopathic PD, particularly during the early stages of disease progression. Consequently, misdiagnosis rates in early PD may reach 20%-30%.

Although imaging modalities, cerebrospinal fluid (CSF), blood-based biomarkers, and genetic markers show considerable promise, no single biomarker has yet demonstrated sufficient sensitivity and specificity for routine clinical diagnosis. Furthermore, factors such as cost, limited availability, and the invasive nature of certain procedures, including lumbar puncture, restrict their widespread clinical application [95]. To address these limitations, multimodal diagnostic approaches integrating clinical evaluation with imaging, biochemical, and genetic markers are currently being investigated. The development of machine learning and wearable technology have also presented the potential of

continuous symptom tracking and early detection. Nevertheless, screening PD in its prodrome is one of the objectives of the modern research [96].

7. Experimental Models of PD

7.1 Toxin-Based Models of PD

Toxin-based models are among the most widely used experimental systems for studying PD because they effectively reproduce dopaminergic neuronal degeneration and motor dysfunction [97]. Common neurotoxins used in PD research include 1-methyl-4-phenyl-1,2,3,6-tetrahydropyridine (MPTP), 6-hydroxydopamine (6-OHDA), rotenone, and paraquat. MPTP selectively damages dopaminergic neurons in the SN and is extensively used in murine and primate models. Similarly, 6-OHDA induces oxidative stress and selective degeneration of catecholaminergic neurons, making it valuable for investigating motor deficits and neuroprotective therapies [98].

Rotenone and paraquat models are particularly useful for studying mitochondrial dysfunction, oxidative stress, and alpha-synuclein aggregation, which closely resemble pathological features observed in human PD. However, toxin-based models often fail to fully replicate the progressive and multifactorial nature of PD, especially NMS and chronic disease progression. Despite these limitations, toxin-induced models remain essential for mechanistic studies and preclinical therapeutic evaluation [99].

7.2 Genetic Models

Genetic models of PD give insightful information on familial and early-onset of the disease [97]. Some of the most investigated include mutations in genes, including *SNCA* (alpha-synuclein), *PARK2* (Parkin), *PINK1*, *DJ-1*, and *LRRK2*. Other models of alpha-synuclein include the overexpression of the wild-type or mutant forms (i.e. *A53T*, *A30P*) in mice, which results in the aggregation of proteins, mitochondrial dysfunction and, in some cases, progressive neurodegeneration. These models approximate some of the most important pathological processes of PD, including Lewy body formation and synaptic losses [98]. Parkin knockout mice, with defective E3 ubiquitin ligase, are also able to be utilized to examine mitochondrial quality control and are pertinent to autosomal recessive juvenile PD. Nevertheless, these knock out models do not usually exhibit significant loss of dopaminergic neurons unless as a result of environmental or metabolic injury [99]. Although genetic models are quite convenient in modelling particular molecular processes of PD, they do not usually reproduce the entire range of clinical phenomena, especially the progressive motor symptom and degeneration of dopaminergic neurons observed in patients. A major benefit is that they enable experimental study of particular genetic pathways and interactions. Furthermore, other models can be used together with transgenic models (e.g. toxin-based) to understand gene-environment interactions. Genetic models, despite their shortcomings in their own modelling of sporadic PD, are necessary in the testing of gene-targeted therapies and in the comprehension of the functions of particular mutations. They also offer useful platforms to the investigation of initial pathogenic events which can be very hard to observe in toxin induced models. All in all, genetic models cannot be ignored in the dynamic PD research [100].

7.3 IPSC-Derived Neuronal Models

The iPSCs-based neuronal models are an innovative technology in the research of PD, allowing the investigation of patient-specific pathogenesis of the condition in vitro [101]. iPSCs are induced by reprogramming normal cells, like skin fibroblasts or blood cells into a pluripotent state, and subsequently differentiated into the prototypical cells of the midbrain, dopaminergic neurons, which are the primary target cells in PD. Such models are especially useful in investigating both familial and sporadic disease forms, as well as disease-relevant phenotypes of iPSCs [102]. Notably, the technology of iPSC provides a human model, which overcomes the shortcomings of animal models, such as differences in species, or ethical issues. In addition, it allows longitudinal research on the disease development and individual screening of drugs. Nevertheless, models that are developed using iPSCs also have difficulties. The process of differentiation is cumbersome and it may lead to the formation of heterogeneous cell populations [103]. Moreover, these models do not usually have the complicated circuits of neurons, glial connections and aging properties of human brain. Nevertheless, iPSC technology continues to progress at a fast pace, where various differentiation regimens, 3D organoid systems and co-culture models are being improved to better represent *in vivo* environments. Consequently, neurons derived out of the iPSCs are the potent instruments to clarify the pathophysiology of PD, identify biomarkers, and come up with personalized treatment. They can play a key role in the translation of basic research into clinical practice, providing a dynamic platform of translational neuroscience [104].

7.4 Strengths and Weaknesses of Existing Models

The currently available models of PD, including toxin-based, genetic, and iPSCs-derived models, each possess distinct advantages and limitations that must be carefully considered [105]. Toxin-based models such as MPTP, 6-OHDA, and rotenone are widely used to induce dopaminergic neuronal loss and motor dysfunction, making them valuable tools for evaluating neuroprotective therapies. However, these models often fail to fully replicate the progressive and

multifactorial nature of human PD, particularly NMS and alpha-synuclein pathology, unless additional modifications are introduced.

Genetic models, including alpha-synuclein overexpression and Parkin knockout models, are essential for investigating specific molecular mechanisms and familial forms of PD. Nevertheless, many genetic models do not exhibit substantial neurodegeneration or pronounced motor impairment unless combined with environmental stressors.

iPSC-derived neuronal models provide an important human-based platform for studying disease pathophysiology, particularly in a patient-specific context [106]. These models offer considerable potential for personalized medicine and high-throughput drug screening. However, they frequently lack cellular maturity, aging-associated phenotypes, and the complex neural network architecture observed in vivo. In addition, their development is technically demanding and time-consuming.

Overall, each experimental model reproduces only selected aspects of PD because of the disease's complex and multifactorial nature. Increasing evidence suggests that interactions between genetic susceptibility and environmental factors contribute significantly to disease pathogenesis. Consequently, combinatorial approaches, including co-culture systems and organoid-based models, are gaining attention for their ability to better replicate multicellular interactions and disease complexity. Understanding the strengths and limitations of each model is essential for selecting appropriate experimental systems to address specific research questions. Further advancements in humanized and three-dimensional (3D) models are expected to play a crucial role in reducing the translational gap and accelerating therapeutic discovery in PD research [107].

8. Existing Therapeutic Methods

8.1 Levodopa and Dopamine Agonist

Levodopa is the gold standard pharmacological agent of PD that is used to treat mainly motor symptoms, which include bradykinesia, rigidity, and tremor [108]. It is an antecedent of dopamine which crosses the blood brain barrier and is converted into dopamine in the brain to restore lost levels. To avoid early conversion of levodopa outside the brain, it is generally used with a peripheral dopa-decarboxylase inhibitor [109]. Long-term levodopa use has been shown to cause motor complications such as on-off fluctuations and dyskinesias even though its efficacy is high. To slow down such complications, dopamine agonists are commonly prescribed i.e. pramipexole, ropinirole, rotigotine especially to younger patients. These are direct stimulating agents of dopamine receptors and may be administered on its own or together with levodopa. Despite being less effective than levodopa, dopamine agonists are longer lived and may decrease motor fluctuations. Nonetheless, they can lead to side effects like impulse control disorders, hallucinations and sleepiness during the day. The regimen of treatment is tailored depending on symptom intensity, age of patients and tolerance. Although levodopa is incomparable with the symptom relief, dopamine agonists are critical in the long-term management approach in order to maximize the quality of life and functionality in PD patients [110].

8.2 MAO-B and COMT Inhibitors

Adjunct interventions that improve the effectiveness of levodopa and increase the control of symptoms in PD are the monoamine oxidase-B (MAO-B) and catechol-O-methyltransferase (COMT) inhibitors [111]. MAO-B inhibitors, e.g. selegiline and rasagiline act by inhibiting the enzyme that breaks down the availability of dopamine in the brain hence enhancing its supply. These medications are commonly prescribed in early PD or as an addition to levodopa treatment to allow a patient to even out motor variations. MAO-B inhibitors should be tolerated well and have weak neuroprotective effects, but this is still under research. Entacapone and opicapone are levels of COMT inhibitors that prevent the activity of peripheral COMT, which breaks down levodopa prior to reaching the brain [112]. COMT inhibitors can be used to decrease the duration of off periods and to increase the motor symptoms control by increasing the half-life of levodopa. They are used in patients usually having wearing-off effects due to long-term use of levodopa. The following are however possible side effects, which include diarrhoea, nausea and excess dyskinesia. These two groups of drugs are useful elements of the overall PD management plan. MAO-B and COMT inhibitors used with judicious doses with levodopa may result in some very useful improvements in motor functioning and quality of life with few side effects (motor complications) in the long-term with dopamine replacement therapy.

