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Parkinson's disease: A narrative review of epidemiology, pathogenesis, and current diagnostic and therapeutic approaches

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Parkinson's Disease; Neurodegenerative Disorders; Dopaminergic Treatment; Alpha-Synuclein; Diagnosis

Abstract

Background: Parkinson's disease (PD) is the second most common and fastest-growing neurodegenerative disease in the world. Patients with PD may experience a variety of motor and non-motor symptoms that require appropriate management. This review aims to provide an overview of the current diagnostic and therapeutic approaches for PD.

Methods: Articles for this narrative review were selected through searches of PubMed database. The review synthesizes information by critically evaluating high-quality review/original articles and considering new strategies.

Results: Despite technological advances in recent years, PD remains primarily diagnosed through clinical evaluation. Physicians should suspect parkinsonism syndrome in patients presenting with bradykinesia, resting tremor, and/or muscle rigidity. A thorough assessment is necessary to confirm the diagnosis of PD, taking into account signs and symptoms that support or contradict it. Managing PD requires a holistic approach that addresses both motor and non-motor symptoms. Current pharmacotherapeutic agents for PD primarily provide symptomatic relief. The mainstay of oral treatment for motor symptoms is the combination of levodopa with peripheral decarboxylase inhibitors. For non-motor symptoms, various medical and rehabilitative treatments have been proposed.

Conclusion: The diverse signs and symptoms of PD emphasize the physician's role in both diagnosis and treatment.

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Currently, the gold standard for diagnosing PD is clinical evaluation. Further studies are needed to develop objective measures for diagnosing and monitoring the disease. While various therapeutic strategies have been established for both motor and non-motor symptoms of PD, there is an urgent need for more clinical trials focused on disease-modifying therapies for this relentlessly progressive disorder.

Introduction

Parkinson's disease (PD) is the second most common neurodegenerative disorder and is currently regarded as the fastest-growing condition in clinical neuroscience, largely due to its socioeconomic impact.[1] Consequently, timely diagnosis and appropriate management are essential. Parkinsonism is clinically defined as the presence of bradykinesia accompanied by tremor at rest and/or muscle rigidity.[2] PD is the most prevalent cause of parkinsonism. It is typically characterized by three main symptoms: bradykinesia (slowness of movement), muscle rigidity, and resting tremor. Additionally, detailed diagnostic criteria have been established, which include essential signs and symptoms, supporting items, and exclusion features to aid in the diagnosis of the disease.[3]

Although the degeneration of dopaminergic neurons in the substantia nigra (SN) was once considered the primary cause of PD and was thought to primarily affect motor functions, recent studies have shown that the pathology of PD extends beyond the SN. Consequently, PD involves a broad spectrum of both motor and non-motor symptoms.[4]

In this narrative review, we summarize current epidemiological and pathobiological data about PD and present the latest evidence for diagnosis and treatment strategies.

Materials and Methods

This narrative review was conducted through a systematic search of medical literature, supplemented by the authors' clinical expertise. A comprehensive search was performed using the PubMed database for English-language publications spanning from 2010 to 2025. The search strategy utilized the following terms within article titles and abstracts: (Parkinson's disease OR PD) AND (diagnosis OR management OR therapy OR treatment OR epidemiology OR pathogenesis). Initial screening included all review and original articles published in journals with an impact factor > 2.0. Following an initial review by all authors, the lead author (A.SH) performed the final selection of seminal relevant articles, prioritizing high-quality and frequently cited studies. If in a final selected article, an important point had been mentioned based on another article, the primary original article was studied and cited in the review.

Wide terminology used in the search strategy was a major strength of this review. However, several limitations should be acknowledged, including reliance on a single database (PubMed), the exclusion of the main text of the articles in the original search, and the omission of non-English databases.

