JOURNAL OF PHARMA INSIGHTS AND RESEARCH ISSN NO. 3048-5428

REVIEW ARTICLE

Etiopathogenesis, Clinical Manifestations, and Management of Parkinson's Disease

Anusha G[1], Dhana Lakshmi G*[2], Meghana A[1], Gangadhar J[1], Naga Lakshmi A[1], Durga Naresh Kumar G[1]

[1] *UG Scholar, Department of Pharmacology, Koringa College of Pharmacy, Korangi, Kakinada, Andhra Pradesh, India*
[2] *Associate Professor, Department of Pharmacology, Koringa College of Pharmacy, Korangi, Kakinada, Andhra Pradesh, India*

Publication history: Received on 16th July 2025; Revised on 24th Aug 2025; Accepted on 31st August 2025

Article DOI: 10.69613/ndgvdc46

Abstract: Parkinson's disease (PD) is a progressive neurodegenerative disorder characterized by the profound loss of dopaminergic neurons in the substantia nigra pars compacta and the intracellular aggregation of alpha-synuclein, forming Lewy bodies. This neuropathological process manifests clinically through cardinal motor symptoms—bradykinesia, resting tremor, rigidity, and postural instability—complemented by a complex array of non-motor symptoms, including autonomic dysfunction, cognitive impairment, and sleep disorders, which significantly impair quality of life. The etiology of PD is multifactorial, involving a complex interplay of genetic predispositions, such as mutations in LRRK2 or SNCA, and environmental risk factors, including pesticide exposure. Diagnosis remains primarily clinical, guided by established criteria, though advanced imaging like dopamine transporter scanning offers valuable support. Management is symptomatic, with levodopa therapy representing the gold standard for motor symptom control. However, long-term levodopa use is associated with motor complications, necessitating sophisticated management strategies. A holistic, multidisciplinary approach combining pharmacological treatment, physiotherapy, and patient support is essential. Current research is invariably focused on identifying disease-modifying therapies that can stop or reverse the underlying neurodegenerative cascade, representing the foremost therapeutic goal.

Keywords: Parkinson's disease; Neurodegeneration; Alpha-synuclein; Levodopa; Dopaminergic neurons

1. Introduction

Parkinson's disease (PD) is a progressive disorder of the nervous system, first systematically described in 1817 by James Parkinson as the "shaking palsy" [1]. It stands as the second most common neurodegenerative condition globally, surpassed only by Alzheimer's disease. Epidemiological data from 2016 indicated a worldwide prevalence of approximately 6.1 million individuals, a figure that has more than doubled since 1990, reflecting both improved diagnostics and an aging global population [2]. The disease exhibits a slight male predilection, with a reported male-to-female ratio of approximately 1.4:1 [3]. While the majority of PD cases are classified as idiopathic or sporadic, a growing body of research highlights a complex etiopathogenesis involving genetic susceptibility and environmental exposures.

Clinically, PD is defined by a quartet of cardinal motor features: bradykinesia (slowness of movement), resting tremor, rigidity, and, in later stages, postural instability [4]. However, it is now unequivocally recognized that PD is a complex systemic disease. It presents with a wide spectrum of non-motor symptoms (NMS) that often predate the motor diagnosis by years or even decades. These include hyposmia, constipation, REM sleep behavior disorder (RBD), depression, and anxiety [5]. As the disease advances, NMS, particularly autonomic dysfunction and cognitive decline, become major determinants of disability and reduced quality of life [6].

The core neuropathological signature of PD is the selective and progressive degeneration of dopaminergic (DA) neurons within the substantia nigra pars compacta (SNpc), leading to a profound depletion of dopamine in the striatum [7]. Histopathologically, the disease is characterized by the presence of intraneuronal proteinaceous inclusions known as Lewy bodies, primarily composed of misfolded alpha-synuclein protein [8].

Management of PD is multifaceted and aims to alleviate symptoms, maintain function, and optimize quality of life. Levodopa, a precursor to dopamine, remains the most effective symptomatic therapy since its introduction in the 1960s [9]. However, its long-term use frequently leads to motor complications, including "wearing-off" phenomena and dyskinesias. Consequently, therapeutic strategies must be highly individualized, employing a multidisciplinary team to integrate pharmacological agents, rehabilitative

* Corresponding author: Dhana Lakshmi G

therapies, and, for select patients, advanced interventions like deep brain stimulation (DBS) [10]. This review provides an overview of the etiopathogenesis, clinical spectrum, diagnosis, and management of Parkinson's disease.

2. Etiopathogenesis of Parkinson's Disease

The precise cause of neuronal death in PD remains elusive, though it is clear that the disease arises from a complex interaction between genetic vulnerability and environmental factors, culminating in several downstream cellular pathologies.

2.1. The Neuropathological Hallmarks

2.1.1. Dopaminergic Neurodegeneration

The primary motor symptoms of PD are a direct consequence of the extensive loss (60-80%) of DA neurons in the SNpc, which projects to the dorsal striatum (caudate and putamen) [7, 11]. This nigrostriatal dopamine deficiency disrupts the fine balance of the basal ganglia motor circuitry. Specifically, reduced dopamine levels lead to overactivity in the indirect pathway and underactivity in the direct pathway, resulting in increased inhibitory output from the basal ganglia to the thalamus, which subsequently reduces cortical excitation and produces the characteristic hypokinetic state (bradykinesia) [12].