8.3 Anticholinergics and Amantadine

Amantadine and anticholinergics are regarded as an additional pharmacology in PD, which is frequently applied in certain clinical conditions [113]. Trixyphenidyl and benztropine are examples of anticholinergics, and their mechanism of action is the inhibition of acetylcholine, which is comparatively overactive because of a lack of dopamine. They work best in the treatment of tremors and are mostly applied to younger patients with tremor-dominant PD. They are however restricted in use because they have cognitive side effects such as confusion, memory impairment and hallucinations particularly among older adults. Originally, amantadine was an antiviral agent but it has weak antiparkinsonian effects. It can increase dopamine release, decrease dopamine uptake, and show antagonism effects on NMDA receptors, and this could help explain its effect in reducing levodopa-induced dyskinesias [114]. It works very well in the treatment of

motor complications in advanced stages of the disease. Amantadine has side effects such as insomnia, hallucinations and livedo reticularis (a mottled discoloration of the skin). Although anticholinergics and amantadine are not first-line interventions, they are useful in the personalized approach to treatment, with supplementing the symptomatic response to the traditional dopaminergics or in patients with poor tolerance. Close selection and attention to patients need to be used to reduce undesirable effects and maximize therapeutic utility of these adjunctive drugs [115].

8.4 Deep Brain Stimulation (DBS)

DBS is already a standard surgical procedure used to treat advanced PD and especially those whose symptoms are characterized by motor variability, dyskinesias, or medication-resistant tremors. DBS entails the insertion of an electrode into certain areas of the brain, which is usually the subthalamic nucleus or the globus pallidus interna [116]. These electrodes provide high frequency electrical stimulation, which can alter abnormal neuronal activity that is linked with PD. The device is linked to a pulse generator that can be implanted under the skin in the chest and the stimulation can be set to programmable and adjustable levels. DBS does not stop the development of the disease but has a considerable positive impact on motor symptoms, decreases medicine use, and positively changes the quality of life of the competently chosen patient. Patients who respond best to levodopa usually have disabling side effects or variability. Contraindications are cognitive decline, severe psychiatric symptoms or atypical PD. Even though DBS is considered to be safe, it can be said to have potential risks of infection, haemorrhage, and stimulation-related side effects like speech disturbance or balance issues [117]. The most important thing to maximize benefit is to use postoperative programming and long-term follow-up. DBS is a significant innovation in the neurosurgical treatment of PD, which is associated with a long-term reduction of symptoms in case of decreased efficacy of pharmacological options [118].

8.5 Lesioning Techniques

Pallidotomy and thalamotomy are lesioning procedures that were once among the earliest surgical interventions in treatment of PD, even prior to the DBS [119]. Such surgeries target the generation of lesions in particular brain areas, most commonly the globus pallidus interna of the pallidotomy surgery or the ventral intermediate nucleus of the thalamus of the thalamotomy surgery to disconnect abnormal brain circuits causing PD. Pallidotomy may be useful in the treatment of dyskinesias and motor fluctuation whereas thalamotomy is most useful in the treatment of tremor. The procedures of lesioning are mostly irreversible and their results very much depend on accurate targeting and surgical skills. The lesioning process is also not associated with the need to implant hardware or long-term maintenance of the device as compared to DBS, which can be of benefit in resource-constrained environments or patients ineligible to receive DBS [120]. But there is a risk of speech difficulties, cognitive impairment or weakness in case of incidental involvement of adjacent brain structures. Over the last few years, there has been a renewed interest in lesioning methods and non-invasive methods of lesion creation, such as focused ultrasound thalamotomy, where surgical injuries are not needed to create lesions. Although lesioning is not employed as frequently as DBS, lesioning is a feasible treatment option within certain clinical situations, particularly when the cost, comorbidities, or preference of the patient restrict the application of more complicated therapies [121].

8.6 Physiotherapy and Occupational Therapy

Physiotherapy and occupational therapy are an inseparable part of the overall management of PD, and is ~~are~~ intended to maintain mobility, independence and quality of life [122]. Physiotherapy aims at enhancing gait, balance, flexibility, strength and posture. The symptoms of frozen gait and reduced functional mobility can be reduced with the help of resistance training, treadmill exercises, and cueing strategies. Early intervention has been proved to prevent disability and a fall risk. In supplementing physiotherapy, occupational therapy assists patients to remain independent in the day-to-day activities including dressing, cooking and personal hygiene. Therapists can suggest assistive equipment, home adaptations and energy conservation and hand function maximization. In the course of PD, fine motor and coordination problems, and task sequencing can be problematic, Occupational therapy offers remedies to these issues by considering adaptive solutions and environmental modifications. Both treatments are highly personalized considering the stage of the disease, goals of the patient, and mental ability. They do not alter the course of the disease, but these treatments are the things that improve day-to-day functioning and psychological well-being considerably. Physiotherapy/occupational therapy should be incorporated into the regular care process and multidisciplinary rehabilitation practices are viewed as a necessity to comprehensive PD treatment [123].

8.7 Speech Therapy

Speech therapy, mainly by the speech-language pathologists, is an important part of managing the PD, because as many as 90 percent of the patients develop speech and swallowing problems. Hypokinetic dysarthria, with poor vocal volume, monotone intonation, inaccurate articulation, and a breathy voice, is the most frequent speech difficulty with PD [124]. These are quite serious problems enhancing communication and socialization. Aspiration pneumonia, malnutrition and choking may happen due to swallowing impairments (dysphagia). Speech therapy interventions are designed to enhance vocal strength, vocal clarity and control over the respiratory system. The Lee Silverman Voice Treatment (LSVT LOUD) is one exercise method based on increasing vocal intensity and enhancing speech intelligibility, achieved by using structured and high-intensity vocal exercises with high intensity [125]. In the case of dysphagia, the therapists evaluate

the swallowing capabilities and prescribe diet and exercise changes, posture, and exercises that result in safety and efficiency. Complications can be avoided by early referral to speech therapy and preserve communication abilities. Notably, the therapy plans depend on the needs of the patient and the level of the disease, and the periodic re-examination is critical because the symptoms change. Although speech therapy does not change the disease process, it has a significant positive effect on quality of life, social life, and overall health outcomes of PD patients.

8.8 Nutritional and Lifestyle Interventions

Nutritional and lifestyle interventions have been increasingly considered as a significant component of holistic care in PD, as an addition to medical treatment and surgery [126]. Nutrition is important in the management of non-motor and motor symptoms. Plentiful antioxidants, fiber and omega diet. Fatty acids can promote general brain health, lessen constipation, and be used to regulate weight gains and losses. There is some evidence that the Mediterranean or plant-based diets might also have neuroprotective action. The timing of protein consumption is also a key factor, because protein-containing foodstuffs can negatively interfere with absorption of levodopa, and timing of protein-rich meals in relation to drug intake can maximize drug effect. Hydration is required to avoid orthostatic hypotension and constipation- a frequent complication in PD. Motor functioning, and balance as well as mood and perhaps deceleration of disease progression have been found to be improved by lifestyle changes such as regular aerobic exercise. Walking, swimming, tai chi and yoga also help to increase flexibility and decrease the risk of falls. Mental health and cognitive functioning are crucial to adequate sleep hygiene, reducing stress, and engaging socially. Critically, the interventions are supposed to be based on the preferences and physical abilities. Dietitian, therapist, and support group education and support enables the patient to become more actively involved in his or her care, which promotes long-term lifestyle changes and resilience [127].

9. Emerging and Future Therapies

9.1 Gene Therapy Strategies

Gene therapy is one of the future directions in treating neurodegenerative and genetic diseases and is intended to redress, or replace defective genes that cause the disease [128]. Gene therapy approaches are used in neuromuscular disorders, including in neuromuscular dystrophy and various types of muscular dystrophy, and in the treatment of neuromuscular diseases like PD, Huntington disease and muscular dystrophy. Such vectors can directly insert therapeutic genes into target areas of the brain or into muscle tissue to repair normal activity or prevent the progression of a disease. Other methods like *CRISPR-Cas9* gene editing have the potential to be used to correct precisely the genes and in particular cases of monogenic disorders. Among them is the Adeno Associated Virus mediated gene replacement therapy of spinal muscular atrophy (SMA), which has shown much clinical efficacy [129]. The obstacles still exist, such as immunological reactions against viral vectors, off-target effects, and the lack of effective delivery of genes across the blood-brain barrier. However, innovations in vectors design, targeted delivery and regulation management are slowly surpassing such challenges. It is possible to develop individualized gene therapy options based on the genetic mutations and disease phenotypes of the individual in future. Due to the evolution of research, gene therapy can revolutionize the approach to the treatment of incurable or progressive debilitating disorders [130].

