Review

Parkinson's Disease: From Gene–Environment Risk to Precision Therapy

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Parkinson's Disease: From Gene–Environment Risk to Precision Therapy

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Abstract

Parkinson's disease (PD) is a progressive and heterogeneous neurodegenerative disorder and one of the fastest-growing causes of neurological disability worldwide. Although classically defined by motor manifestations arising from nigrostriatal dopaminergic degeneration, PD is now recognized as a multisystem disorder in which non-motor symptoms—including autonomic dysfunction, neuropsychiatric features, cognitive impairment, and sleep-related disorders—often precede motor onset by years or decades, defining a clinically meaningful prodromal phase. The aetiology of PD reflects a complex interplay between genetic susceptibility and environmental exposure. Approximately 20% of cases are associated with identifiable pathogenic variants, most commonly involving *LRRK2*, *GBA1*, and *SNCA*, while the majority arise from gene–environment interactions involving toxicant exposure, lifestyle factors, and common genetic risk variants. Despite major advances in understanding disease biology, current therapies remain fundamentally symptomatic. Dopaminergic pharmacotherapy and device-aided interventions improve motor function but do not alter disease progression, and non-motor symptoms remain a dominant determinant of disability and reduced quality of life. Recent conceptual advances propose redefining PD as a biologically defined α-synucleinopathy. Emerging biomarkers, including α-synuclein seed amplification assays in cerebrospinal fluid and peripheral tissues, offer unprecedented opportunities for early diagnosis, biological stratification, and precision clinical trials. However, translation into disease modification has been limited by late-stage intervention, reliance on clinically defined populations, restricted trial generalisability, and profound global inequities in access to advanced diagnostics and therapies. This review synthesizes current evidence on PD epidemiology, diagnosis, aetiology, progression, and treatment, with particular emphasis on gene–environment interactions, the functional limitations of existing therapeutic paradigms, and the transformative—but as yet unrealized—potential of biological classification. By identifying key mechanistic, clinical, and implementation gaps, the review frames future directions that prioritize prevention, early biological definition, patient-centred functional outcomes, and equitable precision care across diverse healthcare settings.

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1. Introduction

Parkinson's disease (PD) is a common, chronic, and progressive neurodegenerative disorder that predominantly affects individuals in later life and represents one of the fastest-growing causes of neurological disability worldwide [1,2]. Clinically, PD is defined by cardinal motor manifestations—bradykinesia, rigidity, resting tremor, and postural instability—that typically emerge asymmetrically and reflect dysfunction of the nigrostriatal dopaminergic system [3]. Pathologically, the disease is characterized by selective neuronal loss and the intraneuronal accumulation of misfolded α-synuclein aggregates, forming Lewy bodies and Lewy neurites, which involve both the central and

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peripheral nervous systems, including the brainstem, limbic regions, neocortex, and the autonomic nervous system [4,5].

Over the past two decades, PD has been reconceptualized as a multisystem disorder extending far beyond its classic motor phenotype. Non-motor manifestations—including hyposmia, rapid eye movement sleep behaviour disorder, autonomic dysfunction, mood disturbances, and cognitive impairment—are now recognized as integral components of the disease and often precede motor symptom onset by years or even decades [6–8]. This prodromal phase challenges traditional clinicopathological paradigms and underscores the limitations of diagnosing PD solely on motor criteria [5,7]. The recognition of early non-motor features has profound implications for disease detection, staging, and the development of preventive and disease-modifying strategies [9].

The aetiology of PD is complex and heterogeneous, arising from the interplay between genetic susceptibility and environmental exposures. Approximately 20% of cases are associated with identifiable pathogenic variants, most commonly involving *LRRK2*, *GBA1*, and *SNCA* [10,11]. These genetic forms have provided critical insights into disease-relevant biological pathways, including lysosomal dysfunction, impaired protein degradation, mitochondrial failure, and neuroinflammation [12,13]. However, the majority of PD cases are sporadic, with heritability estimates of approximately 20% to 30%, indicating a substantial contribution from environmental factors interacting with common genetic variants [14,15].

Among environmental exposures, pesticides and chlorinated solvents have been most consistently linked to increased PD risk, often in a dose-dependent manner [16–18]. Additional risk factors include traumatic brain injury and certain metabolic and inflammatory conditions, whereas lifestyle factors such as cigarette smoking, caffeine consumption, and regular physical activity appear inversely associated with PD risk [19]. Collectively, these findings support the view of PD as a disorder of gene–environment interaction rather than a single-pathway disease entity [15].

Despite major advances in understanding PD pathophysiology, no therapy has yet been shown to alter disease progression. Current pharmacological treatments—principally dopaminergic therapies—remain focused on symptomatic relief and are limited by diminishing efficacy, motor complications, and neuropsychiatric adverse effects over time [20,21]. Deep brain stimulation offers substantial benefit for motor fluctuations in selected patients but does not meaningfully address non-motor symptoms or halt neurodegeneration [22,23]. The repeated failure of neuroprotective trials likely reflects interventions at advanced stages of neuronal loss, highlighting the urgency of identifying biologically defined disease states earlier in the disease course [9,24].