2.1.2. Alpha-Synuclein and Lewy Body Formation

The definitive pathological hallmark of PD is the aggregation of misfolded alpha-synuclein (α-syn) protein, encoded by the *SNCA* gene, into oligomers, fibrils, and ultimately, the inclusions defined as Lewy bodies and Lewy neurites [8]. While it remains debated whether large Lewy body inclusions are toxic or protective, the soluble oligomeric and protofibrillar forms of α-syn are widely considered to be the primary neurotoxic species [13]. These aggregates are thought to impair crucial cellular processes, including synaptic function, protein degradation pathways (ubiquitin-proteasome system and autophagy), and mitochondrial homeostasis [14]. Furthermore, the Braak hypothesis posits that α-syn pathology may originate in the peripheral nervous system (e.g., the enteric nervous system) or the olfactory bulb and spread in a prion-like, cell-to-cell fashion to interconnected regions of the brain, explaining the rostral progression of symptoms [15].

2.2. Genetic Factors

While most PD is sporadic, 5-10% of cases are linked to monogenic forms, which have provided profound insights into the disease's molecular pathways [16]. Mutations in the *SNCA* gene (leading to α-syn multiplication or altered protein structure) cause a rare, autosomal dominant form of PD [17]. The most common genetic contributor identified to date is mutations in the *LRRK2* (leucine-rich repeat kinase 2) gene, which also follow an autosomal dominant inheritance pattern and produce a clinical picture often indistinguishable from idiopathic PD [18]. Recessive, typically early-onset forms of PD are caused by mutations in genes such as *Parkin* (PARK2), *PINK1* (PARK6), and *DJ-1* (PARK7). These three genes converge on a common pathway of mitochondrial quality control, specifically mitophagy, which is the selective removal of damaged mitochondria [19]. Beyond these monogenic forms, large-scale genome-wide association studies (GWAS) have identified over 90 common genetic risk loci that individually confer a small risk but collectively contribute significantly to the susceptibility for sporadic PD [20].

Table 1. Monogenic Forms of Parkinson's Disease

Gene Locus	Gene Name	Inheritance	Associated Protein	Pathological Feature/Pathway
PARK1/4	*SNCA*	Autosomal Dominant	Alpha-synuclein	Central component of Lewy bodies; protein aggregation.
PARK8	*LRRK2*	Autosomal Dominant	Leucine-rich repeat kinase 2	Most common dominant form; kinase activity, lysosomal function.
PARK2	*Parkin*	Autosomal Recessive	Parkin (E3 ubiquitin ligase)	Impaired mitophagy (mitochondrial quality control); proteasomal function.
PARK6	*PINK1*	Autosomal Recessive	PTEN-induced kinase 1	Mitochondrial quality control; partners with Parkin for mitophagy.
PARK7	*DJ-1*	Autosomal Recessive	DJ-1	Oxidative stress sensor; mitochondrial function.