Epidemiology

The incidence of PD increases with age and is higher in male gender.[5] Epidemiological studies have shown a higher prevalence among White individuals compared to Black or Asian populations.[6] Over the past 25 years, the global prevalence of PD has doubled, currently affecting over more than 6 million people worldwide. This number is expected to double again by 2040,[7] prompting several researchers to label the situation a PD pandemic.[8]

The prevalence of PD is approximately 0.5% among individuals over 45 years of age.[9] In Iran, the estimated prevalence is 130 to 140 cases per 100000 people. With population aging, the economic and social burden of the disease increases worldwide.[10] In 2016, the disability-adjusted life years (DALYs) associated with PD in Iran were recorded at 30138, highlighting its significant impact on public health.[7]

Pathophysiology

PD is currently classified as a degenerative proteinopathy. The pathology involves structural changes and aggregation of alpha-synuclein (α-synuclein) proteins within neurons. The loss of normal α-synuclein function, along with the toxic effects of these deposited proteins, contributes to neural degeneration.[11,12]

A key pathological feature is the loss of pigmented neurons, particularly dopaminergic neurons in the SN, which underlies many of the clinical symptoms of PD.[13] The aggregation of α-synuclein can spread to nearby neurons in a prion-like manner. A major pathological sign of PD is the presence of Lewy bodies—clumps within nerve cells primarily composed of misfolded α-synuclein—and Lewy neurites, which are abnormal nerve cell processes containing α-synuclein. These abnormal structures are typical

features of Lewy body disorders (LBDs), including PD and dementia with Lewy bodies (DLB).[14,15]

Although many of the movement symptoms of the disease arise from the death of dopaminergic neurons in the SN and the dysfunction of extrapyramidal circuits, recent evidence suggests that many extra-striatal areas of the brain, as well as the peripheral nervous system (PNS), are also influenced by abnormal α-synuclein accumulation, contributing to the various motor and non-motor symptoms of PD.[11,12] Despite extensive research, the precise cause of cell degeneration in PD remains unclear. Several mechanisms have been proposed, including neuroinflammation, oxidative stress, mitochondrial dysfunction, aberrant initiation of apoptosis, and impaired calcium metabolism, which may act alone or in combination.[11,16]

Factors such as advanced age, Caucasian ethnicity, air pollution, industrialization, modern lifestyles, a history of repeated head trauma, consumption of dairy products and animal fats, exposure to specific toxins (e.g., agricultural pesticides), central nervous system (CNS) infections, and well water consumption have all been linked to a higher incidence of PD in epidemiological studies.[17-20] However, no proven environmental risk factor has been definitively identified.[21-23] Genetic factors also appear to play a role, particularly in juvenile-onset (before age 21) and early-onset (before age 50) variants.[24] Overall, the etiology of PD is widely considered to be multifactorial.

Recently, two new classifications for PD have been proposed: the Neuronal α-Synuclein Disease (NSD) model and the Synucleinopathy–Neurodegeneration–Genetics (SynNeurGe) model. These classifications are based on biological changes related to clinical findings and help foster a more precise understanding of PD, facilitating earlier diagnosis and improving future therapeutic clinical trials. Additionally, these definitions enhance the accuracy of tracking disease stages.[25-27] The NSD model emphasizes three key features: abnormal aggregation of α-synucleins—measured by the cerebrospinal fluid (CSF) α-synuclein seed amplification assay (SAA)—dopaminergic dysfunction—as shown by dopamine transporter (DaT) scan—and genetic status (SNCA). By integrating these features with functional impairments indicated by clinical signs and symptoms, the model leads to a system known as the NSD-integrated staging system (NSD-ISS), which ranges from 0 (G+) to 6 (both "S+" and "D+" plus severe functional impairment).[27] The SynNeurGe model focuses on the presence or absence of pathological α-synuclein (S) in skin or CSF, evidence of underlying neurodegeneration (N) determined by neuroimaging techniques [e.g., positron emission tomography (PET) or DaTscan], and documentation of pathogenic gene variants (G) that either cause or significantly predispose individuals to PD (including SNCA, LRRK2, VPS35, CHCHD2, PRKN, PINK1, and PARK7).[27,28] Both systems aim to characterize PD as a biological disease rather than just a collection of symptoms. They bridge the gap between research and clinical care and move us toward personalized medicine for PD.[26]

Clinical features

PD presents both motor and non-motor symptoms. Motor symptoms typically start on one side of the body and, as the disease progresses, they tend to affect both sides. However, these symptoms usually remain more pronounced on the initial side.[29] Conversely, non-motor symptoms are highly prevalent and can exert a more significant impact on patients' quality of life (QoL) than motor dysfunction. Many of these non-motor symptoms can be observed in the early stages of the disease or even during prodromal phases.