9.2 Stem Cell-Based Therapies

The regeneration of damaged tissue and restoration of lost functions in neurodegenerative diseases and spinal cord trauma, and other central nervous system diseases, has spectacular potential in stem cell-based therapies [131]. Such therapies use the pluripotent stem cells (PSCs), the embryonic stem cells (ESCs), or the iPSCs. These cells have the ability to differentiate into various neural cell types, including neurons, astrocytes, and oligodendrocytes.The transplantation of the neural stem cells to the affected brain or spinal areas is one of the most potential solutions as it may restore lost cells and help the regeneration process. In the case of PD, e.g., dopaminergic neurons induced by stem cells are being examined as an option to restore the production of dopamine and enhance motor activity. Also, neurotrophic secretions by the stem cells aid in the survival and repair of the already existing neurons which is two-fold therapy benefit. There are ongoing clinical trials across the safety, efficacy and incorporation of the cells transplanted into the case tissue. Nevertheless, there is the risk of immune rejection, tumor formation, and ethical issues around embryonic sources that should be dealt with. The developments of reprogramming of somatic cells to iPSCs present a less controversial and more patient-specific alternative, reducing the chances of rejection. In sum, stem cell-based treatments are directed to a paradigm shift in regenerative medicine, and they could allow curing incurable neurodegenerative disorders in the long term [132].

9.3 Anti-aggregation Therapies and Immunotherapy

The recent developments of immunotherapy and anti-aggregation regimens are becoming central to the treatment of protein misfolding and aggregation-related diseases Alzheimer disease, PD, and Huntington disease [133]. They are commonly associated with the build-up of poisonous protein aggregates, such as the amyloid-beta plaques in Alzheimer’s or alpha-synuclein in Parkinson, which causes dysfunction and death of neurons. Immunotherapy aims at

attacking these aggregates with monoclonal antibodies that are capable of identifying and fostering the excretion of pathological proteins. An anti-amyloid antibody, aducanumab, has been approved in Alzheimer, but the clinical benefits of the therapy are controversial. Small molecules which inhibit the misfolding or aggregation of such proteins are also anti-aggregation therapies that are intended to stop the disease process at an early stage. Passive (with help of administered antibodies) and active immunization (enhancing the immune system of the body to produce antibodies) is being studied. The second method is to increase the cell own proteostasis, e.g., autophagy or ubiquitin-proteasome system, to promote aggregate clearance. Although encouraging, these therapeutic approaches have to surmount such obstacles as the inability to cross the blood-brain barrier and prevent undesirable immune responses. With the increasing knowledge of disease-specific protein pathologies, immunotherapy and anti-aggregation treatments are also the ray of hope to modify the disease, and not the management of symptoms [134].

9.4 RNA-Based Therapeutics

RNA-based therapeutics, such as small interfering RNA (siRNA) and antisense oligonucleotides (ASOs) are a novel category of therapeutics, which interact with gene expression on the RNA level [135]. Such approaches have been especially useful in the targeting of undruggable genes in neurodegenerative and genetic diseases, in which case, she guides the RNA-induced silencing complex (RISC) to degrade certain messenger RNAs (mRNAs), thereby inhibiting the synthesis of toxic proteins. ASOs on the other hand attach to mRNA sequences and prevent translation, modify splicing, or degrade them. Nusinersen, an ASO to treat spinal muscular atrophy (SMA), is a landmark product that increases survival and motor outcome by regulating SMN2 gene splicing. Huntington disease, amyotrophic lateral sclerosis (ALS) and Alzheimer disease are other diseases under RNA therapeutics investigation. The specificity is high hence they can be targeted accurately limiting off-target effects which are prevalent with traditional drugs. Delivery is however a major challenge particularly delivery to neurons of the central nervous system. Such techniques as intrathecal injection and nanoparticle-based carriers are being developed to deal with this. With ongoing development of RNA biology, RNA-based treatments may make possible customizable therapeutic approaches to a broad variety of genetic and neurodegenerative diseases, potentially modifying disease pathogenesis at their molecular basis [136].

9.5 Neuroprotective / Disease-Modifying Agents

Neuroprotective and disease-modifying therapeutic agents are designed to maintain neuronal functioning, preventive and treat the etiological basis of neurodegenerative diseases instead of only of ameliorating symptoms [137]. These agents act via attacking pathological processes including the oxidative stress, mitochondrial dysfunction, excitotoxicity, neuroinflammation, and protein aggregation. In the case of antioxidants and mitochondrial stabilizers, the substances would help lessen cell injury in diseases such as Parkinson and ALS. Drugs that suppress inflammatory response in the brain are in development thus becoming anti-inflammatory drugs since the brain immune response is becoming a key contributor of neurodegeneration. Disease-modifying therapies (DMTs) such as interferons and monoclonal antibodies have proven to be effective in the prevention of the disease progression by lowering relapse rates and inflammatory lesions in multiple sclerosis. On the same note, new players in the Alzheimer and PD want to preserve neuronal functions by regulating neurotransmitter systems, Ca+ homeostasis or neurotrophic signalling [138]. Although the existing neuroprotective measures usually have small clinical value, the combination of the biomarker to diagnose the disease early and stratify the patient is enhancing the treatment response. Integration therapies which tackle a range of pathogenic pathways are also under investigation so as to increase efficacy. With the further development of research, neuroprotective and disease-modifying drugs may change the therapeutic paradigm to an early intervention that may stop or even reverse the neurological disease progression [139].

10. Bench to Bedside: Translational Challenges

10.1 Clinical Research to Preclinical

One of the major challenges in translational medicine is bridging the gap between preclinical findings and successful clinical implementation [140]. Although preclinical studies using cell cultures and animal models provide valuable insights into disease mechanisms and potential therapeutic strategies, these findings often fail to accurately predict clinical outcomes in humans. This disparity is largely attributed to biological differences between experimental models and humans, including variations in genetics, metabolism, and immune responses.

Furthermore, many models of neurodegenerative diseases do not fully replicate the complex pathology and progressive nature observed in human patients, which may result in false-positive therapeutic outcomes during preclinical evaluation. Additional limitations such as inconsistencies in experimental design, lack of reproducibility, and publication bias can further compromise the reliability of preclinical data and negatively influence clinical trial development.

To improve translational success, increasing attention is being directed toward the development of more predictive experimental systems, including human-derived organoids and genetically engineered animal models that more closely resemble human disease conditions [141]. Standardization of experimental protocols, improved data transparency, and collaborative research consortia are also essential for aligning preclinical findings with clinical expectations. In addition,

the incorporation of biomarkers and early-stage human studies, such as Phase 0 clinical trials, may facilitate target validation and reduce the risk of failure in subsequent clinical trials.

Ultimately, an interdisciplinary approach integrating basic science, clinical expertise, and patient-derived data is essential for bridging the gap between bench and bedside. Addressing these translational challenges will accelerate the development of safe and effective therapies and enhance the successful translation of laboratory discoveries into meaningful clinical benefits for patients [142].

10.2 Genetic and Cell-Based Therapy Ethical Table

Genetic and cell-based therapies offer unprecedented potential for the treatment of previously incurable diseases; however, they also raise complex ethical concerns [143]. One of the major ethical challenges involves genetic manipulation, particularly germline gene editing, which may have heritable consequences affecting future generations and broader societal implications. Although current clinical applications primarily focus on somatic gene therapies, concerns regarding off-target effects, long-term safety, and unintended biological consequences remain significant.

Obtaining informed consent may also be challenging, especially in pediatric patients or individuals with impaired cognitive capacity, where legal guardians are required to make decisions regarding potentially permanent interventions. In addition, stem cell-based therapies, particularly those involving ESCs, continue to generate ethical debate regarding embryo use and the sourcing of biological materials. Even with iPSCs, important issues related to donor consent, privacy, ownership, and commercialization of cell lines must be carefully addressed [144].

Furthermore, the high cost and limited accessibility of advanced genetic and cellular therapies raise concerns regarding healthcare equity and social justice. Unequal access to these treatments may further widen existing healthcare disparities by restricting availability to financially privileged populations. Consequently, ethical and regulatory frameworks must evolve alongside technological advancements to ensure responsible innovation and patient protection.

Institutional review board (IRB) oversight, transparent public engagement, and adherence to international ethical guidelines established by organizations such as the World Health Organization and UNESCO are essential for safeguarding human dignity and maintaining public trust. Ethical dialogue involving patients, healthcare professionals, researchers, and communities is equally important for promoting socially responsible and inclusive development of transformative therapies [145].