Recent conceptual advances propose redefining PD as a biologically defined α-synucleinopathy rather than a purely clinical syndrome. Emerging biomarkers—including α-synuclein seed amplification assays in cerebrospinal fluid, skin, and peripheral tissues—demonstrate high sensitivity and specificity for synucleinopathies and may enable the identification of PD at prodromal or preclinical stages [25–27]. Such approaches promise to transform PD diagnosis, enable biologically stratified clinical trials, and accelerate the development of precision therapeutics [9,28].

This review synthesizes current knowledge of PD, focusing on the interaction between genetic architecture and environmental exposure, the limitations of existing therapeutic paradigms, and the emerging role of biomarkers in redefining disease classification. By identifying critical gaps in mechanistic understanding and clinical translation, we aim to frame future directions that move the field toward prevention, early intervention, and disease modification—ultimately reshaping the trajectory of PD care.

2. Epidemiology

PD demonstrates a pronounced age-related increase in both incidence and prevalence, with men affected approximately twice as often as women [1,29]. Population-based studies from North America report incidence rates ranging from 47 to 77 cases per 100,000 individuals aged 45 years and older, and from 108 to 212 cases per 100,000 individuals aged 65 years and older, underscoring the strong influence of ageing on disease risk [2,29].

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Epidemiological data indicate variability in PD incidence across racial and ethnic groups, with higher reported incidence among White populations compared with Black or Asian populations [2,29]. However, neuropathological studies demonstrate that the prevalence of Lewy body pathology—a defining feature of PD—is comparable between Black and White individuals at autopsy, suggesting that differences in diagnosed incidence may reflect disparities in access to care, diagnostic practices, or survival rather than true biological differences in disease susceptibility [30].

The prevalence of PD in the United States is estimated at approximately 572 cases per 100,000 individuals aged 45 years and older, with prevalence increasing sharply with advancing age [1]. Mortality among individuals with PD remains substantially elevated, with age- and sex-adjusted mortality rates approximately 60% higher than those observed in the general population, reflecting both disease-related complications and comorbid conditions [1].

Beyond its clinical impact, PD imposes a substantial and growing economic burden. In the United States, the total annual cost of PD—including direct medical expenditures and indirect costs related to lost productivity and caregiving—was estimated at $52 billion in 2017 and is projected to rise to $79 billion by 2037, driven largely by population ageing and increasing disease prevalence [31]. These trends underscore the urgent need for strategies focused on early detection, disease modification, and prevention.

3. Diagnosing Parkinson's Disease

PD, historically defined by its motor manifestations resulting from nigrostriatal dopaminergic neuron loss, is now recognized as a complex multisystem neurological disorder. Non-motor symptoms constitute a core component of the disease and include sleep-related disorders, cognitive impairment, neuropsychiatric symptoms, autonomic dysfunction—such as constipation, urogenital dysfunction, and orthostatic hypotension—and sensory abnormalities, including hyposmia and pain [6–8]. Significantly, several non-motor features, particularly hyposmia and rapid eye movement (REM) sleep behaviour disorder—characterized by loss of normal muscle atonia during REM sleep with dream-enactment behaviours—may precede the onset of motor symptoms by many years, defining a prodromal phase of PD [6–8]. The gradual accumulation and progression of these symptoms contribute substantially to disability and functional decline over the disease course.

To standardize diagnosis, the International Parkinson and Movement Disorder Society (MDS) has established clinical diagnostic criteria for PD and research criteria for prodromal PD [6,8]. These frameworks rely primarily on clinical features, with ancillary investigations used when diagnostic uncertainty exists. Although no imaging modality can definitively confirm PD, functional imaging of the presynaptic dopaminergic system—using ^123I-ioflupane single-photon emission computed tomography (SPECT) or ^18F-fluorodopa positron emission tomography (PET)—is valuable for differentiating PD from conditions such as essential tremor or drug-induced parkinsonism [32]. Meta-analytic data indicate that ^123I-ioflupane SPECT imaging demonstrates sensitivity and specificity exceeding 90% and can lead to changes in diagnosis in approximately one-third of cases and alterations in clinical management in more than half of patients evaluated [32].

Structural magnetic resonance imaging (MRI) plays an important complementary role by identifying features suggestive of alternative neurodegenerative parkinsonian disorders [33]. Characteristic changes involving the basal ganglia or infratentorial structures may point toward diagnoses such as progressive supranuclear palsy or multiple system atrophy, for which specific MDS diagnostic criteria exist [34–36]. Ongoing advances in MRI techniques, including quantitative and high-field imaging, may further enhance diagnostic accuracy and facilitate earlier differentiation among parkinsonian syndromes [33,37].

Neuropathologically, PD is defined by the intraneuronal accumulation of misfolded α-synuclein, forming Lewy bodies and Lewy neurites, which are detected in up to 90% of clinically diagnosed cases at autopsy [38]. This pathology affects a characteristic network of regions, including brainstem nuclei—such as the dorsal motor nucleus of the vagus, locus coeruleus, and substantia

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nigra—the peripheral autonomic nervous system, and limbic and neocortical areas [38]. A defining feature is the marked loss of pigmented, dopamine-producing neurons in the substantia nigra.

Despite established clinical criteria, diagnostic accuracy remains imperfect, particularly in early disease stages. Clinicopathological studies have demonstrated concordance rates as low as 28% between initial clinical diagnosis and autopsy findings, although accuracy improves substantially with longer disease duration, reaching approximately 89% in advanced stages [39]. Diagnostic precision is highest when evaluations are conducted by movement disorder specialists, highlighting the importance of expert clinical assessment in PD diagnosis [39].