Motor symptoms: Tremors are one of the most common symptoms of PD, ultimately affecting up to 70% of patients. These tremors typically present at rest but can also appear as postural or kinetic tremors. Patients who have tremor-dominant PD usually have a better prognosis compared to those with the akinetic-rigid type of the disorder. Muscle rigidity generally begins asymmetrically and later becomes bilateral, eventually involving the trunk and neck. Bradykinesia represents the cardinal feature of PD; its absence in patients who are not receiving any antiparkinsonian medication almost rules out a diagnosis of parkinsonism. Individuals with PD may experience reduced spontaneous movements, have masked facial expressions, and blink less frequently. A shuffling gait is common, often accompanied by symptoms such as festination, stooped postures, freezing episodes, and impaired postural reflexes, which increase the risk of falls, especially in the intermediate and later stages of the disease. Other hallmark features of PD include micrographia (small and often illegible handwriting), low-volume speech (hypophonia) that is often monotone, and bradyphrenia, which refers to a slowing of the thinking process without the presence of a cognitive disorder.[29]

Non-motor symptoms: Non-motor manifestations are prevalent in PD and are increasingly recognized as significant contributors to disability and reduced QoL. While prominent cognitive impairment is not typically observed in the early stages of PD, many patients experience minor cognitive complaints even during the prodromal phase of the disorder. Over time, a variety of cognitive disorders may develop. Many patients exhibit mild cognitive impairment (PD-MCI), which does not yet have a strong impact on their daily lives. However, at least 30% of individuals with PD will eventually develop overt dementia during the course of their illness. Each year, approximately 4%-5% of patients are diagnosed with PD dementia (PDD).[30] Risk factors that may lead to faster cognitive decline include advanced age, severe motor symptoms, rapid eye movement (REM) sleep behavior disorder (RBD), vascular disease, and extensive Lewy body pathology.[31,32]

Depression is a prevalent manifestation that may serve as an early sign of the disease, affecting about one-third of patients. Other frequent non-motor symptoms include sensory issues such as fatigue, limb pain, and restlessness (or akathisia), as well as constipation, weight loss, reduced sense of smell (hyposmia, often occurring in the early stages), drooling, difficulty swallowing (dysphagia), sleep disorders (including insomnia, excessive sleepiness, and RBD), urinary problems (such as frequency, urgency, and urge incontinence), sexual dysfunction, and postural hypotension. While dysautonomia (dysfunction of the autonomic nervous system) is typically a later symptom resulting from the involvement of Lewy bodies, it can appear earlier as a side effect of dopaminergic medications. Similarly, neuropsychiatric symptoms, including hallucinations, delusions, and impulse control disorders (ICDs), can arise from the disease pathology or emerge as treatment-related complications.[33]

Prodromal symptoms: Several non-motor features can appear years or even decades before the onset of motor dysfunction. Two particularly notable examples are hyposmia and RBD. RBD is characterized by the loss of normal muscle atonia during REM sleep, leading to behaviors that may include limb movements mimicking activities like running or flailing.[34,35] Polysomnography (PSG)-confirmed RBD is considered one of the strongest prodromal markers, with a positive likelihood ratio (LR+) of approximately 130. Studies indicate that at least 90% of patients with idiopathic RBD ultimately develop α-synucleinopathies, such as PD.[36] Hyposmia, especially in men, is a consistent prodromal feature with strong predictive value (LR+ ≈ 6.4).[34]

In addition to the well-established features, several non-motor clinical markers may significantly aid in the diagnosis of prodromal PD. These markers include constipation, excessive daytime sleepiness (EDS), erectile dysfunction, urinary dysfunction, and orthostatic hypotension (OH)—particularly the neurogenic type, which has a LR+ of approximately 18.5. Additionally, depression may present with or without anxiety. The updated Movement Disorder Society (MDS) criteria have also introduced new markers, including type II diabetes mellitus (DM) (LR+ ≈ 1.5), global cognitive deficits (LR+ ≈ 1.8), physical inactivity (LR+ ≈ 1.3), and low plasma urate levels in men (LR+ ≈ 1.8).[34]