10.3 Clinical Trial issues

There are regulatory and clinical trial barriers to the research-to-clinic translation of innovative therapies [146]. The conventional drug development models are not necessarily capable of assessing the safety and efficacy of complicated interventions like gene editing, stem cell interventions or tailored-made treatment. Such treatments can include the use of living cells, genetic material or customised manufacturing, necessitating specific regulatory pathways. An example is that gene therapies need to be stringently studied on off-target effects, immune reactions and long-term safety, which may require prolonged follow-up longer than a normal trial schedule. Moreover, rare or heterogeneous diseases do not possibly have large well-defined groups of patients that are suitable to design a trial, choose endpoint and have statistical power. There are growing efforts to address these limitations by developing adaptive trial designs and real-world evidence, which, however, yield novel methodological and regulatory uncertainties. Regulatory authorities such as the FDA and EMA are striving to modify their systems, providing expedited approval programs or labels such as Breakthrough Therapy to fast track development [147]. Nevertheless, these systems consume a lot of resources and regulatory knowledge, which is usually restrictive to a large institution or company. Consistency and quality control of manufacturing is also a key danger, particularly with cell-based products where the variability of a batch can influence outcomes. Popularity, global standardization and continuous surveillance of the market after sales is crucial to the safety of the patients and the trust of citizens. Finally, a compromise needs to be found to overcome regulatory and clinical trial obstacles; the need to promote innovation must not compromise human health and ethical integrity [148].

10.4 Patient-Centered Approaches

Patient-centred approaches are critical to realizing the translation of biomedical innovations in bench to bedside [149]. The strategies focus on values, needs and preferences of patients during the research, development and implementation. Conventionally, the patients were considered only as participants of trials or the recipients of care, but according to the current translational studies, their active role as partners is welcomed. This incorporates the co-design of clinical trials, input in the decision on endpoints, which are of greatest importance to quality of life, and the input of the real-world disease burden and treatment expectations. Early involvement would enhance the relevance, recruitment, and adherence of patients and consequently increase the effectiveness of a clinical trial. Moreover, patient-reported outcomes (PROs) are becoming a part of trial metrics to reflect meaningful benefit not measured by biological or clinical outcomes [150]. In a precision medicine world, the customization of treatments according to genetic, lifestyle and psychosocial variables must be highly engaged with a variety of patients to be inclusive and equitable. Digital health technology, wearable devices and telemedicine application also enable patients to take a more active role in their treatment and data gathering. Still, there are difficulties, such as the need to guarantee knowledgeable involvement, overcome digital divides, and

secure information privacy. Nonetheless, the development of trust and transparency by means of constant communication can close these gaps. Not only do patient-centred approaches bring the scientific goals into conformity with the realities of the patients but also develop ethical and socially responsive avenues to innovation. With the development of translational science, the central role of the patient is no longer a choice, but its essential part of the effective and long-term improvement of healthcare [151].

11. Conclusion

PD is not considered as a movement disorder only but it is a complex system neurodegenerative disease. As symptomatic treatment, levodopa and DBS still one of the primary forms of care, they do not correct the pathogenic mechanisms. The critical importance of protein misfolding, mitochondrial is emphasized by recent research. Path physiology, oxidative stress, and neuroinflammation in the development of disease, and provides novel. therapeutic targets. Future progress in gene therapy, RNA-based solutions, immunotherapy's and stem cell models are promising but have considerable translational and regulatory challenges. Patient-centered approaches, development of biomarkers and early diagnosis are needed to facilitate the interventions between molecular findings and clinical practice. Finally, a precision medicine model involving multiple disciplines has the ability to change how PD is managed symptomatic to disease prevention and long-term prevention.

Acknowledgements

The authors would like to thank their respective institutions for providing the necessary facilities and academic support to complete this review. The authors also express their sincere gratitude to all researchers whose published work contributed to the preparation of this manuscript.

Ethics Statement

This article is a review based exclusively on previously published literature and does not involve any studies with human participants or animals performed by the authors. Therefore, ethical approval and informed consent were not required.

Data Availability Statement

No new datasets were generated or analyzed during the preparation of this review article. All information included in this manuscript is derived from published literature, and the corresponding references are provided within the article.

Author Contributions

Conceptualization: Jeewanjot Singh, Prabhjot Singh, and Shafkat Hussain; Literature search and data curation: Jeewanjot Singh and Subhi Sharma; Writing–original draft preparation: Jeewanjot Singh; Writing–review and editing: All authors. All authors have read and approved the final manuscript.

Conflict of Interest

The authors declare that they have no known competing financial interests or personal relationships that could have influenced the work reported in this manuscript.

Generative AI Statement

The authors used generative artificial intelligence (AI) tools solely to assist with language refinement and improve the readability of the manuscript. All scientific content, interpretation of the literature, critical analysis, and final responsibility for the manuscript remain entirely with the authors. The authors carefully reviewed and verified the accuracy of all AI-assisted content before submission.

Reference

[1] Church FC. Treatment options for motor and non-motor symptoms of Parkinson's disease. Biomolecules, 2021, 11(4), 612. DOI: 10.3390/biom11040612

[2] Pourzinal D, Brooks D, Sriram D, Mccann E, King JM, Pachana NA, et al. Best practice guidelines for the diagnosis, evaluation, and management of cognitive disorders in Parkinson's disease. Age Ageing, 2026, 55(3), afag063. DOI: 10.1093/ageing/afag063

[3] Singh J, Singh P. *In silico* evaluation of elaeocarpus serratus bioactive compounds for parkinson's disease: Network analysis and quercetin docking. International Journal of Research Publication and Reviewsv, 2025, 6(11): 4968-4987. DOI: 10.55248/GENGPI.06.1125.38174