4. Etiology of Parkinson's Disease

PD is a complex and heterogeneous disorder arising from the interplay between genetic susceptibility and environmental exposures. Approximately 20% of PD cases are attributable to identifiable pathogenic genetic variants, collectively referred to as monogenic PD [10,11]. Among autosomal dominant forms with incomplete penetrance, mutations in LRRK2 are the most prevalent, accounting for approximately 1% to 2% of all PD cases and up to 40% of familial cases in specific populations [11]. Variants in GBA1, which encodes the lysosomal enzyme glucocerebrosidase, are present in approximately 5% to 15% of PD cases, with particularly high prevalence among individuals of Ashkenazi Jewish and North African ancestry [10]. Less common dominant mutations, including those in SNCA and VPS35, account for fewer than 1% of cases [11].

Autosomal recessive forms of PD, most commonly caused by mutations in PRKN, PINK1, and DJ1, are typically associated with early-onset disease and distinct clinical phenotypes [11]. Although rare, these variants represent the most common genetic causes of PD in younger patients. Pathologically, abnormal α-synuclein accumulation is a defining feature of PD and is commonly observed in cases associated with SNCA and GBA1 mutations and in approximately half of LRRK2-associated cases [10]. In contrast, recessive forms of PD often exhibit minimal α-synuclein pathology, fewer non-motor symptoms, and more prominent dystonia, underscoring important biological heterogeneity across genetic subtypes [11].

Beyond monogenic forms, genome-wide association studies have substantially expanded the genetic architecture of PD by identifying more than 90 risk loci, each conferring modest individual effects [10]. Many of these loci cluster near known causative genes, implicating shared pathogenic pathways. However, most genetic studies have disproportionately focused on populations of European ancestry, limiting generalisability. Recent work in underrepresented populations has identified novel variants, including a GBA1 variant accounting for approximately 39% of PD cases among individuals of African ancestry, highlighting the importance of inclusive global genetic research [40].

In individuals without high-penetrance mutations, heritability estimates for PD range from 20% to 30%, indicating a substantial contribution from environmental factors [16]. Identifying specific environmental risks has proven challenging due to methodological limitations, exposure misclassification, and the multifactorial nature of disease causation. Epidemiological studies have often examined individual exposures in isolation, despite evidence that PD likely emerges from cumulative environmental insults acting on a background of genetic vulnerability [15].

Among environmental factors, exposure to pesticides and industrial solvents has been most consistently associated with increased PD risk. Residential or occupational exposure to agents such as paraquat, rotenone, 2,4-dichlorophenoxyacetic acid, and chlorinated solvents—including trichloroethylene and perchloroethylene—has been linked to dose-dependent increases in PD risk, frequently exceeding 40% [16–18]. Experimental models corroborate these epidemiological findings, demonstrating that these toxicants induce mitochondrial dysfunction, oxidative stress, and selective dopaminergic neurodegeneration [12].

Additional environmental and lifestyle factors may further modify PD risk. High consumption of dairy products has been associated with increased PD risk, potentially mediated by higher brain concentrations of organochlorine compounds, such as heptachlor epoxide [41]. Traumatic brain

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injury has also been linked to elevated risk of PD and related synucleinopathies, with reported risk increases ranging from modest to several-fold depending on injury severity and timing [19]. Other proposed risk factors—including exposure to metals, type 2 diabetes mellitus, inflammatory conditions, and infections—have shown less consistent associations across studies [15].

Conversely, several lifestyle factors appear to confer protection against PD. Cigarette smoking, caffeine consumption, and regular physical activity have each been associated with reduced disease risk and improved outcomes [42]. Converging evidence from genetic and sporadic PD suggests that diverse risk factors ultimately converge on shared biological pathways, including neuroinflammation, immune dysregulation, oxidative stress, mitochondrial dysfunction, impaired autophagy, protein aggregation, and endolysosomal system failure [12,13].

5. Parkinson's Disease Progression

The clinical progression of PD is characterized by a dynamic, heterogeneous combination of motor and non-motor manifestations, with substantial interindividual variability in onset, severity, and progression rate. Motor symptoms—including bradykinesia, rigidity, tremor, and postural instability—typically begin asymmetrically and gradually evolve to bilateral involvement as neurodegeneration advances [3]. Over time, many patients develop significant functional impairment driven by worsening motor disability, gait and balance disturbances, cognitive decline, and an increased risk of falls and fractures, although the tempo of progression varies widely across individuals [1,43].

Non-motor symptoms frequently precede the onset of motor dysfunction by years or even decades, reflecting early involvement of non-dopaminergic and extra-nigral systems. Common prodromal features include hyposmia, autonomic dysfunction, and rapid eye movement (REM) sleep behaviour disorder, which are now recognized as strong clinical markers of impending PD [6–8]. As the disease progresses, additional autonomic disturbances—such as orthostatic hypotension, impaired gastrointestinal motility, urinary dysfunction, erectile dysfunction, and altered thermoregulation—often emerge and tend to worsen over time, contributing substantially to morbidity and reduced quality of life [8].