Research is currently exploring several new laboratory and paraclinical biomarkers for identifying prodromal PD. These include phosphorylated α-synuclein found in skin or salivary gland biopsies,[37-39] advanced imaging techniques like nigral magnetic resonance imaging (MRI) and cardiac metaiodobenzylguanidine (MIBG) scans,[40] as well as gut-related markers such as inflammatory bowel disease (IBD) and changes in the gut microbiome.[41]

Prodromal PD consists of various non-motor symptoms. Some symptoms, such as RBD and hyposmia, are very specific to the condition. Others are less specific but still provide valuable information when considered collectively. A thorough evaluation of these symptoms is crucial for early diagnosis, risk assessment, and planning potential future disease-modifying treatments in the early stages of the disease.[34,42]

Diagnosis

PD is mainly diagnosed based on clinical observations in accordance with the MDS Clinical Diagnostic Criteria for PD.[36] Additional diagnostic tools, such as brain MRI, dopamine PET scans, single photon emission computed tomography (SPECT) imaging, and laboratory biomarkers, are currently considered complementary for diagnosis. When evaluating a patient suspected of having PD, it is essential to first establish the presence of parkinsonism, which is defined as bradykinesia accompanied by tremor at rest and/or rigidity. Diagnosing PD requires an understanding of the signs and symptoms that support the diagnosis

(supporting features), those that indicate it may not be PD (red flags), and findings that help rule out the diagnosis (exclusion criteria).[43]

Supporting features of PD include a marked response to levodopa treatment, significant olfactory dysfunction, limb tremor at rest, and dyskinesia induced by levodopa. However, certain features can rule out PD. These include marked cerebellar symptoms, downward gaze palsy, significant behavioral changes suggesting frontotemporal dementia, symptoms confined to the lower limbs for more than three years, no response to an adequate dose of levodopa over an appropriate duration, development of parkinsonism after using anti-dopamine medications, presence of unequivocal sensory cortical dysfunction, and identification of an alternative cause for the parkinsonism. Red flags that could indicate a diagnosis other than PD include a rapid progression of the disease that requires the use of a wheelchair within five years, frequent falls within the first three years of onset, no progression of symptoms for more than five years, early onset of dysphagia and speech disorders within the first five years, inspiratory stridor, severe autonomic symptoms in the first five years, severe antecollis or limb deformity within the first ten years, absence of any non-motor symptoms in the first five years, symmetrical occurrence of symptoms, and presence of unexplained pyramidal symptoms. These criteria can aid in the differential diagnosis of PD.

To establish a diagnosis of PD, a patient must exhibit parkinsonism, demonstrate no signs or symptoms that could rule out the disease, and display no more than two red flags, provided that there are at least as many supporting symptoms as there are red flags, as shown in figure 1.[44]