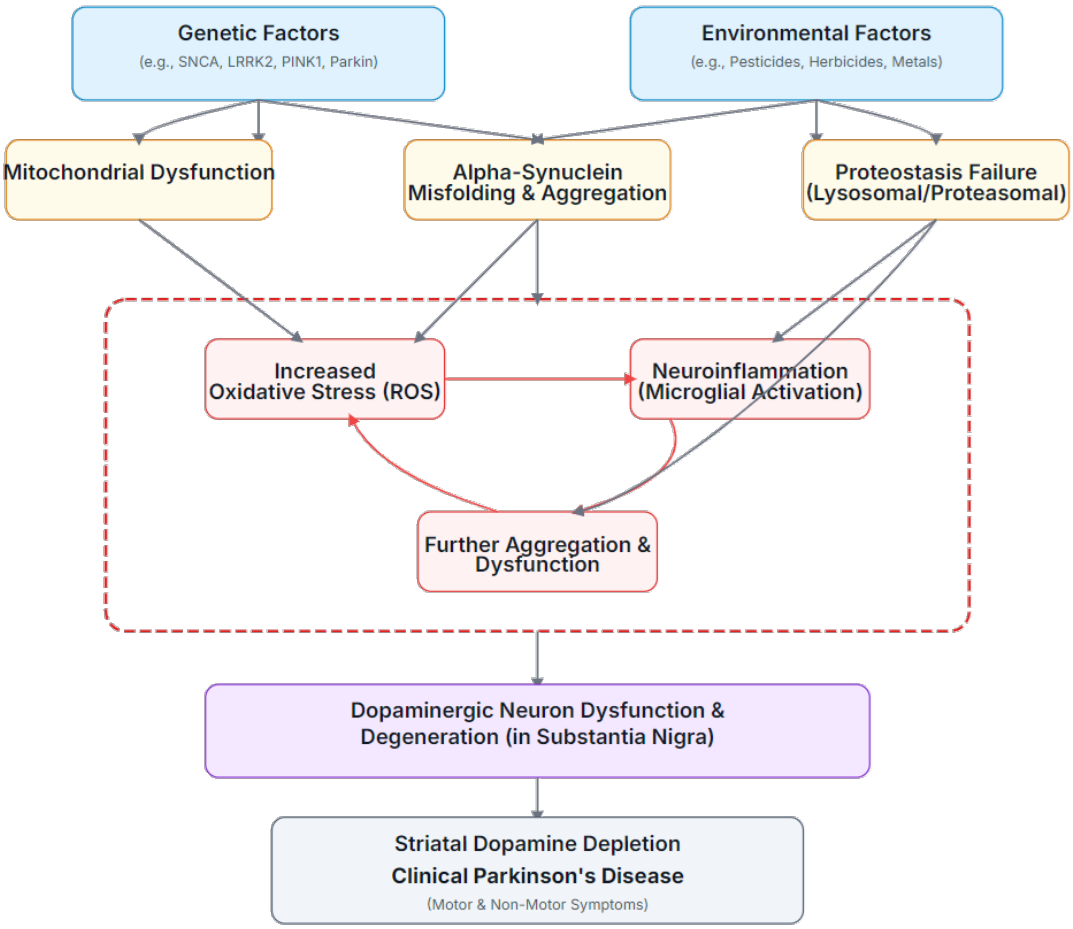

Figure 1. Etiopathogenesis of Parkinson's Disease

2.3. Environmental and Lifestyle Factors

Epidemiological studies have consistently linked exposure to certain environmental agents, particularly pesticides and herbicides (e.g., paraquat and rotenone), with an increased risk of developing PD [21]. Rotenone, a mitochondrial complex I inhibitor, can reliably reproduce features of parkinsonism in animal models. Exposure to heavy metals, such as manganese, and solvents like trichloroethylene has also been implicated [22]. Conversely, some lifestyle factors have been associated with a reduced risk of PD, most notably tobacco smoking and caffeine consumption, though the biological mechanisms underlying these negative associations are still being investigated [23].

2.4. Cellular Pathophysiological mechanisms

Several interconnected cellular processes are believed to drive the neurodegenerative cascade in PD.

2.4.1. Mitochondrial Dysfunction

Impaired mitochondrial function is a central feature of both genetic and sporadic PD [19]. Dopaminergic neurons of the SNpc are particularly vulnerable due to their high energy demands and extensive, unmyelinated axonal arborizations. Mitochondrial complex I deficiency, impaired mitophagy (as implicated by *PINK1* and *Parkin* mutations), and increased mitochondrial DNA damage all contribute to an energy deficit and the overproduction of reactive oxygen species (ROS) [24].

2.4.2. Oxidative Stress

The SNpc exists in a state of high basal oxidative stress. This is due in part to the enzymatic and auto-oxidation of dopamine itself, which generates ROS such as hydrogen peroxide and quinones. When combined with mitochondrial dysfunction and reduced levels of antioxidants like glutathione, the resulting oxidative stress overwhelms cellular defenses, leading to damage of lipids, proteins, and nucleic acids, ultimately triggering cell death pathways [25].

2.4.3. Neuroinflammation

Post-mortem studies consistently show evidence of chronic neuroinflammation in the brains of PD patients, characterized by the activation of microglial cells and astrocytes in the substantia nigra [26]. While initially a protective response, this sustained inflammatory state can become neurotoxic through the release of pro-inflammatory cytokines, chemokines, and ROS, creating a self-perpetuating cycle of inflammation and neuronal degeneration [27].

3. Clinical Manifestations

The clinical presentation of PD is heterogeneous, evolving through a long premotor phase before the classic motor signs become apparent.

3.1. Motor Symptoms

The diagnosis of parkinsonism rests on the presence of bradykinesia combined with at least one other cardinal motor sign [4].

3.1.1. Bradykinesia

This refers to slowness of movement initiation and a progressive reduction in the speed and amplitude of repetitive actions (sequence effect). It is the most characteristic feature of PD and contributes to difficulties with fine motor tasks, reduced arm swing during gait, and a masked facial expression (hypomimia).

3.1.2. Resting Tremor

The classic PD tremor is a 4-6 Hz "pill-rolling" tremor, most often beginning asymmetrically in a distal limb. It is present at rest, typically attenuates during voluntary action, and disappears during sleep.

3.1.3. Rigidity

This is an increase in muscle tone, perceived by the examiner as a constant (lead-pipe) or intermittent (cogwheel) resistance to passive movement throughout the range of motion.

3.1.4. Postural Instability

This is a later-stage feature, resulting from impairment of postural reflexes. It leads to poor balance and a high risk of falls, becoming a major source of disability.

Other associated motor features include micrographia (small, cramped handwriting), hypophonia (soft, monotone speech), dysphagia (difficulty swallowing), and a shuffling, festinating gait with reduced stride length.

Table 2. Comparison of Cardinal Motor and Common Non-Motor Symptoms

Symptom Category	Clinical Features	Examples
Motor Symptoms	Bradykinesia	Slowness of movement, reduced amplitude (e.g., micrographia), hypomimia.
	Resting Tremor	4-6 Hz "pill-rolling" tremor, typically asymmetric at onset.
	Rigidity	"Cogwheel" or "lead-pipe" stiffness on passive movement.
	Postural Instability	Impaired balance, shuffling gait, risk of falls (typically a later feature).
Non-Motor Symptoms	Autonomic	Orthostatic hypotension, constipation, urinary urgency, erectile dysfunction.
	Neuropsychiatric	Depression, anxiety, apathy, impulse control disorders.
	Cognitive	Mild Cognitive Impairment (PD-MCI), Parkinson's Disease Dementia (PDD).
	Sleep	REM Sleep Behavior Disorder (RBD), insomnia, excessive daytime sleepiness.
	Sensory	Hyposmia (loss of smell), pain, paresthesias.