Cognitive dysfunction represents a major determinant of long-term disability in PD. Subtle deficits in executive function, attention, and visuospatial processing may be detectable early and can precede motor symptoms in some individuals [44]. Longitudinal studies suggest that approximately 10% of patients with PD develop mild cognitive impairment or PD dementia annually, with cumulative risk increasing with disease duration [43,45]. Dementia with Lewy bodies, a closely related synucleinopathy, is characterized by early and prominent cognitive and neuropsychiatric symptoms—including visual hallucinations—in conjunction with parkinsonism and may represent either a clinical variant within the PD spectrum or a partially distinct entity with overlapping pathology [46].

Neuropathological studies reveal substantial overlap between PD and Alzheimer's disease–related pathology. Alzheimer-type changes are present in approximately 38% of clinically diagnosed PD cases and in up to 89% of dementia with Lewy bodies cases, highlighting the contribution of mixed pathologies to cognitive decline and disease progression [47]. These findings underscore the biological complexity underlying clinical heterogeneity in PD.

Efforts to define clinical subtypes of PD with distinct trajectories of progression have yielded inconsistent and poorly reproducible results across cohorts [48]. However, emerging evidence suggests that biologically defined subgroups may offer greater prognostic value. For example, patients carrying *GBA1* variants exhibit a higher risk of early cognitive decline and more rapid disease progression, whereas individuals with *PRKN* mutations often demonstrate slower progression and relative sparing of cognitive function [10,11]. Continued refinement of biologically informed classification systems is expected to improve prognostication, patient counselling, and stratification in clinical trials.

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6. Non-Motor Symptoms of Parkinson's Disease

PD is increasingly recognized as a multisystem neurodegenerative disorder in which non-motor symptoms constitute core manifestations rather than secondary consequences of motor dysfunction (Table 1). These symptoms often precede the onset of classical motor features by years and progressively dominate the clinical course, shaping disability, quality of life, and prognosis. The diversity of non-motor symptoms reflects widespread degeneration across central and peripheral nervous system networks, involving autonomic, sensory, sleep–wake, neuropsychiatric, and cognitive systems, and implicating neurotransmitter systems extending well beyond dopamine, including serotonergic, noradrenergic, and cholinergic pathways [7,49].

Autonomic dysfunction represents one of the earliest and most pervasive non-motor domains. Gastrointestinal symptoms—particularly constipation—often emerge decades before diagnosis and are linked to α-synuclein pathology in the enteric nervous system and the dorsal motor nucleus of the vagus, supporting gut–brain axis models of disease propagation [50,51]. Cardiovascular autonomic failure, including orthostatic hypotension and impaired heart rate variability, reflects sympathetic denervation and baroreflex dysfunction and contributes substantially to falls and mortality [7,52]. Genitourinary, sexual, thermoregulatory, and cutaneous manifestations further underscore that PD involves peripheral autonomic structures early and systematically.

Sensory alterations form another prominent component of the non-motor phenotype. Olfactory dysfunction is among the most robust prodromal features of PD, reflecting early Lewy pathology in the olfactory bulb and limbic regions and correlating with subsequent cognitive decline, REM sleep behaviour disorder, and neuropsychiatric symptoms [7,53]. Visual disturbances arise from combined retinal dopaminergic loss and cortical dysfunction and contribute to falls, hallucinations, and impaired visuospatial processing. Pain and paresthesias, often preceding motor onset, reflect degeneration across nociceptive, limbic, spinal, and peripheral nerve pathways and reinforce the systemic nature of PD [54].

Sleep-related disorders provide a unique window into early neurodegeneration. REM sleep behaviour disorder (RBD) is among the most specific prodromal markers of synucleinopathies, with longitudinal studies demonstrating high conversion rates to PD and related disorders [7,8]. Insomnia, excessive daytime sleepiness, restless legs syndrome, and obstructive sleep apnoea reflect degeneration of brainstem monoaminergic nuclei, hypothalamic arousal systems, and circadian regulatory circuits. Beyond their symptomatic burden, sleep disturbances may impair glymphatic clearance of misfolded proteins, potentially accelerating α-synuclein accumulation and disease progression [55].

Within this multisystem landscape, neuropsychiatric symptoms emerge as a central and conceptually revealing domain. Depression, anxiety, apathy, hallucinations, and related affective and perceptual disturbances frequently arise in the prodromal or early stages and exert a disproportionate impact on quality of life, caregiver burden, and survival. Importantly, these symptoms are not reactive responses to chronic disability but reflect intrinsic degeneration of limbic, paralimbic, and associative networks [43].

Depression affects approximately one-third to nearly half of individuals with PD and often precedes motor onset [56]. Parkinson's-related depression is clinically distinct, characterized by anhedonia, irritability, psychomotor slowing, and apathy rather than pervasive sadness. Neurobiologically, it reflects degeneration of mesolimbic dopaminergic projections, serotonergic raphe nuclei, noradrenergic locus coeruleus neurons, and limbic structures such as the amygdala and thalamus [50,57]. Structural and functional imaging studies demonstrate disrupted frontolimbic connectivity, underscoring that mood disturbances arise from network-level failure rather than isolated neurotransmitter deficits.

Anxiety is similarly prevalent and clinically consequential, often coexisting with depression but representing a partially independent phenotype. Anxiety disorders in PD include generalized anxiety, panic disorder, and social anxiety, frequently fluctuating with motor states and autonomic instability [58]. Neuroimaging studies implicate altered amygdala reactivity, impaired prefrontal

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regulation, and salience network dysfunction, while emerging evidence links anxiety to α-synuclein pathology, oxidative stress, and inflammatory mechanisms [59].