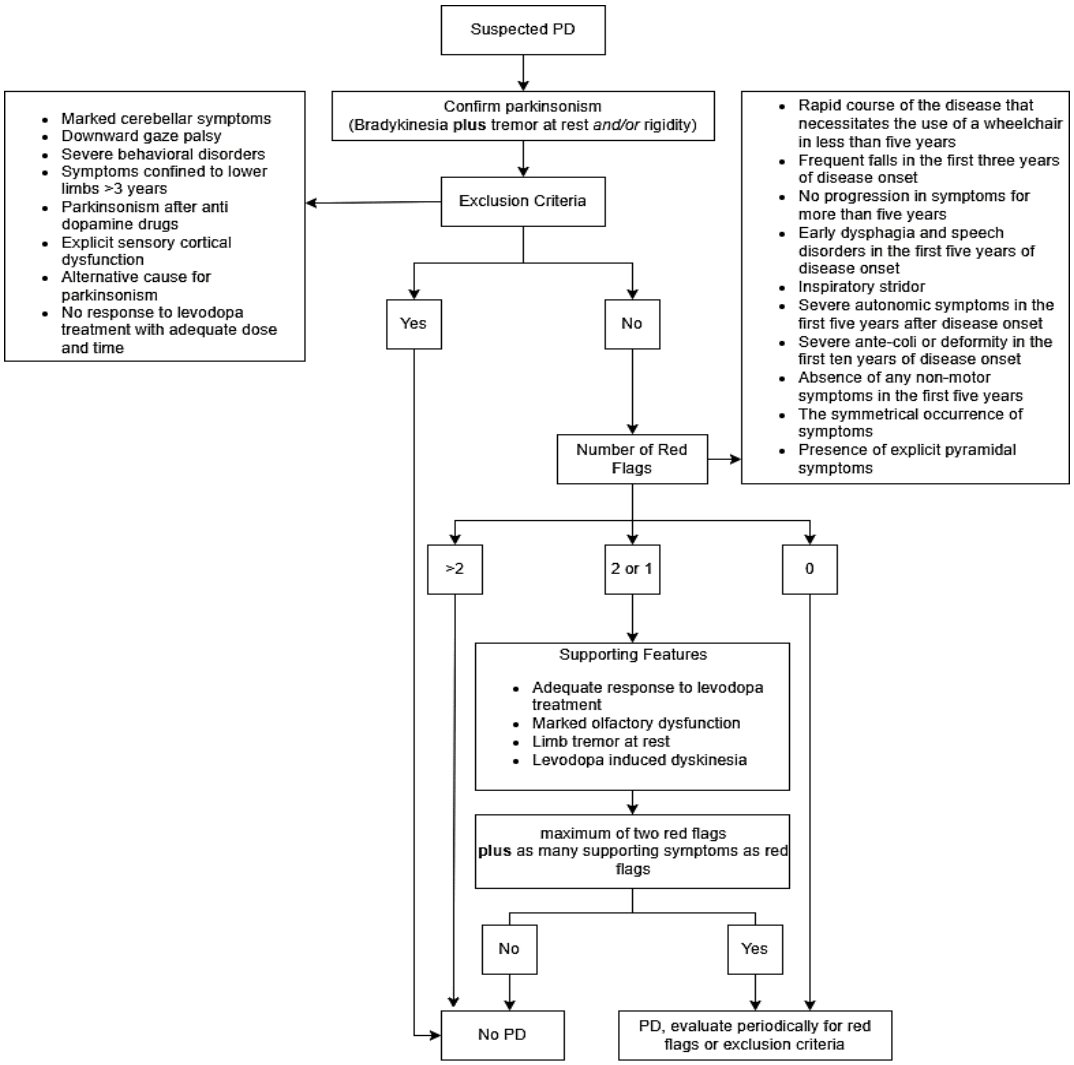


Figure 1. Diagnosis of Parkinson's disease (PD)

Along with clinical evaluation, diagnostic tools can enhance diagnostic accuracy. A routine brain MRI often appears normal in the early stages of the disease.[45] Other imaging modalities, such as PET scans, DaTscans, and SPECT, can help evaluate nigrostriatal dopaminergic function. These scans can reveal asymmetrical striatal dopamine loss, particularly with a dominant loss in the posterior putamen, especially in the early stages of PD. However, it is important to note that DaT SPECT cannot accurately differentiate between PD and other degenerative parkinsonian syndromes.[46] New MRI techniques, including neuromelanin-sensitive MRI and iron-sensitive MRI [utilizing the quantitative susceptibility mapping (QSM) method], along with specific biomarkers such as misfolded α-synuclein in tissue samples like skin biopsies and CSF, are being explored to enhance the diagnosis of PD. These advancements aim to better differentiate PD from other movement disorders.[44,47]

Treatment

Treatment of PD requires a multidisciplinary approach. Neurologists, neurosurgeons specialized in functional surgeries, psychiatrists, clinical psychologists, trained physiotherapists, speech therapists, occupational therapists, social workers, and skilled nurses are all involved in various stages of PD treatment.