3.2. Non-Motor Symptoms (NMS)

NMS are ubiquitous in PD and significantly impact patient well-being, often more so than motor symptoms, especially in advanced disease [5, 6].

3.2.1. Autonomic Dysfunction

Dysfunction of the autonomic nervous system is common. Orthostatic hypotension (a drop in blood pressure upon standing) can cause dizziness and syncope [28]. Gastrointestinal dysmotility, particularly constipation, can be a very early premotor symptom. Other features include urinary urgency and frequency, erectile dysfunction, and thermoregulatory (sweating) abnormalities.

3.2.2. Neuropsychiatric and Cognitive Symptoms

Depression and anxiety are highly prevalent, affecting up to 50% of patients [14]. Apathy (loss of motivation) is also common. Cognitive changes range from Mild Cognitive Impairment (PD-MCI), which affects a large subset of patients even at diagnosis, to Parkinson's Disease Dementia (PDD). PDD develops in a majority of patients with long disease duration and is characterized by deficits in executive function, visuospatial processing, and attention [29]. Psychotic symptoms, such as visual hallucinations and delusions, can occur, particularly in advanced disease or as a side effect of dopaminergic medications.

3.2.3. Sensory and Sleep Disturbances

Hyposmia (reduced sense of smell) is one of the earliest and most specific premotor signs of PD [5]. Pain and paresthesias are also frequently reported. Sleep disturbances are nearly universal. REM Sleep Behavior Disorder (RBD), a condition where individuals act out their dreams, is a highly specific prodromal marker for synucleinopathies, including PD [30]. Insomnia, fragmented sleep, and excessive daytime sleepiness (EDS) are also highly prevalent.

4. Diagnosis and Disease Staging

4.1. Diagnostic Process

The diagnosis of PD remains primarily clinical. It relies on a thorough neurological history and examination to identify the characteristic motor syndrome [4]. The Movement Disorder Society (MDS) Clinical Diagnostic Criteria are now the standard, requiring the presence of parkinsonism (bradykinesia plus rigidity or tremor), a clear and beneficial response to dopaminergic therapy, and the absence of "red flags" or atypical features that would suggest an alternative diagnosis [31]. These red flags include early, severe falls; symmetric onset; lack of tremor; and poor response to levodopa.

No blood test or standard imaging can definitively diagnose PD. Neuroimaging, such as Magnetic Resonance Imaging (MRI) or Computed Tomography (CT) of the brain, is primarily used to exclude structural mimics of PD, such as stroke, tumors, or normal pressure hydrocephalus [32]. The most valuable ancillary test is dopamine transporter single-photon emission computed tomography (DaTscan). This scan visualizes the density of dopamine transporters in the striatum. In PD, it typically reveals an asymmetric loss of signal, particularly in the posterior putamen, confirming a deficit in the presynaptic dopaminergic system [33].

4.2. Differential Diagnosis

"Parkinsonism" is a broader clinical syndrome, and PD is only its most common cause. A crucial diagnostic step is to differentiate idiopathic PD from atypical parkinsonian syndromes (also known as "Parkinson-plus") and secondary parkinsonism.

4.2.1. Atypical Parkinsonian Syndromes

These are distinct, more rapidly progressive neurodegenerative disorders. They include Multiple System Atrophy (MSA), characterized by severe, early autonomic failure; Progressive Supranuclear Palsy (PSP), marked by early falls and a vertical supranuclear gaze palsy; and Corticobasal Degeneration (CBD), which typically presents with asymmetric apraxia, dystonia, and cortical sensory loss [34]. These conditions generally show a limited or transient response to levodopa.

4.2.2. Secondary Parkinsonism

This includes Drug-Induced Parkinsonism, most commonly caused by dopamine-blocking agents (e.g., antipsychotics, some antiemetics), and Vascular Parkinsonism, which results from cerebrovascular disease (strokes) affecting the basal ganglia circuits [35].

Table 3: Clinical Differentiation of Parkinsonian Syndromes.

Feature	Idiopathic PD	Multiple System Atrophy (MSA)	Progressive Supranuclear Palsy (PSP)	Corticobasal Degeneration (CBD)
Symmetry	Asymmetric onset	Often symmetric	Symmetric	Markedly asymmetric
Levodopa Response	Good, sustained	Poor or transient	Poor or transient	Poor or absent
Key Motor Sign	Resting tremor, bradykinesia	Cerebellar ataxia (MSA-C) or severe parkinsonism (MSA-P)	Early falls, vertical supranuclear gaze palsy	Asymmetric apraxia, dystonia, "alien limb"
Autonomic Failure	Mild to moderate, later	Early, severe (e.g., orthostatic hypotension, stridor)	Mild	Mild
Cognitive	Later-onset dementia (PDD)	Variable, fronto-subcortical	Early frontal dysfunction, apathy	Frontal deficits, apraxia