[4] Ogunjobi TT, Gbayisomore TJ, Nneji PO, Olofin OO, Olowe EN, Gigam-Ozuzu CD, et al. Environmental epigenetics and its impacts on disease susceptibility: A comprehensive review. Medinformatics, 2024. DOI: 10.47852/bonviewMEDIN42022945
[5] Su D, Cui Y, He C, Yin P, Bai R, Zhu J, et al. Projections for prevalence of Parkinson's disease and its driving factors in 195 countries and territories to 2050: Modelling study of Global Burden of Disease Study 2021. BMJ, 2025, 388, e080952. DOI: 10.1136/bmj-2024-080952
[6] Zhang J, Fan Y, Liang H, Zhang Y. Global, regional and national temporal trends in Parkinson's disease incidence, disability-adjusted life year rates in middle-aged and older adults: A cross-national inequality analysis and bayesian age-period-cohort analysis based on the global burden of disease 2021. Neurological Sciences, 2025, 46(4), 1647-1660. DOI: 10.1007/s10072-024-07941-7
[7] Albin RL. Parkinson disease. Oxford University Press, 2022. DOI: 10.1093/med/9780190843014.001.0001
[8] Walusinski O. Jean-Martin Charcot (1825-1893). In Oxford Research Encyclopedia of Neuroscience. DOI: 10.1093/acrefore/9780190264086.013.546
[9] Gouda NA, Elkamhawy A, Cho J. Emerging therapeutic strategies for Parkinson's disease and future prospects: A 2021 update. Biomedicines, 2022, 10(2), 371. DOI: 10.3390/biomedicines10020371
[10] Picca A, Guerra F, Calvani R, Romano R, Coelho-Júnior HJ, Bucci C, et al. Mitochondrial dysfunction, protein misfolding and neuroinflammation in Parkinson's disease: Roads to biomarker discovery. Biomolecules, 2021, 11(10), 1508. DOI: 10.3390/biom11101508
[11] Meganck RM, Baric RS. Developing therapeutic approaches for twenty-first-century emerging infectious viral diseases. Nature Medicine, 2021, 27(3), 401-410. DOI: 10.1038/s41591-021-01282-0
[12] Pandey SK, Singh RK. Recent developments in nucleic acid-based therapies for Parkinson's disease: Current status, clinical potential, and future strategies. Frontiers in Pharmacology, 2022, 13, 986668. DOI: 10.3389/fphar.2022.986668
[13] Muleiro Alvarez M, Cano-Herrera G, Osorio Martínez MF, Vega Gonzales-Portillo J, Monroy GR, Murguiondo Pérez R, et al. A comprehensive approach to parkinson's disease: Addressing its molecular, clinical, and therapeutic aspects. International Journal of Molecular Sciences, 2024, 25(13), 7183. DOI: 10.3390/ijms25137183
[14] Dong-Chen X, Yong C, Yang X, Chen-Yu S, Li-Hua P. Signaling pathways in Parkinson's disease: Molecular mechanisms and therapeutic interventions. Signal Transduction and Targeted Therapy, 2023, 8(1), 73. DOI: 10.1038/s41392-023-01353-3
[15] Clarkin CM, Smith DG, McGough EL, Mahler LA. Centering the person in development of a model of care for people with Parkinson's disease: A qualitative study. Disability and Rehabilitation, 2025, 47(8), 1976-1987. DOI: 10.1080/09638288.2024.2387689
[16] Jankovic J, Lang AE. Diagnosis and assessment of Parkinson disease and other movement disorders. Bradley's Neurology in Clinical Practice E-Book, 2021, 24, 310-333.
[17] Bologna M, Espay AJ, Fasano A, Paparella G, Hallett M, Berardelli A. Redefining bradykinesia. Movement disorders: Official Journal of the Movement Disorder Society, 2023, 38(4), 551. DOI: 10.1002/mds.29362
[18] Ganguly J, Kulshreshtha D, Almotiri M, Jog M. Muscle tone physiology and abnormalities. Toxins, 2021, 13(4), 282. DOI: 10.3390/toxins13040282
[19] Blesa J, Foffani G, Dehay B, Bezard E, Obeso JA. Motor and non-motor circuit disturbances in early Parkinson disease: Which happens first? Nature Reviews Neuroscience, 2022, 23(2), 115-128. DOI: 10.1038/s41583-021-00542-9
[20] Jankovic J, Hallett M, Okun MS, Comella CL, Fahn S. Principles and practice of movement disorders E-book. Elsevier Health Sciences, 2021.
[21] Rinaldi D. Motor and non-motor symptoms in advanced Parkinson's disease: current insights and future directions. 2025.
[22] Lubomski M, Davis RL, Sue CM. Cognitive influences in Parkinson's disease patients and their caregivers: Perspectives from an australian cohort. Frontiers in Neurology, 2021, 12, 673816. DOI: 10.3389/fneur.2021.673816
[23] Antelmi E, Lippolis M, Biscarini F, Tinazzi M, Plazzi G. REM sleep behavior disorder: Mimics and variants. Sleep Medicine Reviews, 2021, 60, 101515. DOI: 10.1016/j.smrv.2021.101515
[24] Mather M. Autonomic dysfunction in neurodegenerative disease. Nature Reviews Neuroscience, 2025, 26(5), 276-292. DOI: 10.1038/s41583-025-00911-8
[25] Harsh S, Rather HJ, Dwivedi A, Bala S, Velladurai P, Anantharaman S. The neuropsychology of chronic neurological disorders: A review of cognitive and emotional impairments. Cureus, 2025, 17(10), e93642. DOI: 10.7759/cureus.93642
[26] Singh J. Parkinson's disease: Pathophysiology, current treatments, and future therapeutic approaches. RMC Global Journal, 2026, 2, 1-7. DOI: 10.25259/RMCGJ_9_2025
[27] Chahine LM, Merchant K, Siderowf A, Sherer T, Tanner C, Marek K, et al. Proposal for a biologic staging system of Parkinson's disease. Journal of Parkinson's Disease, 2023, 13(3), 297-309. DOI: 10.3233/JPD-225111
[28] Bouça-Machado R. Functional mobility in Parkinson's disease. Universidade de Lisboa (Portugal), 2021.
[29] Tofaris GK. Initiation and progression of α-synuclein pathology in Parkinson's disease. Cellular and Molecular Life Sciences, 2022, 79(4), 210. DOI: 10.1007/s00018-022-04240-2
[30] Kumar S, Rani S, Sharma S, Min H. Multimodality fusion aspects of medical diagnosis: A comprehensive review. Bioengineering, 2024, 11(12), 1233. DOI: 10.3390/bioengineering11121233
[31] Coughlin DG, Dickson DW, Josephs KA, Litvan I. Progressive supranuclear palsy and corticobasal degeneration. In Frontotemporal Dementias: Emerging Milestones of the 21st Century. Cham: Springer International Publishing, 2021, 151-176.
[32] Pitton Rissardo J, Caprara ALF. Neuroimaging techniques in differentiating parkinson's disease from drug-induced parkinsonism: A comprehensive review. Clinics and Practice, 2023, 13(6), 1427-1448. DOI: 10.3390/clinpract13060128
[33] Guatteo E, Berretta N, Monda V, Ledonne A, Mercuri NB. Pathophysiological features of nigral dopaminergic neurons in animal models of Parkinson's disease. International Journal of Molecular Sciences, 2022, 23(9), 4508. DOI: 10.3390/ijms23094508
[34] Jiang Y, Qi Z, Zhu H, Shen K, Liu R, Fang C, et al. Role of the globus pallidus in motor and non-motor symptoms of Parkinson's disease. Neural Regeneration Research, 2025, 20(6), 1628-1643. DOI: 10.4103/NRR.NRR-D-23-01660
[35] Gonzalez-Robles C, Bandmann O, Schapira AHV. Neuroprotection in Parkinson disease. Neurology and Therapy, 2025, 14(5), 1747-1767. DOI: 10.1007/s40120-025-00793-z
[36] Ghiglieri V, Calabrese V, Calabresi P. Alpha-synuclein: From early synaptic dysfunction to neurodegeneration. Frontiers in Neurology, 2018, 9, 295. DOI: 10.3389/fneur.2018.00295

[37] Borghammer P. The α-synuclein origin and connectome model (SOC model) of Parkinson's disease: Explaining motor asymmetry, non-motor phenotypes, and cognitive decline. Journal of Parkinson's Disease, 2021, 11(2), 455-474. DOI: 10.3233/JPD-202481
[38] Chmielarz P, Domanskyi A. Alpha-synuclein preformed fibrils: A tool to understand Parkinson's disease and develop disease modifying therapy. Neural Regeneration Research, 2021, 16(11), 2219-2221. DOI: 10.4103/1673-5374.310686
[39] Harackiewicz O, Grembecka B. The role of microglia and astrocytes in the pathomechanism of neuroinflammation in Parkinson's disease-focus on alpha-synuclein. Journal of Integrative Neuroscience, 2024, 23(11), 203. DOI: 10.31083/j.jin2311203
[40] Huang X, Hussain B, Chang J. Peripheral inflammation and blood-brain barrier disruption: Effects and mechanisms. CNS Neuroscience & Therapeutics, 2021, 27(1), 36-47. DOI: 10.1111/cns.13569
[41] Hanna L, Poluyi E, Ikwuegbuenyi C, Morgan E, Imaguezegie G. Peripheral inflammation and neurodegeneration; a potential for therapeutic intervention in Alzheimer's disease (AD), Parkinson's disease (PD) and amyotrophic lateral sclerosis (ALS). Egyptian Journal of Neurosurgery, 2022, 37(1), 15. DOI: 10.1186/s41984-022-00150-4
[42] Henrich MT, Oertel WH, Surmeier DJ, Geibl FF. Mitochondrial dysfunction in Parkinson's disease–a key disease hallmark with therapeutic potential. Molecular Neurodegeneration, 2023, 18(1), 83. DOI: 10.1186/s13024-023-00676-7
[43] Imberechts D, Kinnart I, Wauters F, Terbeek J, Manders L, Wierda K, et al. DJ-1 is an essential downstream mediator in PINK1/parkin-dependent mitophagy. Brain, 2022, 145(12), 4368-4384. DOI: 10.1093/brain/awac313
[44] Kim TY, Lee BD. Current therapeutic strategies in Parkinson's disease: Future perspectives. Molecules and Cells, 2025, 48(11), 100274. DOI: 10.1016/j.mocell.2025.100274
[45] Chen Y, Luo X, Yin Y, Thomas ER, Liu K, Wang W, et al. The interplay of iron, oxidative stress, and α-synuclein in Parkinson's disease progression. Molecular Medicine, 2025, 31(1), 154. DOI: 10.1186/s10020-025-01208-3
[46] Singh J, Kumar D, Kaur J, et al. The rhythm of decline: Circadian disruption in neurodegeneration. Journal of Food and Drug Analysis, 2025, 33(3), 224-240. DOI: 10.38212/2224-6614.3553
[47] Luo S, Wang D, Zhang Z. Post-translational modification and mitochondrial function in Parkinson's disease. Frontiers in Molecular Neuroscience, 2024, 16, 1329554. DOI: 10.3389/fnmol.2023.1329554
[48] Prajjwal P, Flores Sanga HS, Acharya K, Tango T, John J, Rodriguez RSC, et al. Parkinson's disease updates: Addressing the pathophysiology, risk factors, genetics, diagnosis, along with the medical and surgical treatment. Annals of Medicine and Surgery, 2023, 85(10), 4887-4902. DOI: 10.1097/MS9.0000000000001142
[49] Masaldan S, Callegari S, Dewson G. Therapeutic targeting of mitophagy in Parkinson's disease. Biochemical Society Transactions, 2022, 50(2), 783-797. DOI: 10.1042/BST20211107
[50] Muse ED, Chen SF, Torkamani A. Monogenic and polygenic models of coronary artery disease. Current Cardiology Reports, 2021, 23(8), 107. DOI: 10.1007/s11886-021-01540-0
[51] Wang K, Liu H, Hu Q, Wang L, Liu J, Zheng Z, et al. Epigenetic regulation of aging: implications for interventions of aging and diseases. Signal Transduction and Targeted Therapy, 2022, 7(1), 374. DOI: 10.1038/s41392-022-01211-8
[52] Wu KM, Zhang Y, Wang TT, et al. Advancing disease-modifying therapies for Parkinson's disease: Current strategies and future directions. The Innovation, 2025. DOI: 10.1016/j.xinn.2025.101112
[53] Khan MS, Nasiripour S, Bopassa JC. Parkinson disease signaling pathways, molecular mechanisms, and potential therapeutic strategies: A comprehensive review. International Journal of Molecular Sciences, 2025, 26(13), 6416. DOI: 10.3390/ijms26136416
[54] Eldeeb MA, Thomas RA, Ragheb MA, Fallahi A, Fon EA. Mitochondrial quality control in health and in Parkinson's disease. Physiological Reviews, 2022, 102(4), 1721-1755. DOI: 10.1152/physrev.00041.2021
[55] Erskine D, Koss D, Korolchuk VI, Outeiro TF, Attems J, McKeith I. Lipids, lysosomes and mitochondria: insights into Lewy body formation from rare monogenic disorders. Acta Neuropathologica, 2021, 141(4), 511-526. DOI: 10.1007/s00401-021-02266-7
[56] Sharma M, Burré J. α-Synuclein in synaptic function and dysfunction. Trendsin Neurosciences, 2023, 46(2), 153-166. DOI: 10.1016/j.tins.2022.11.007
[57] Le Guerroué F, Youle RJ. Ubiquitin signaling in neurodegenerative diseases: An autophagy and proteasome perspective. Cell Death & Differentiation, 2021, 28(2), 439-454. DOI: 10.1038/s41418-020-00667-x
[58] Oliveira LMA, Gasser T, Edwards R, Zweckstetter M, Melki R, Stefanis L, et al. Alpha-synuclein research: defining strategic moves in the battle against Parkinson's disease. npj Parkinson's Disease, 2021, 7(1), 65. DOI: 10.1038/s41531-021-00203-9
[59] Ravinther AI, Dewadas HD, Tong SR, Foo CN, Lin YE, Chien CT, et al. Molecular pathways involved in lrrk2-linked parkinson's disease: A systematic review. International Journal of Molecular Sciences, 2022, 23(19), 11744. DOI: 10.3390/ijms231911744
[60] Usmani A, Shavarebi F, Hiniker A. The cell biology of LRRK2 in Parkinson's disease. Molecular and Cellular Biology, 2021, 41(5), e00660-20. DOI: 10.1128/MCB.00660-20
[61] Müller-Rischart AK, Pilsl A, Beaudette P, Patra M, Hadian K, Funke M, et al. The E3 ligase parkin maintains mitochondrial integrity by increasing linear ubiquitination of NEMO. Molecular Cell, 2013, 49(5), 908-921. DOI: 10.1016/j.molcel.2013.01.036
[62] Iorio R, Celenza G, Petricca S. Mitophagy: Molecular mechanisms, new concepts on parkin activation and the emerging role of AMPK/ULK1 axis. Cells, 2021, 11(1), 30. DOI: 10.3390/cells11010030
[63] Borsche M, Pereira SL, Klein C, Grünewald A. Mitochondria and Parkinson's disease: Clinical, molecular, and translational aspects. Journal of Parkinson's Disease, 2021, 11(1), 45-60. DOI: 10.3233/JPD-201981
[64] Olszewska DA, McCarthy A, Soto-Beasley AI, Walton RL, Ross OA, Lynch T. PARKIN, PINK1, and DJ1 analysis in early-onset Parkinson's disease in Ireland. Irish Journal of Medical Science, 2022, 191(2), 901-907. DOI: 10.1007/s11845-021-02563-w
[65] Vizziello M, Borellini L, Franco G, Ardolino G. Disruption of mitochondrial homeostasis: The role of PINK1 in Parkinson's disease. Cells, 2021, 10(11), 3022. DOI: 10.3390/cells10113022
[66] Xiao B, Kuruvilla J, Tan EK. Mitophagy and reactive oxygen species interplay in Parkinson's disease. npj Parkinson's Disease, 2022, 8(1), 135. DOI: 10.1038/s41531-022-00402-y