Apathy is one of the most disabling neuropsychiatric syndromes in PD and is distinct from both depression and cognitive impairment. Characterized by diminished motivation, emotional blunting, and reduced goal-directed behaviour, apathy reflects disruption of mesocorticolimbic circuits involving the ventral tegmental area, the nucleus accumbens, the orbitofrontal cortex, and the anterior cingulate cortex [60]. Its presence is strongly associated with cognitive decline and progression to dementia, positioning apathy as both a major determinant of disability and a prognostic marker of disease evolution.

Psychotic symptoms, particularly visual hallucinations, mark a critical inflection point in the neuropsychiatric trajectory of PD. These symptoms arise from convergent cholinergic degeneration, dysfunction of the visual association cortex, and impaired thalamocortical filtering, and are strongly associated with cognitive impairment and institutionalisation [43]. Less common phenomena such as phantosmia further illustrate disruption of predictive coding within sensory–limbic networks and reinforce the breadth of perceptual dysfunction in PD.

In summary, non-motor symptoms reveal PD as a distributed, network-level disorder in which neuropsychiatric manifestations occupy a central position [7]. Integrating the full panorama of non-motor symptoms into diagnostic, research, and therapeutic frameworks is essential for advancing precision medicine approaches and aligning clinical care with the biological reality and lived experience of PD.

Table 1. Non-motor symptoms of Parkinson's disease: domains, clinical features, mechanisms, and translational relevance.

Domain	Symptom	Typical stage	Core mechanisms/substrates	Clinical relevance
Autonomic	Constipation	Prodromal	α-Synuclein pathology in the enteric nervous system, dorsal motor nucleus of the vagus; gut dysbiosis	Early biomarker; years before motor onset
	Orthostatic hypotension	Early–late	Sympathetic denervation; norepinephrine depletion; baroreflex failure	Falls, syncope, and mortality risk
	Urinary dysfunction (urgency, nocturia, retention)	Early–late	Pontine micturition centre, sacral parasympathetic nuclei, pelvic plexus involvement	Quality of life, sleep disruption
	Sexual dysfunction	Early	Hypothalamic, limbic and spinal autonomic degeneration	Underreported; psychosocial impact
	Sialorrhoea	Early	Brainstem cholinergic dysfunction; impaired swallowing	Aspiration risk, social disability
	Dysphagia	Early–late	Nucleus ambiguus and DMV degeneration	Pneumonia, mortality
	Seborrhoea / seborrhoeic dermatitis	Early	Autonomic skin denervation; sebaceous gland α-synuclein	Peripheral biomarker potential
	Hyperhidrosis / anhidrosis	Early–late	Hypothalamic and sympathetic dysfunction	Thermoregulatory instability
	Cardiac autonomic dysfunction	Early	Cardiac sympathetic denervation (MIBG loss)	Sudden death risk
Sensory	Hyposmia	Prodromal	Olfactory bulb Lewy pathology; limbic spread	Strong prodromal marker
	Ageusia	Early–late	Orbitofrontal cortex, insula, cholinergic loss	Nutritional consequences
	Visual disturbances	Early	Retinal dopamine loss; visual cortex involvement	Falls, hallucination risk
	Pain (musculoskeletal, dystonic, neuropathic)	Prodromal–late	Spinal cord, limbic and nociceptive network dysfunction	Disability, reduced quality of life

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	Paresthesias	Prodromal	Small-fiber neuropathy; peripheral α-synuclein	Peripheral nervous system involvement
Sleep-related	REM sleep behaviour disorder	Prodromal	Pontine tegmentum degeneration; REM atonia failure	Highly specific synucleinopathy marker
	Insomnia/sleep fragmentation	Early–late	Brainstem monoaminergic degeneration	Cognitive and mood deterioration
	Excessive daytime sleepiness	Early–late	Hypothalamic hypocretin loss; medication effects	Accident risk
	Restless legs syndrome	Early	Dopaminergic and iron dysregulation	Sleep quality impairment
	Obstructive sleep apnoea	Late	Upper airway control, autonomic dysfunction	Cognitive decline, hypoxia
Neuropsychiatric	Depression	Prodromal–late	Limbic, serotonergic and noradrenergic degeneration	Predictor of faster progression
	Anxiety	Prodromal–late	Amygdala and salience network dysfunction	Motor fluctuation exacerbation
	Apathy	Early–late	Mesocorticolimbic dopamine disruption	Predictor of dementia
	Visual hallucinations	Early–late	Cholinergic deficit; visual network dysintegration	Dementia risk
	Phantosmia	Early	Olfactory predictive-coding disruption	Hallucination spectrum marker
Cognitive	Inattention / executive dysfunction	Prodromal	Frontostriatal dopaminergic loss	Early cognitive phenotype
	Bradyphrenia	Early	Subcortical–frontal network slowing	Functional impairment
	Impulse-control disorders	Early	Mesolimbic dopamine overstimulation	Treatment-related complication
	Parkinson's disease dementia	Late	Cortical α-synuclein ± tau/amyloid co-pathology	Institutionalization, mortality

7. Treatment of Parkinson's Disease

7.1. Rethinking Treatment Effectiveness in Parkinson's Disease

PD is a progressive neurodegenerative disorder in which disability emerges from the dynamic interaction between motor impairment, non-motor symptoms, cognitive decline, and environmental context. Traditionally, treatment success has been defined by improvement in motor signs, particularly bradykinesia and rigidity. However, large longitudinal studies and randomised trials now demonstrate that motor improvement alone poorly predicts long-term functional independence or quality of life [7,20,49].