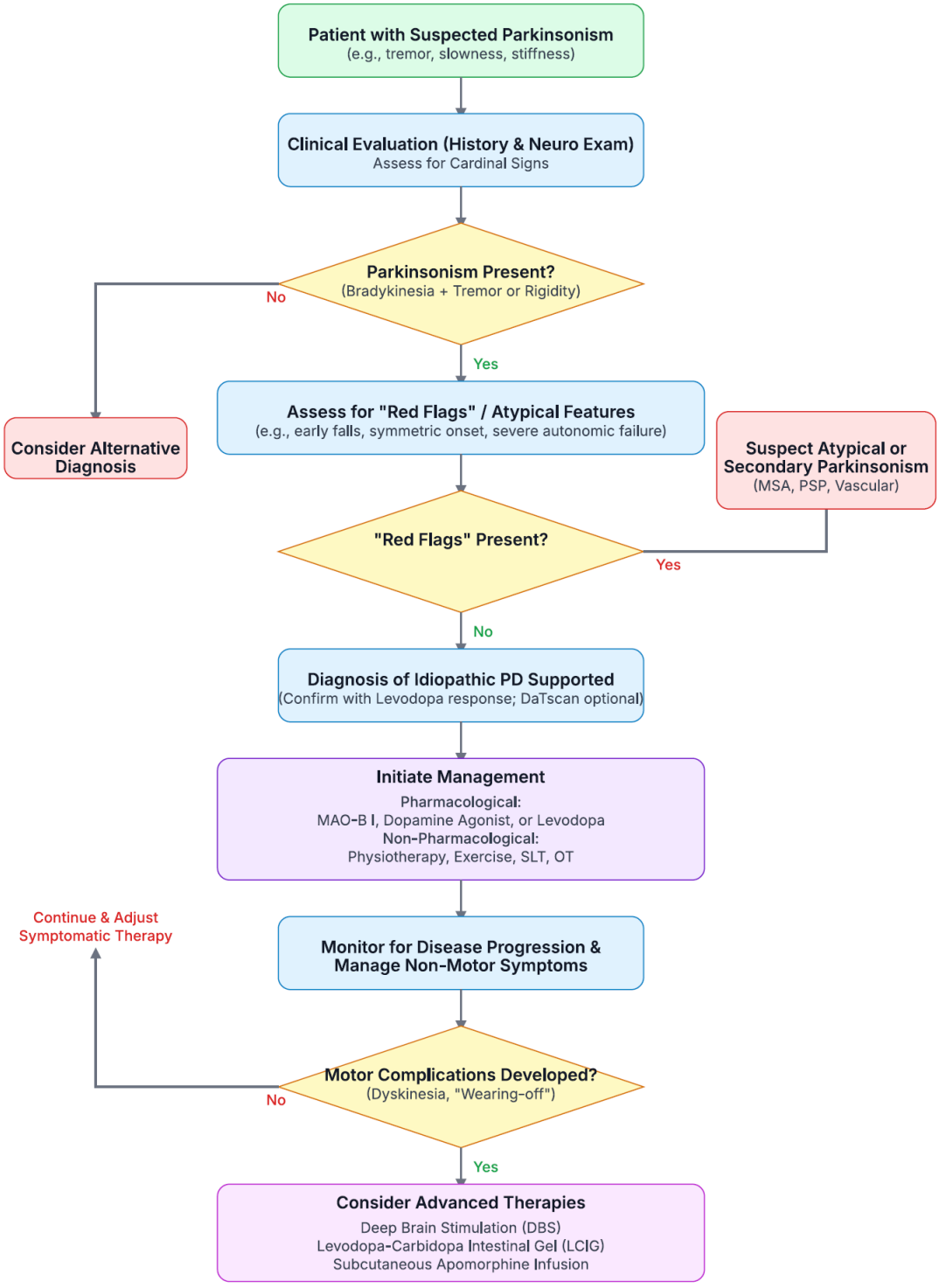

Figure 2. Clinical Diagnosis and Management Algorithm for PD

4.3. Disease Staging

Several scales are used to track disease progression. The Hoehn and Yahr (H&Y) scale is a simple 5-stage system based on motor signs and functional disability, ranging from Stage 1 (unilateral involvement) to Stage 5 (wheelchair-bound or bedridden) [36]. While simple, it is not linear and is heavily weighted toward postural instability. The most widely used tool in clinical practice and research is the MDS-Unified Parkinson's Disease Rating Scale (MDS-UPDRS). This comprehensive scale provides a detailed assessment of both motor and non-motor experiences of daily living, as well as motor examination findings and complications of therapy [37].

Table 4. Hoehn and Yahr (H&Y) Staging Scale

Stage	Description of Clinical State
Stage 1	Unilateral involvement only, usually with minimal or no functional impairment.
Stage 2	Bilateral involvement without impairment of balance.
Stage 3	Mild to moderate bilateral disease; some postural instability, but physically independent.
Stage 4	Severe disability; still able to walk or stand unassisted.
Stage 5	Wheelchair-bound or bedridden unless aided

5. Management of PD

As no disease-modifying therapy currently exists, all PD treatments are symptomatic, aimed at correcting the neurochemical imbalance and managing motor and non-motor complications through a multidisciplinary team approach.

5.1. Pharmacological Therapy

5.1.1. Levodopa

Levodopa, the metabolic precursor of dopamine, remains the most potent medication for controlling the motor symptoms of PD [9]. It is administered in combination with a peripheral decarboxylase inhibitor (e.g., carbidopa or benserazide) to prevent its conversion to dopamine outside the brain, thereby increasing its central bioavailability and reducing peripheral side effects like nausea and orthostatic hypotension [38].