[67] Kumar L, Malhotra M, Singh AP, Singh AP. Comprehensive review on Parkinson's disease: insights into prevalence, pathophysiology, diagnosis, and multifaceted treatment approaches. Journal of Drug Delivery & Therapeutics, 2024, 14(6), 200-213. DOI: 10.22270/jddt.v14i6.6637
[68] Sahoo S, Padhy AA, Kumari V, Mishra P. Role of ubiquitin-proteasome and autophagy-lysosome pathways in α-synuclein aggregate clearance. Molecular Neurobiology, 2022, 59(9), 5379-5407. DOI: 10.1007/s12035-022-02897-1
[69] Chen R, Duffy Á, Do R. Genomics of drug target prioritization for complex diseases. Nature Reviews Genetics, 2026, 27(3), 231-245. DOI: 10.1038/s41576-025-00904-4
[70] Calabresi P, Di Lazzaro G, Marino G, Campanelli F, Ghiglieri V. Advances in understanding the function of alpha-synuclein: implications for Parkinson's disease. Brain, 2023, 146(9), 3587-3597. DOI: 10.1093/brain/awad150
[71] Singh J, Kumar D. *In vivo* and *in vitro* perspectives in Parkinson's disease: Mechanisms and the role of phytomedicine. Journal of Food and Drug Analysis, 2025, 33(3), 193. DOI: 10.38212/2224-6614.3557
[72] Jan A, Gonçalves NP, Vaegter CB, Jensen PH, Ferreira N. The prion-like spreading of alpha-synuclein in Parkinson's disease: Update on models and hypotheses. International Journal of Molecular Sciences, 2021, 22(15), 8338. DOI: 10.3390/ijms22158338
[73] Vidović M, Rikalovic MG. Alpha-synuclein aggregation pathway in Parkinson's disease: Current status and novel therapeutic approaches. Cells, 2022, 11(11), 1732. DOI: 10.3390/cells11111732
[74] Dolgacheva LP, Zinchenko VP, Goncharov NV. Molecular and cellular interactions in pathogenesis of sporadic Parkinson disease. International Journal of Molecular Sciences, 2022, 23(21), 13043. DOI: 10.3390/ijms232113043
[75] Ni A, Ernst C. Evidence that substantia nigra pars compacta dopaminergic neurons are selectively vulnerable to oxidative stress because they are highly metabolically active. Frontiers in Cellular Neuroscience, 2022, 16, 826193. DOI: 10.3389/fncel.2022.826193.
[76] Malpartida AB, Williamson M, Narendra DP, Wade-Martins R, Ryan BJ. Mitochondrial dysfunction and mitophagy in Parkinson's disease: From mechanism to therapy. Trends in Biochemical Sciences, 2021, 46(4), 329-343. DOI: 10.1016/j.tibs.2020.11.007
[77] Calabresi P, Mechelli A, Natale G, Volpicelli-Daley L, Di Lazzaro G, Ghiglieri V. Alpha-synuclein in Parkinson's disease and other synucleinopathies: From overt neurodegeneration back to early synaptic dysfunction. Cell Death & Disease, 2023, 14(3), 176. DOI: 10.1038/s41419-023-05672-9
[78] Prasuhn J, Davis RL, Kumar KR. Targeting mitochondrial Impairment in Parkinson's disease: challenges and opportunities. Frontiers in Cell and Developmental Biology, 2021, 8, 615461. DOI: 10.3389/fcell.2020.615461
[79] Li Y, Li S, Wu H. Ubiquitination-proteasome system (UPS) and autophagy two main protein degradation machineries in response to cell stress. Cells, 2022, 11(5), 851. DOI: 10.3390/cells11050851
[80] Smith L, Schapira AHV. GBA variants and parkinson disease: Mechanisms and treatments. Cells, 2022, 11(8), 1261. DOI: 10.3390/cells11081261
[81] Bi M, Du X, Jiao Q, Chen X, Jiang H. Expanding the role of proteasome homeostasis in Parkinson's disease: Beyond protein breakdown. Cell Death & Disease, 2021, 12(2), 154. DOI: 10.1038/s41419-021-03441-0
[82] Harms AS, Ferreira SA, Romero-Ramos M. Periphery and brain, innate and adaptive immunity in Parkinson's disease. Acta Neuropathologica, 2021, 141(4), 527-545. DOI: 10.1007/s00401-021-02268-5
[83] Passaro AP, Lebos AL, Yao Y, Stice SL. Immune response in neurological pathology: Emerging role of central and peripheral immune crosstalk. Frontiers in Immunology, 2021, 12, 676621. DOI: 10.3389/fimmu.2021.676621
[84] Weiner HL. Immune mechanisms and shared immune targets in neurodegenerative diseases. Nature Reviews Neurology, 2025, 21(2), 67-85. DOI: 10.1038/s41582-024-01046-7.
[85] Latif S, Jahangeer M, Razia DM, Ashiq M, Ghaffar A, Akram M, et al. Dopamine in Parkinson's disease. Clinica Chimica Acta, 2021, 522, 114-126.
[86] Srinivasan E, Chandrasekhar G, Chandrasekar P, Anbarasu K, Vickram AS. Karunakaran R, et al. Alpha-synuclein aggregation in Parkinson's disease. Frontiers in Medicine, 2021, 8, 736978. DOI: 10.3389/fmed.2021.736978
[87] Rasool A, Manzoor R, Ullah K, Afzal R, Ul-Haq A, Imran H, Kaleem I, et al. Oxidative stress and dopaminergic metabolism: A major PD pathogenic mechanism and basis of potential antioxidant therapies. CNS & Neurological Disorders-Drug Targets, 2024, 23(7), 852-864. DOI: 10.2174/1871527322666230609141519
[88] Rahman A. Positron-emission tomography (PET) and single-photon-emission computed tomography (SPECT) diagnosis of neurological disorders. Bangladesh Journal of Medicine, 2024, 36(1), 3-14. DOI: 10.3329/bjm.v36i1.78589
[89] Vijiaratnam N, Simuni T, Bandmann O, Morris HR, Foltynie T. Progress towards therapies for disease modification in Parkinson's disease. The Lancet Neurology, 2021, 20(7), 559-572. DOI: 10.1016/S1474-4422(21)00061-2
[90] Ma J, Tang Z, Wu Y, Zhang J, Wu Z, Huang L, et al. Differences in blood and cerebrospinal fluid between parkinson's disease and related diseases. Cellular and Molecular Neurobiology, 2024, 45(1), 9. DOI: 10.1007/s10571-024-01523-z
[91] Jia F, Fellner A, Kumar KR. Monogenic Parkinson's disease: Genotype, phenotype, pathophysiology, and genetic testing. Genes, 2022, 13(3), 471. DOI: 10.3390/genes13030471
[92] Dratch L, Azage M, Baldwin A, Johnson K, Paul RA, Bardakjian TM, et al. Genetic testing in adults with neurologic disorders: Indications, approach, and clinical impacts. Journal of Neurology, 2024, 271(2), 733-747. DOI: 10.1007/s00415-023-12058-6
[93] Cook L, Schulze J, Kopil C, Hastings T, Naito A, Wojcieszek J, et al. Genetic testing for Parkinson disease: Are we ready? Neurology: Clinical Practice, 2021, 11(1), 69-77. DOI: 10.1212/CPJ.0000000000000831
[94] Mitchell T, Lehéricy S, Chiu SY, Strafella AP, Stoessl AJ, Vaillancourt DE. Emerging neuroimaging biomarkers across disease stage in Parkinson disease: A review. JAMA Neurology, 2021, 78(10), 1262-1272. DOI: 10.1001/jamaneurol.2021.1312
[95] Hampel H, Shaw LM, Aisen P, Chen C, Lleó A, Iwatsubo T, et al. State-of-the-art of lumbar puncture and its place in the journey of patients with Alzheimer's disease. Alzheimer's & Dementia, 2022, 18(1), 159-177. DOI: 10.1002/alz.12372
[96] Berg D, Borghammer P, Fereshtehnejad SM, Heinzel S, Horsager J, Schaeffer E, et al. Prodromal Parkinson disease subtypes-key to understanding heterogeneity. Nature Reviews Neurology, 2021, 17(6), 349-361. DOI: 10.1038/s41582-021-00486-9
[97] Martinez TN, Greenamyre JT. Toxin models of mitochondrial dysfunction in Parkinson's disease. Antioxidants & Redox Signaling, 2012, 16(9), 920-934. DOI: 10.1089/ars.2011.4033
[98] Mustapha M, Mat Taib CN. MPTP-induced mouse model of Parkinson's disease: A promising direction of therapeutic strategies. Bosnian Journal of Basic Medical Sciences, 2021, 21(4), 422-433. DOI: 10.17305/bjbms.2020.5181