In this review, effective treatment is defined as therapy that stabilizes daily functioning, reduces disability progression, and preserves quality of life, rather than achieving isolated reductions in motor scores or OFF time. This framework recognizes PD as a multisystem disorder and aligns therapeutic goals with patient-centered outcomes, an approach increasingly advocated in contemporary clinical research and practice [61].

7.2. Disease Progression and the Elusive Goal of Neuroprotection

A disease-modifying therapy is one that alters the underlying neurodegenerative process. Despite extensive investigation, no pharmacological treatment has convincingly demonstrated disease-modifying effects in PD. Early enthusiasm for monoamine oxidase–B inhibitors was tempered by subsequent trials showing that apparent benefits reflected symptomatic dopaminergic effects rather than slowed neurodegeneration [24].

A major biological limitation is the advanced neuronal loss present at clinical diagnosis. Neuropathological and imaging studies indicate that by the time cardinal motor symptoms emerge, approximately two-thirds of nigrostriatal dopaminergic neurons are already dysfunctional or lost

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[62]. This has driven a shift toward intervention in prodromal or biologically defined stages, supported by biomarkers of α-synuclein pathology. However, trials targeting α-synuclein aggregation or clearance, including studies in genetically enriched populations (e.g., GBA1 and LRRK2 mutation carriers), have thus far produced mixed or negative results [28,63].

As a result, current PD management remains fundamentally symptomatic, with emphasis on optimizing long-term function and minimizing treatment-related harm rather than pursuing unproven neuroprotective strategies [61].

7.3. Multidisciplinary Care and Neurorehabilitation as Disease-Stabilizing Strategies

Multidisciplinary care refers to coordinated management delivered by multiple health professionals addressing complementary aspects of disease. In PD, this model is not ancillary but central to effective treatment, given the disorder's multisystem involvement and evolving symptom profile.

Neurorehabilitation addresses domains that pharmacological therapy cannot modify. High-quality evidence supports physiotherapy for gait, balance, and fall prevention; occupational therapy for activities of daily living and environmental adaptation; speech and language therapy for hypophonia and dysphagia; and cognitive and psychological interventions for executive dysfunction and mood disorders [64,65]. Importantly, these interventions produce measurable functional benefits even in advanced disease, often independent of motor score improvement.

Escalation of pharmacological therapy without parallel rehabilitation frequently yields diminishing returns. Effective treatment therefore requires continuous integration of medication management with neurorehabilitation and psychosocial support, a principle increasingly emphasized in comprehensive PD care models [61].

7.4. Pharmacological Treatment of Motor Symptoms: Beyond Levodopa Responsiveness

7.4.1. Levodopa as the Therapeutic Foundation

Levodopa remains the most effective treatment for motor symptoms in PD and continues to serve as the pharmacological foundation across disease stages. A sustained response supports diagnostic accuracy, whereas poor responsiveness suggests alternative parkinsonian syndromes [66].

With disease progression, however, the brain's capacity to buffer fluctuating dopamine levels diminishes, leading to motor fluctuations, defined as alternating periods of satisfactory mobility (ON-time) and re-emergence of motor symptoms (OFF-time). These fluctuations represent a combined consequence of disease progression and intermittent oral dosing [61].

7.4.2. Adjunctive Therapies and the Limits of OFF-Time Reduction

Adjunctive pharmacological therapies aim to reduce OFF-time by prolonging levodopa availability or stimulating dopaminergic pathways through complementary mechanisms. As summarised in Table 2, high-certainty evidence supports extended-release levodopa formulations, dopamine agonists (notably pramipexole), opicapone, rotigotine, and safinamide in reducing daily OFF-time by approximately 1 hour or more [67–69].

However, across trials, functional improvement and quality-of-life gains are modest, inconsistent, or absent, despite statistically significant motor benefits. Dopamine agonists demonstrate the most consistent functional effects but are limited by neuropsychiatric and behavioral adverse events, including impulse-control disorders and somnolence (Weintraub et al., 2010). Moderate-certainty evidence supports monoamine oxidase–B inhibitors, catechol-O-methyltransferase inhibitors, zonisamide, and non-dopaminergic agents such as istradefylline, which provide incremental benefit but rarely alter disability trajectories [61].

These findings underscore a critical principle: OFF-time reduction is a necessary but insufficient target. Adjunctive therapies should be viewed as tools for fine-tuning treatment rather than definitive solutions for advanced disease [61].

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7.4.3. Continuous Dopaminergic Delivery: Functional Relevance Over Motor Metrics

Continuous dopaminergic delivery aims to minimize plasma dopamine fluctuations by providing stable stimulation over extended periods [61]. This strategy directly addresses the pathophysiological limitations of intermittent oral therapy.