5.1.2. Motor Complications

While highly effective, chronic levodopa therapy is complicated by the development of motor fluctuations and dyskinesias in a majority of patients after 5-10 years. "Wearing-off" refers to the re-emergence of motor symptoms as the effect of a levodopa dose wanes. Levodopa-induced dyskinesia (LID) refers to involuntary, choreiform (dance-like) movements, typically occurring at peak levodopa plasma concentrations [39]. Managing these complications involves adjusting levodopa dosing frequency, adding other medications, or considering advanced therapies.

Table 5. Major Pharmacological Classes for Parkinson's Disease Management

Drug Class	Examples	Mechanism of Action	Clinical Use
Dopamine Precursor	Levodopa/Carbidopa	Converted to dopamine in the brain.	Most effective for motor symptoms (bradykinesia, rigidity).
Dopamine Agonists	Pramipexole, Ropinirole, Rotigotine	Directly stimulate dopamine receptors.	Monotherapy in early PD or adjunct in later PD to reduce "off" time.
MAO-B Inhibitors	Rasagiline, Selegiline, Safinamide	Inhibit the breakdown of dopamine by the MAO-B enzyme.	Mild symptomatic benefit in early PD or adjunct to levodopa.
COMT Inhibitors	Entacapone, Opicapone	Block the peripheral metabolism of levodopa, extending its half-life.	Used with levodopa to reduce "wearing-off" phenomena.
NMDAR Antagonist	Amantadine	Complex mechanism, including NMDA receptor blockade.	Mild symptomatic benefit; primarily used to reduce dyskinesias.
Anticholinergics	Trihexyphenidyl	Block muscarinic acetylcholine receptors, rebalancing striatal activity.	Used for tremor in younger patients (limited by side effects).

5.1.3. Other Dopaminergic Agents

Dopamine Agonists: Drugs such as pramipexole, ropinirole, and rotigotine directly stimulate postsynaptic dopamine receptors. They are used as monotherapy in early PD (to delay the need for levodopa) or as an adjunct to levodopa in later stages to reduce "off" time [40]. Their use can be limited by side effects, including nausea, EDS, and, notably, impulse control disorders (e.g., compulsive gambling, shopping, or hypersexuality) [41].

MAO-B Inhibitors: Selegiline, rasagiline, and safinamide inhibit the monoamine oxidase B (MAO-B) enzyme, which metabolizes dopamine in the brain. This provides a mild symptomatic benefit and can be used in early disease or as an adjunct to levodopa to prolong its effect [42].

COMT Inhibitors: Entacapone, opicapone, and tolcapone block the catechol-O-methyltransferase (COMT) enzyme, another pathway for levodopa metabolism. When co-administered with levodopa, they extend its plasma half-life, thereby increasing "on" time and reducing "wearing-off" [43].

5.1.4. Non-Dopaminergic Agents

Anticholinergic agents (e.g., trihexyphenidyl) are occasionally used, primarily for tremor in younger patients, but their utility is limited by cognitive and autonomic side effects [44]. Amantadine, which has complex mechanisms including NMDA receptor antagonism, offers mild symptomatic relief and is particularly useful for reducing levodopa-induced dyskinesia [45]. The management of NMS is equally critical and targets specific symptoms, such as using SSRIs or SNRIs for depression, cholinesterase inhibitors (e.g., rivastigmine) for PDD, and laxatives for constipation [6].

6. Non-Pharmacological and Supportive Care

A multidisciplinary team (MDT) is essential for overall PD care [10].

6.1. Physiotherapy

Exercise is crucial. Physical therapists design programs to improve gait, balance, flexibility, and cardiovascular fitness, which have been shown to improve motor scores and quality of life [46].

6.2. Speech and Language Therapy

This is vital for addressing hypophonia (e.g., through Lee Silverman Voice Treatment - LSVT LOUD) and managing dysphagia to prevent aspiration pneumonia [47].

6.3. Occupational Therapy

Occupational therapists help patients maintain independence and safety in activities of daily living by recommending adaptive strategies and environmental modifications.

6.4. Other Therapies

For patients who develop motor complications that are inadequately controlled by oral or transdermal medications, advanced therapies are considered.

6.4.1. Deep Brain Stimulation (DBS)

This is a neurosurgical procedure involving the implantation of electrodes into specific basal ganglia targets, most commonly the subthalamic nucleus (STN) or globus pallidus interna (GPi) [29, 48]. The electrodes deliver high-frequency electrical stimulation, which modulates the abnormal network activity. DBS is highly effective at controlling motor fluctuations, tremor, and dyskinesia.

6.4.2. Continuous Infusion Therapies

These strategies aim to provide more continuous, stable dopaminergic stimulation. This includes levodopa-carbidopa intestinal gel (LCIG), delivered via a percutaneous gastro-jejunostomy (PEG-J) tube, and continuous subcutaneous apomorphine (a potent dopamine agonist) infusion via a portable pump [49, 50].

7. Conclusion

Parkinson's disease is a heterogeneous, multisystem disorder originating from a combination of genetic and environmental factors that drive a cascade of cellular pathologies, including protein misfolding, mitochondrial dysfunction, and neuroinflammation. Its clinical presentation includes a debilitating array of non-motor symptoms that evolve over the disease course. Diagnosis remains clinical, supported by ancillary imaging to confirm dopaminergic loss and exclude mimics. Current management is entirely symptomatic, with levodopa as the therapeutic cornerstone. While pharmacological and surgical interventions can provide excellent control of motor symptoms, they do not alter the relentless progression of the underlying neurodegeneration. Current research is focused on this goal, with promising strategies targeting the aggregation and spread of alpha-synuclein (e.g., immunotherapies), correcting mitochondrial dysfunction, modulating neuroinflammation, and repurposing existing drugs (e.g., GLP-1 agonists).