Pharmacotherapy in PD: Pharmacological treatment for PD is recommended when motor or non-motor symptoms disrupt daily life or social activities. While some researchers support starting levodopa therapy right after a PD diagnosis, there is no universal agreement on the best time to begin treatment.[48] Currently, no disease-modifying therapies have been identified for PD. However, several potential disease-modifying agents, including α-synuclein immunotherapies and glucagon-like peptide-1 (GLP-1) receptor agonists, are under investigation.[49,50] Current pharmacological approaches primarily address symptoms, focusing on controlling clinical manifestations instead of altering disease progression. Pharmacotherapy in PD can be broadly classified into treatments for motor and non-motor symptoms.

Pharmacotherapy of motor symptoms

Levodopa: Levodopa, when administered in combination with carbidopa or benserazide, is considered the gold standard for treating motor symptoms in PD. Carbidopa and benserazide are both 3,4-dihydroxyphenylalanine (DOPA) decarboxylase (DDC) inhibitors that prevent the conversion of levodopa to dopamine in the bloodstream. This action reduces the amount of circulating peripheral dopamine, allowing levodopa to cross the blood-brain barrier (BBB) and be converted into dopamine in the brain, thereby increasing its central bioavailability. Since these DDC inhibitors do not penetrate the BBB, they do not affect dopamine levels in the brain. While carbidopa and benserazide are very similar in function, it is important to note that benserazide is contraindicated during pregnancy according to some references.[51]

Formulations include immediate-release (IR), extended-release (ER), and controlled-release (CR) preparations. Special ER oral formulations, such as carbidopa/levodopa (CD/LD) ER capsules (Rytary), are designed to provide an initial rapid absorption of levodopa that is comparable to that of IR CD/LD. These formulations aim to maintain stable levodopa levels in the bloodstream, thereby reducing fluctuations in plasma concentrations. This stability helps to minimize motor fluctuations associated with the pulsatile stimulation of dopamine receptors and reduces the risk of dyskinesia.[52] CREXONT is a novel ER oral formulation of CD/LD that offers a fast onset and a prolonged duration of the "on" state. This formulation has been designed to further optimize levodopa pharmacokinetics and extend symptomatic benefits. Similarly, IPX-203 is a new formulation recently developed to address the short half-life of the usual CD/LD. IPX-203 has demonstrated a favorable safety and tolerability, alongside significant improvements in 'good on' time.[53] These formulations may improve convenience and motor control, particularly in patients experiencing wearing-off phenomena.

Although levodopa provides the greatest symptomatic benefit, prolonged use is linked to motor complications, such as fluctuations and dyskinesia.[50] The previously accepted "dopamine-sparing" approach, which postponed the initiation of levodopa in younger patients, is now largely discouraged. Current evidence supports the early use of levodopa to enhance functional outcomes (Figure 2).[48]

Dopamine agonists: Non-ergot dopamine agonists—pramipexole (IR, ER), ropinirole (IR, ER), and rotigotine—possess lower potency than levodopa but are associated with fewer motor complications. However, these drugs carry a higher risk of non-motor side effects, including ICDs, which may necessitate discontinuation.[50]

The presence of these complications, along with their lower efficacy compared to levodopa, has limited the use of these medication groups in modern PD treatment regimens.[54,55] It is advisable to evaluate liver and kidney function before initiating treatment, as pramipexole is preferred in cases of liver dysfunction and ropinirole is prioritized in patients with renal impairment.[55]