As detailed in Table 1, levodopa–carbidopa intestinal gel, continuous subcutaneous apomorphine infusion, and subcutaneous foslevodopa–foscarbidopa achieve larger and more consistent reductions in OFF time than oral adjunctive therapies. Importantly, levodopa–carbidopa intestinal gel has demonstrated clinically meaningful improvements in functional outcomes and quality of life, not merely motor scores [70].

Beyond motor smoothing, continuous delivery may reduce fluctuation-related anxiety and enhance participation in rehabilitation and daily activities. Nevertheless, invasiveness, device-related complications, and infrastructure requirements substantially limit accessibility, particularly outside specialized centers [61].

Non-Motor Symptoms: Central Determinants of Patient Experience

Non-motor symptoms encompass cognitive impairment, mood and anxiety disorders, psychosis, autonomic dysfunction, sleep-related disorders, fatigue, and pain. These symptoms often evolve independently of motor impairment and are the primary determinants of quality of life in PD [7,49].

Pharmacological treatment remains symptom-specific and largely palliative. Acetylcholinesterase inhibitors offer modest benefit for cognitive impairment; antidepressants for mood disorders; pimavanserin or selected atypical antipsychotics for psychosis; and targeted therapies for autonomic dysfunction and sleep disorders [61]. Pain remains under-recognized and undertreated, with limited high-quality evidence guiding management beyond optimization of dopaminergic therapy and multidisciplinary approaches.

Failure to systematically address non-motor symptoms is a major cause of perceived treatment failure, even in patients with adequate motor control [61].

7.4.4. Surgical and Device-Aided Therapies: High Efficacy, High Selectivity

Deep-brain stimulation (DBS) represents the most established surgical therapy for PD. As summarized in Table 3, high-certainty evidence supports globus pallidus internus stimulation in patients with levodopa-responsive motor symptoms complicated by disabling fluctuations or dyskinesias. DBS produces sustained improvements in motor function, functional capacity, and quality of life, but does not modify disease progression and has a limited impact on non-motor symptoms [71,72].

Unilateral pallidotomy retains limited relevance in settings where DBS is unavailable, while other ablative or experimental approaches, including neurotrophic factor delivery, have not demonstrated consistent benefit and remain investigational.

7.4.5. Access, Equity, and the Gap Between Evidence and Practice

A defining challenge in PD treatment is the disconnect between therapeutic efficacy and real-world availability. As highlighted in Tables 2 and 3, many of the most effective pharmacological and device-aided therapies remain inaccessible in low- and middle-income countries due to regulatory, economic, and infrastructural barriers [61].

Effective treatment of PD must therefore be understood as a systems-level challenge, requiring integration of high-quality evidence, neurorehabilitation capacity, and equitable health policy to translate scientific advances into meaningful population-level benefit [61,73].

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Table 2. Pharmacological treatments for motor fluctuations in Parkinson's disease.

Treatment	Evidence Certainty*	Effect on OFF Time	Functional Outcome (UPDRS-II)	Quality of Life (PDQ-39/EQ-5D)	Availability in LMICs†
Levodopa–carbidopa extended release (IPX066)	High	↓ ~1.2 h/day	Small improvement (below MCID)	No clinically meaningful change	Rare
Opicapone	High	↓ ~0.7–2.0 h/day	Minimal	No clinically meaningful change	Limited
Pramipexole (IR/ER)	High	↓ ≥1 h/day	Clinically relevant improvement	Variable	Wide
Rotigotine (transdermal)	High	↓ ≥1 h/day	Variable	Inconsistent	Limited
Safinamide	High	↓ ~1 h/day	Not consistently assessed	Inconsistent	Limited
Levodopa–carbidopa intestinal gel (LCIG)	Moderate	↓ ~1.9 h/day	Clinically meaningful improvement	Clinically meaningful improvement	Not available
Foslevodopa–foscarbidopa (subcutaneous)	Moderate	↓ ~1.8 h/day	Not assessed	Not assessed	Not available
Apomorphine (continuous infusion)	Moderate	↓ ~1.9 h/day	Modest	No sustained benefit	Select centres
Rasagiline	Moderate	↓ ~0.5–0.9 h/day	Small (below MCID)	Small (below MCID)	Wide
Zonisamide	Moderate	↓ ~0.7–1.4 h/day	Modest	Not assessed	Regional
Ropinirole (IR)	Moderate	↓ ~1 h/day	Modest	Inconsistent	Wide
Entacapone	Moderate	↓ ~0.6–1 h/day	Minimal	Insufficient evidence	Wide
Amantadine ER	Moderate	Modest	Not assessed	Not assessed	Rare
Istradefylline	Moderate	↓ ~0.7–1 h/day	Limited	Not assessed	Limited
Levodopa–carbidopa CR	Low	Inconsistent	No improvement	No benefit	Wide
Selegiline	Low	Inconsistent	No sustained benefit	No benefit	Wide
Nicotine (patch)	Very low	Uncertain	Not assessed	Not assessed	Not used
Terguride	Very low	No benefit	No benefit	Not assessed	Not available
Perampanel	Very low	No benefit	No benefit	Not assessed	Not available

* Evidence certainty assessed using GRADE methodology. † Availability reflects inclusion in national formularies and market access across Latin American countries.

Table 3. Surgical and device-aided interventions for motor fluctuations.