References

[1] Parkinson J. An essay on the shaking palsy. London: Sherwood, Neely, and Jones; 1817.

[2] GBD 2016 Parkinson's Disease Collaborators. Global, regional, and national burden of Parkinson's disease, 1990–2016: a systematic analysis for the Global Burden of Disease Study 2016. Lancet Neurol. 2018 Nov;17(11):939-53.

[3] Poewe W, Seppi K, Tanner CM, Halliday GM, Brundin P, Volkmann J, et al. Parkinson disease. Nat Rev Dis Primers. 2017 Mar 23;3:17013.

[4] Jankovic J. Parkinson's disease: clinical features and diagnosis. J Neurol Neurosurg Psychiatry. 2008 Apr;79(4):368-76.

[5] Schapira AHV, Chaudhuri KR, Jenner P. Non-motor features of Parkinson disease. Nat Rev Neurosci. 2017 Jul;18(7):435-50.

[6] Martinez-Martin P, Rodriguez-Blazquez C, Kurtis MM, Chaudhuri KR; NMSS Validation Group. The impact of non-motor symptoms on health-related quality of life of patients with Parkinson's disease. Mov Disord. 2011 Mar;26(3):399-406.

[7] Hornykiewicz O. The discovery of dopamine deficiency in Parkinson's disease. J Neural Transm Suppl. 2006;(70):9-15.

[8] Spillantini MG, Schmidt ML, Lee VM, Trojanowski JQ, Jakes R, Goedert M. Alpha-synuclein in Lewy bodies. Nature. 1997 Aug 28;388(6645):839-40.

[9] Cotzias GC, Papavasiliou PS, Gellene R. Modification of Parkinsonism--chronic treatment with L-dopa. N Engl J Med. 1969 Feb 13;280(7):337-45.

[10] Bloem BR, de Vries NM, Ebersbach G. Multidisciplinary strategies for the management of Parkinson's disease. Parkinsonism Relat Disord. 2015 Jul;21(Suppl 1):S137-41.

[11] Fearnley JM, Lees AJ. Ageing and Parkinson's disease: substantia nigra regional selectivity. Brain. 1991 Oct;114(Pt 5):2283-301.

[12] DeLong MR. Primate models of movement disorders of basal ganglia origin. Trends Neurosci. 1990 Jul;13(7):281-5.

[13] Lashuel HA, Oueslati A, Masliah E. The many faces of alpha-synuclein: from structure and toxicity to therapeutic target. Nat Rev Neurosci. 2013 Jan;14(1):38-48.

[14] Goedert M, Spillantini MG, Del Tredici K, Braak H. 100 years of Lewy bodies. Nat Rev Neurol. 2013 Jan;9(1):13-24.

[15] Braak H, Del Tredici K, Rüb U, de Vos RA, Jansen Steur EN, Braak E. Staging of brain pathology related to sporadic Parkinson's disease. Neurobiol Aging. 2003 Mar-Apr;24(2):197-211.

[16] Kalia LV, Lang AE. Parkinson's disease. Lancet. 2015 Aug 29;386(9996):896-912.

[17] Polymeropoulos MH, Lavedan C, Leroy E, Ide SE, Dehejia A, Dutra A, et al. Mutation in the alpha-synuclein gene identified in families with Parkinson's disease. Science. 1997 Jun 27;276(5321):2045-7.

[18] Zimprich A, Biskup S, Leitner P, Lichtner P, Farrer M, Lincoln S, et al. Mutations in LRRK2 cause autosomal-dominant parkinsonism with pleomorphic pathology. Neuron. 2004 Nov 18;44(4):601-7.

[19] Pickrell AM, Youle RJ. The roles of PINK1, parkin, and mitochondrial quality control in Parkinson's disease. Neuron. 2015 Jan 21;85(2):257-73.

[20] Blauwendraat C, Nalls MA, Singleton AB. The genetic architecture of Parkinson's disease. Lancet Neurol. 2020 Feb;19(2):170-8.

[21] Tanner CM, Kamel F, Ross GW, Hoppin JA, Goldman SM, Korell M, et al. Rotenone, paraquat, and Parkinson's disease. Environ Health Perspect. 2011 Jun;119(6):866-72.

[22] Goldman SM. Environmental toxins and Parkinson's disease. Annu Rev Pharmacol Toxicol. 2014;54:141-64.

[23] Ascherio A, Schwarzschild MA. The epidemiology of Parkinson's disease: risk factors and prevention. Lancet Neurol. 2016 Nov;15(12):1257-72.

[24] Schapira AH, Cooper JM, Dexter D, Jenner P, Clark JB, Marsden CD. Mitochondrial complex I deficiency in Parkinson's disease. J Neurochem. 1990 Mar;54(3):823-7.

[25] Jenner P. Oxidative stress in Parkinson's disease. Ann Neurol. 2003;53(S3):S26-38.

[26] McGeer PL, Itagaki S, Boyes BE, McGeer EG. Reactive microglia are positive for HLA-DR in the substantia nigra of Parkinson's and Alzheimer's disease brains. Neurology. 1988 Aug;38(8):1285-91.