[99] Wang XL, Feng ST, Wang ZZ, Yuan YH, Chen NH, Zhang Y. Parkin, an E3 ubiquitin ligase, plays an essential role in mitochondrial quality control in Parkinson's disease. Cellular and Molecular Neurobiology, 2021, 41(7), 1395-1411. DOI: 10.1007/s10571-020-00914-2
[100] Dawson TM, Ko HS, Dawson VL. Genetic animal models of Parkinson's disease. Neuron, 2010, 66(5), 646-661. DOI: 10.1016/j.neuron.2010.04.034
[101] Coccia E, Ahfeldt T. Towards physiologically relevant human pluripotent stem cell (hPSC) models of Parkinson's disease. Stem Cell Research & Therapy, 2021, 12(1), 253. DOI: 10.1186/s13287-021-02326-5
[102] Spathopoulou A, Edenhofer F, Fellner L. Targeting α-synuclein in Parkinson's disease by induced pluripotent stem cell models. Frontiers in Neurology, 2022, 12, 786835. DOI: 10.3389/fneur.2021.786835
[103] Hager C, Jehanno C, Bentires-Alj M. Reactivation of multipotency in the mammary gland-a ripple in the pond and a turn of the tide. Journal of Mammary Gland Biology and Neoplasia, 2025, 30(1), 11. DOI: 10.1007/s10911-025-09586-4.
[104] Hermann DM, Bacigaluppi M, Bassetti CL, Bassotti G, Boltze J, Chan A, et al. Most prominent challenges in translational neuroscience and strategic solutions to bridge the gaps: Perspectives from an editorial board interrogation. Exploration of Neuroscience, 2025, 4, 1006106. DOI: 10.37349/en.2025.1006106
[105] Ke M, Chong CM, Zhu Q, Zhang K, Cai CZ, Lu JH, et al. Comprehensive perspectives on experimental models for Parkinson's disease. Aging and Disease, 2021, 12(1), 223-246. DOI: 10.14336/AD.2020.0331
[106] Imani Farahani N, Lin L, Nazir S, Naderi A, Rokos L, McIntosh AR, et al. Advances in physiological and clinical relevance of hiPSC-derived brain models for precision medicine pipelines. Frontiers in Cellular Neuroscience, 2025, 18, 1478572. DOI: 10.3389/fncel.2024.1478572
[107] McComish SF, MacMahon Copas AN, Caldwell MA. Human brain-based models provide a powerful tool for the advancement of Parkinson's disease research and therapeutic development. Frontiers in Neuroscience, 2022, 16, 851058. DOI: 10.3389/fnins.2022.851058
[108] di Biase L, Pecoraro PM, Carbone SP, Caminiti ML, Di Lazzaro V. Levodopa-induced dyskinesias in Parkinson's disease: An overview on pathophysiology, clinical manifestations, therapy management strategies and future directions. Journal of Clinical Medicine, 2023, 12(13), 4427. DOI: 10.3390/jcm12134427
[109] Lees A, Tolosa E, Stocchi F, Ferreira JJ, Rascol O, Antonini A, et al. Optimizing levodopa therapy, when and how? Perspectives on the importance of delivery and the potential for an early combination approach. Expert Review of Neurotherapeutics, 2023, 23(1), 15-24. DOI: 10.1080/14737175.2023.2176220
[110] Stocchi F, Bravi D, Emmi A, Antonini A. Parkinson disease therapy: Current strategies and future research priorities. Nature Reviews Neurology, 2024, 20(12), 695-707. DOI: 10.1038/s41582-024-01034-x
[111] Gray R, Patel S, Ives N, Rick C, Woolley R, Muzerengi S, et al. Long-term effectiveness of adjuvant treatment with catechol-o-methyltransferase or monoamine oxidase b inhibitors compared with dopamine agonists among patients with Parkinson disease uncontrolled by levodopa therapy: The PD MED randomized clinical trial. JAMA Neurology, 2022, 79(2), 131-140. DOI: 10.1001/jamaneurol.2021.4736
[112] Jenner P, Rocha JF, Ferreira JJ, Rascol O, Soares-da-Silva P. Redefining the strategy for the use of COMT inhibitors in Parkinson's disease: The role of opicapone. Expert Review of Neurotherapeutics, 2021, 21(9), 1019-1033. DOI: 10.1080/14737175.2021.1968298
[113] Rascol O, Fabbri M, Poewe W. Amantadine in the treatment of Parkinson's disease and other movement disorders. The Lancet Neurology, 2021, 20(12), 1048-1056. DOI: 10.1016/S1474-4422(21)00249-0
[114] Bandopadhyay R, Mishra N, Rana R, Kaur G, Ghoneim MM, Alshehri S, et al. Molecular mechanisms and therapeutic strategies for levodopa-induced dyskinesia in parkinson's disease: A perspective through preclinical and clinical evidence. Frontiers in Pharmacology, 2022, 13, 805388. DOI: 10.3389/fphar.2022.805388
[115] Carreño M, Gil-Nagel A, Serratosa JM, Toledo M, Rodriguez-Uranga JJ, Villanueva V. Spanish consensus on the management of concomitant antiseizure medications when using cenobamate in adults with drug-resistant focal seizures. Epilepsia Open, 2024, 9(3), 1051-1058. DOI: 10.1002/epi4.12936
[116] Starr PA. Placement of deep brain stimulators into the subthalamic nucleus or Globus pallidus internus: technical approach. Stereotactic and Functional Neurosurgery, 2002, 79(3-4), 118-145. DOI: 10.1159/000070828
[117] Patel DM, Walker HC, Brooks R, Omar N, Ditty B, Guthrie BL. Adverse events associated with deep brain stimulation for movement disorders: Analysis of 510 consecutive cases. Operative Neurosurgery, 2015, 11 (1), 190-199. DOI: 10.1227/NEU.0000000000000659
[118] Limousin P, Foltynie T. Long-term outcomes of deep brain stimulation in Parkinson disease. Nature Reviews Neurology, 2019, 15(4), 234-242. DOI: 10.1038/s41582-019-0145-9
[119] Starr PA, Vitek JL, Bakay RA. Ablative surgery and deep brain stimulation for Parkinson's disease. Neurosurgery, 1998, 43(5), 989-1013; discussion 1013-1015. DOI: 10.1097/00006123-199811000-00001
[120] Podder S, Gupta VR, Khator S, Koley R, Goswami SR. Fusion of blockchain and artificial intelligence of things in E-healthcare. In AIoT. Auerbach Publications. 2025, 57-98.
[121] Hooper AK, Okun MS, Foote KD, Fernandez HH, Jacobson C, Zeilman P, et al. Clinical cases where lesion therapy was chosen over deep brain stimulation. Stereotactic and Functional Neurosurgery, 2008, 86(3), 147-152. DOI: 10.1159/000120426
[122] Bett S, Igiraneza D. The role of rehabilitation in improving quality of life of patient with Parkinson's disease: A literature review. 2021.
[123] Weise D, Claus I, Dresel C, Kalbe E, Liepelt-Scarfone I, Lorenzl S, et al. Multidisciplinary care in Parkinson's diseas. Journal of Neural Transmission, 2024, 131(10), 1217-1227. DOI: 10.1007/s00702-024-02807-w
[124] Atalar MS, Oguz O, Genc G. Hypokinetic dysarthria in Parkinson's disease: A narrative review. The Medical Bulletin of Sisli Etfal Hospital, 2023, 57(2), 163-170. DOI: 10.14744/SEMB.2023.29560
[125] Baldanzi C, Crispiatico V, Foresti S, Groppo E, Rovaris M, Cattaneo D, et al. Effects of intensive voice treatment (The Lee Silverman Voice Treatment [LSVT LOUD]) in subjects with multiple sclerosis: A pilot study. Journal of Voice, 2022, 36(4), 585. e1-585. e13. DOI: 10.1016/j.jvoice.2020.07.025
[126] Subramanian I, Ricciardi L, Schrag A, Appel-Cresswell S, Kola S, Domingos JM, et al. A holistic wellness prescription for Parkinson's disease: Evidence-based perspectives and unmet needs. Movement Disorders Clinical Practice, 2026, 13(3), 631-646. DOI: 10.1002/mdc3.70381