Intervention	Evidence Certainty*	Motor Outcome	Functional Outcome	Quality of Life	Safety Profile	Availability in LMICs
GPi Deep Brain Stimulation	High	Large, sustained improvement	Clinically meaningful	Clinically meaningful	Favourable cognitive profile	Limited
Unilateral Pallidotomy	Moderate	Sustained improvement	Modest	Modest	Irreversible; no sham controls	Select
Subthalamotomy	Low	Modest	Not assessed	Not assessed	High risk of hemiballismus	Rare
Zona incerta DBS	Very low	Inconsistent	No clear benefit	No clear benefit	High risk of bias	Not available
GDNF (intraputaminal)	Very low	No benefit	No benefit	No benefit	Safe but ineffective	Experimental

* Certainty based on randomized trials and high-quality observational data.

8. Discussion

The future of PD research and care depends on transformative strategies that move beyond symptomatic management toward prevention, early intervention, and biologically informed disease modification. A critical long-term goal is the prevention of PD through coordinated global efforts that address upstream determinants of risk, including environmental toxicant exposure, lifestyle factors, and social inequities. Reducing exposure to pesticides and industrial solvents, while promoting physical activity and cardiovascular health, offers a plausible population-level strategy to lower disease incidence, yet implementation remains uneven across regions and socioeconomic strata [9].

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Expanding genetic research to include historically underrepresented populations represents another essential priority. Current genetic knowledge is disproportionately derived from individuals of European ancestry, limiting generalisability and perpetuating inequities in precision medicine. Recent discoveries of population-specific risk variants underscore both the scientific and ethical imperatives to broaden inclusion in genetic and biomarker studies [40]. Without such efforts, advances in targeted therapies risk exacerbating existing disparities in access and outcomes.

Technological innovation is poised to reshape PD care but introduces new challenges. Artificial intelligence–driven analytics, digital biomarkers, and wearable technologies promise earlier diagnosis, continuous symptom monitoring, and personalised treatment adjustments [74]. However, the clinical integration of these tools is constrained by variability in data quality, lack of standardized endpoints, regulatory uncertainty, and unequal access to digital infrastructure. Telemedicine and remote monitoring can mitigate geographic barriers, yet their benefits are unevenly distributed, particularly in low- and middle-income countries, where advanced therapies and device-aided treatments remain largely inaccessible [61,73].

The development of reliable biological biomarkers remains a cornerstone unmet need. α-Synuclein–based assays have demonstrated high sensitivity and specificity for synucleinopathies and offer unprecedented opportunities to identify PD at prodromal or preclinical stages [25,27]. Nonetheless, major gaps persist, including limited longitudinal validation, uncertainty regarding prognostic value, and the absence of consensus on how biomarker positivity should guide clinical decision-making. Notably, most disease-modifying trials to date have failed, in part, because interventions were initiated too late in the disease course and relied on clinically defined rather than biologically stratified populations [9].

From a therapeutic standpoint, this review highlights critical challenges in translating effective symptomatic therapies into durable, globally scalable solutions. Advanced pharmacological and device-aided treatments—including continuous dopaminergic infusion therapies and deep brain stimulation—are supported by robust evidence but are constrained by high cost, infrastructure requirements, and limited availability outside specialised centres [61,73]. Moreover, current clinical trials often exclude older patients, those with cognitive impairment, and individuals from resource-limited settings, limiting external validity and real-world applicability.

Collectively, these gaps underscore the need for a paradigm shift in PD research—from short-term symptomatic endpoints toward long-term, biologically grounded outcomes; from siloed interventions toward integrated care models; and from regionally concentrated innovation toward globally equitable implementation.

9. Conclusions

PD is a complex and heterogeneous neurodegenerative disorder characterized by progressive motor and non-motor manifestations that impose an escalating burden on individuals, healthcare systems, and societies worldwide. Although substantial advances have been made in elucidating genetic risk, environmental contributors, and disease biology, current treatments remain predominantly symptomatic and fail to alter the underlying neurodegenerative process.

Recent progress in biomarker discovery, genetic stratification, and advanced therapeutic technologies offers a credible pathway toward earlier diagnosis and precision medicine. However, persistent challenges—including late intervention, limited trial generalisability, unequal access to advanced therapies, and global disparities in care—continue to impede meaningful disease modification and population-level impact [61,73].

The next era of PD management must prioritize prevention, biological definition, and equitable access. Achieving this will require coordinated global investment, inclusive research practices, and health-system innovations that ensure advances benefit all patients, not only those in high-resource settings. By aligning scientific discovery with implementation and equity, the field stands poised to transition from managing Parkinson's disease to fundamentally altering its trajectory.

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Abbreviations

The following abbreviations are used in this manuscript:

PD	Parkinson's disease
MDS	Movement Disorder Society
REM	Rapid eye movement
RBD	Rapid eye movement sleep behaviour disorder
MRI	Magnetic resonance imaging
PET	Positron emission tomography
SPECT	Single-photon emission computed tomography
DBS	Deep brain stimulation
CSF	Cerebrospinal fluid
α-synuclein	Alpha-synuclein
LRRK2	Leucine-rich repeat kinase 2
GBA1	Glucocerebrosidase 1
SNCA	Alpha-synuclein gene
PRKN	Parkin
PINK1	PTEN-induced kinase 1
DJ1	Parkinson disease protein 7
ON-time	Periods of optimal motor function
OFF-time	Periods of reduced motor function
AI	Artificial intelligence

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