[27] Hirsch EC, Hunot S. Neuroinflammation in Parkinson's disease: a target for neuroprotection? Lancet Neurol. 2009 Apr;8(4):382-97.

[28] Goldstein DS. Orthostatic hypotension as an early finding in Parkinson's disease. Clin Auton Res. 2006 Feb;16(1):4-11.

[29] Aarsland D, Batzu L, Halliday G, Geurtsen GJ, Ballard C, Chaudhuri KR, et al. Parkinson disease-associated cognitive impairment. Nat Rev Dis Primers. 2021 Jul 1;7(1):47.

[30] Schenck CH, Boeve BF, Mahowald MW. Delayed emergence of a parkinsonian disorder or dementia in 81% of older men initially diagnosed with idiopathic REM sleep behavior disorder: a 16-year update on a 44-patient cohort. Sleep Med. 2013 Aug;14(8):744-8.

[31] Postuma RB, Berg D, Stern M, Poewe W, Olanow CW, Obeso J, et al. MDS clinical diagnostic criteria for Parkinson's disease. Mov Disord. 2015 Oct;30(12):1591-601.

[32] Brooks DJ. Imaging approaches to Parkinson disease. J Nucl Med. 2010 Apr;51(4):596-609.

[33] Benamer HT, Patterson J, Grosset DG, Booij J, de Bruin K, van Royen E; [123I]-FP-CIT Study Group. Accurate differentiation of parkinsonism and essential tremor using visual assessment of [123I]-FP-CIT SPECT imaging. Mov Disord. 2000 May;15(3):503-10.

[34] Armstrong MJ, Okun MS. Diagnosis and treatment of Parkinson disease: a review. JAMA. 2020 Feb 11;323(6):548-60.

[35] Zijlmans JCM, Daniel SE, Hughes AJ, Révész T, Lees AJ. Clinicopathological investigation of vascular parkinsonism, including clinical criteria for diagnosis. Mov Disord. 2004 Jun;19(6):630-40.

[36] Hoehn MM, Yahr MD. Parkinsonism: onset, progression, and mortality. Neurology. 1967 May;17(5):427-42.

[37] Goetz CG, Tilley BC, Shaftman SR, Stebbins GT, Fahn S, Martinez-Martin P, et al. Movement Disorder Society-sponsored revision of the Unified Parkinson's Disease Rating Scale (MDS-UPDRS): scale presentation and clinimetric testing. Mov Disord. 2008 Nov 15;23(15):2129-70.

[38] Tambasco N, Romoli M, Calabresi P. Levodopa in Parkinson's disease: current status and future developments. Curr Neuropharmacol. 2018;16(8):1239-52.

[39] Cenci MA. Levodopa-induced dyskinesia: pathology and mechanisms. Parkinsonism Relat Disord. 2014 Jan;20(Suppl 1):S73-8.

[40] Schapira AHV. The clinical application of dopamine agonists. J Neurol. 2008;255(Suppl 1):32-7.

[41] Weintraub D, Koester J, Potenza MN, Siderowf AD, Stacy M, Voon V, et al. Impulse control disorders in Parkinson disease: a cross-sectional study of 3090 patients. Arch Neurol. 2010 May;67(5):589-95.

[42] Riederer P, Lachenmayer L, Laux G. Clinical applications of MAO-inhibitors. Curr Med Chem. 2004 Aug;11(15):2033-43.

[43] Fabbri M, Ferreira JJ, Antonini A. The role of COMT inhibitors in the new millennium of Parkinson's disease therapy. Expert Rev Neurother. 2017 Jul;17(7):699-709.

[44] Kalia LV, Lang AE. Parkinson's disease. Lancet. 2015 Aug 29;386(9996):896-912.

[45] Wolf E, Seppi K, Katzenschlager R, Poewe W. Long-term antidyskinetic efficacy of amantadine in Parkinson's disease. Mov Disord. 2010 Jul 30;25(10):1357-63.

[46] Tomlinson CL, Patel S, Meek C, Herd CP, Clarke CE, Stowe R, et al. Physiotherapy intervention in Parkinson's disease: systematic review and meta-analysis. BMJ. 2012 Aug 6;345:e5004.

[47] Ramig LO, Halpern A, Spielman J, Fox C, Freeman K. Speech treatment in Parkinson's disease: a career-long quest for effective intervention. J Med Speech Lang Pathol. 2018;25(4):1-18.

[48] Deuschl G, Schade-Brittinger C, Krack P, Völkmann J, Wawrzyniak M, Hidding E, et al. A randomized trial of deep-brain stimulation for Parkinson's disease. N Engl J Med. 2006 Aug 31;355(9):896-908.

[49] Olanow CW, Kieburtz K, Odin P, Espay AJ, Stocchi F, Schapira AH, et al. Continuous intrajejunal infusion of levodopa-carbidopa intestinal gel for patients with advanced Parkinson's disease: a randomised, controlled, double-blind, double-dummy study. Lancet Neurol. 2014 Feb;13(2):141-9.

[50] Katzenschlager R, Poewe W, Rascol O, Trenkwalder C, Deuschl G, Sampaio C, et al. Apomorphine subcutaneous infusion in patients with Parkinson's disease with persistent motor fluctuations (TOLEDO): a multicentre, double-blind, randomised, placebo-controlled trial. Lancet Neurol. 2018 Sep;17(9):749-59.