[127] Iłowiecka K, Glibowski P, Skrzypek M, Styk W. The long-term dietitian and psychological support of obese patients who have reduced their weight allows them to maintain the effects. Nutrients, 2021, 13(6), 2020. DOI: 10.3390/nu13062020
[128] Iqubal A, Iqubal MK, Khan A, Ali J, Baboota S, Haque SE. Gene therapy, a novel therapeutic tool for neurological disorders: current progress, challenges and future prospective. Current Gene Therapy, 2020, 20(3), 184-194. DOI: 10.2174/1566523220999200716111502
[129] Pattali R, Mou Y, Li XJ. AAV9 vector: A Novel modality in gene therapy for spinal muscular atrophy. Gene Therapy, 2019, 26(7-8), 287-295. DOI: 10.1038/s41434-019-0085-4
[130] Khan MS. Gene therapy: Current trends and future prospects in treating genetic disorders. Multidisciplinary Journal of Biochemistry, 2024, 1(1), 72-81.
[131] Velikic G, Maric DM, Maric DL, Supic G, Puletic M, Dulic O, et al. Harnessing the stem cell niche in regenerative medicine: innovative avenue to combat neurodegenerative diseases. International Journal of Molecular Sciences, 2024, 25(2), 993. DOI: 10.3390/ijms25020993
[132] Hussen BM, Taheri M, Yashooa RK, Abdullah GH, Abdullah SR, Kheder RK, et al. Revolutionizing medicine: recent developments and future prospects in stem-cell therapy. International Journal of Surgery, 2024, 110(12), 8002-8024. DOI: 10.1097/JS9.0000000000002109
[133] Rani S, Tuteja M. Chaperones as potential pharmacological targets for treating protein aggregation illness. Current Protein & Peptide Science, 2025, 26(6), 451-466. DOI: 10.2174/0113892037338028241230092414
[134] Dhariwal R, Jain M, Mir YR, Singh A, Jain B, Kumar P, et al. Targeted drug delivery in neurodegenerative diseases: the role of nanotechnology. Frontiers in Medicine, 2025, 12, 1522223. DOI: 10.3389/fmed.2025.1522223
[135] Bajan S, Hutvagner G. RNA-based therapeutics: from antisense oligonucleotides to miRNAs. Cells, 2020, 9(1), 137. DOI: 10.3390/cells9010137
[136] Choonara YE, Pillay V, Du Toit LC, Modi G, Naidoo D, Ndesendo VMK, et al. Trends in the molecular pathogenesis and clinical therapeutics of common neurodegenerative disorders. International Journal of Molecular Sciences, 2009, 10(6), 2510-2557. DOI: 10.3390/ijms10062510
[137] Gadhave DG, Sugandhi VV, Jha SK, Nangare SN, Gupta G, Singh SK, et al. Neurodegenerative disorders: Mechanisms of degeneration and therapeutic approaches with their clinical relevance. Ageing Research Reviews, 2024, 99, 102357. DOI: 10.1016/j.arr.2024.102357
[138] Zündorf G, Reiser G. Calcium dysregulation and homeostasis of neural calcium in the molecular mechanisms of neurodegenerative diseases provide multiple targets for neuroprotection. Antioxidants & Redox Signaling, 2011, 14(7), 1275-88. DOI: 10.1089/ars.2010.3359
[139] Cummings J. Disease modification and Neuroprotection in neurodegenerative disorders. Translational Neurodegeneration, 2017, 6, 25. DOI: 10.1186/s40035-017-0096-2
[140] Seyhan AA. Lost in translation: the valley of death across preclinical and clinical divide-identification of problems and overcoming obstacles. Translational Medicine Communications, 2019, 4(1), 18. DOI: 10.1186/s41231-019-0050-7
[141] Loewa A, Feng JJ, Hedtrich S. Human disease models in drug development. Nature Reviews Bioengineering, 2023, 1-15. DOI: 10.1038/s44222-023-00063-3
[142] Subramanyam M, Goyal J. Translational biomarkers: From discovery and development to clinical practice. Drug Discovery Today: Technologies, 2016, 21, 3-10. DOI: 10.1016/j.ddtec.2016.10.001
[143] Buzhor E, Leshansky L, Blumenthal J, Barash H, Warshawsky D, Mazor Y, et al. Cell-based therapy approaches: The hope for incurable diseases. Regenerative Medicine, 2014, 9(5), 649-672. DOI: 10.2217/rme.14.35
[144] Moradi S, Mahdizadeh H, Šarić T, Kim J, Harati J, Shahsavarani H, et al. Research and therapy with induced pluripotent stem cells (iPSCs): Social, legal, and ethical considerations. Stem Cell Research & Therapy, 2019, 10(1), 341. DOI: 10.1186/s13287-019-1455-y
[145] Cohen MH. Future medicine: ethical dilemmas, regulatory challenges, and therapeutic pathways to health care and healing in human transformation. University of Michigan Press, 2009.
[146] Greener M. The good, the bad and the ugly red tape of biomedical research. How could regulators lower bureaucratic hurdles in clinical research without compromising the safety of patients? EMBO Reports, 2009, 10(1), 17-20. DOI: 10.1038/embor.2008.237
[147] Kepplinger EE. FDA's Expedited approval mechanisms for new drug products. Biotechnology Law Report, 2015, 34(1), 15-37. DOI: 10.1089/blr.2015.9999
[148] Luyckx VA. Ethical challenges of clinical innovations and medical progress. Nephrology Dialysis Transplantation, 2024, 39(9), 1375-1377. DOI: 10.1093/ndt/gfae067
[149] Waldman SA, Terzic A. Clinical and translational science: From bench-bedside to global village. Clinical and Translational Science, 2010, 3(5), 254-257. DOI: 10.1111/j.1752-8062.2010.00227.x
[150] Rivera SC, Kyte DG, Aiyegbusi OL, Slade AL, McMullan C, Calvert MJ. The impact of patient-reported outcome (PRO) data from clinical trials: A systematic review and critical analysis. Health and Quality of Life Outcomes, 2019, 17(1), 156. DOI: 10.1186/s12955-019-1220-z
[151] Hunter C, Chew-Graham C, Langer S, Stenhoff A, Drinkwater J, Guthrie E, et al. A qualitative study of patient choices in using emergency health care for long-term conditions: The importance of candidacy and recursivity. Patient Education and Counseling, 2013, 93(2), 335-341. DOI: 10.1016/j.pec.2013.06.001