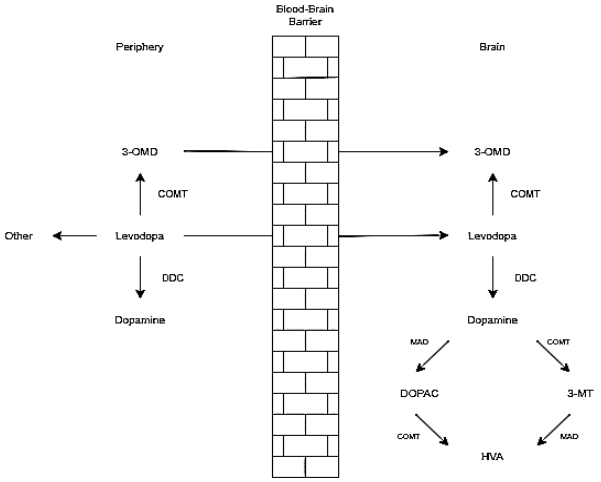


Figure 2. Mechanism of action of dopaminergic agents in Parkinson's disease (PD)
COMT: Catechol-O-methyltransferase; DDC: DOPA decarboxylase; 3-OMD: 3-O-methyldopa; MAO: Monoamine oxidase; DOPAC: 3,4-dihydroxyphenylacetic acid; 3-MT: 3-methoxytyramine; HVA: Homovanillic acid

Catechol-O-methyltransferase (COMT) inhibitors: Entacapone and opicapone work by inhibiting the metabolism of levodopa in the periphery, which helps to extend its half-life. These medications are used alongside levodopa to increase the duration of "on" time—when symptoms are well-controlled—and to reduce "off" time—when symptoms return. However, COMT inhibitors may worsen dyskinesia and are typically reserved for patients with intermediate or advanced stages of PD.[50]

Monoamine oxidase-B (MAO-B) inhibitors: Agents like selegiline, rasagiline, safinamide, and zonisamide work by inhibiting the breakdown of dopamine in the brain. While there was an initial hypothesis suggesting these agents might have neuroprotective effects, this idea has largely been refuted. Their benefits for managing PD are relatively modest, and they are primarily used as adjuncts to other dopaminergic medications.[48]

N-methyl-D-aspartate (NMDA) antagonist: Amantadine is the only medication proven to reduce levodopa-induced dyskinesia (LID). However, its therapeutic benefits may decline with long-term use.[50] It should be prescribed with caution to elderly patients and those with renal failure;[51,55] moreover, it is not recommended during pregnancy and should not be used alone for early PD.[51] Psychiatric side effects, such as hallucinations, should be monitored during prescription, especially in the elderly.[51]

Anticholinergic agents: Anticholinergics, such as trihexyphenidyl and biperiden, are infrequently used due to their significant cognitive and systemic side effects.[50] There is a strong consensus that anticholinergics should not be used as monotherapy for early PD.[51] Most experts agree that anticholinergic medications have no role in modern PD treatment strategies.

Adenosine A2A receptor antagonist: Istradefylline serves as an antagonist of adenosine A2A receptors and may be used in conjunction with levodopa to enhance "off" periods in advanced PD.[50]

Others: Rivastigmine, donepezil, memantine, and methylphenidate are being researched for their effects on gait disturbances, with rivastigmine showing the most promising results to date. Propranolol has been suggested as a treatment for postural or kinetic tremors. Additionally, the potential therapeutic roles of cannabinoids and acupuncture are still in the experimental phase.[50] The medications for the initial treatment of PD are listed in table 1.[51,56-66]

Complications of motor pharmacotherapies: Effectively treating PD with dopaminergic medications is crucial for managing symptoms; however, it can also lead to various complications as the disease progresses. These complications are typically categorized into motor and non-motor issues. Motor complications include fluctuations in movement and dyskinesia, while non-motor complications may involve psychiatric, cognitive, and autonomic disturbances, among others. Rigorous monitoring and prompt management of these complications are critical to maintaining a satisfactory QoL.[67]

Motor complications of levodopa: Fluctuations and dyskinesia

As the disease progresses and long-term levodopa therapy continues, the therapeutic window for dopamine levels in the brain becomes narrower (Figure 3). As a result, dopamine stimulation of striatal neurons shifts from a continuous state to a pulsatile one. This pulsatile stimulation can lead to two primary types of levodopa-related motor complications: motor fluctuations and dyskinesias.

Table 1. Pharmacologic therapies for initial treatment of Parkinson's disease (PD)

Category	Name	Initial dosage	Maintenance dosage	Dose adjustment
Levodopa	Levodopa/ Carbidopa	100/25 mg: 0.5 tablet, 1–2 times/day	300-600 mg levodopa/day	Unnecessary
Dopamine agonist	Pramipexole	0.125 mg, 3 times/day	1.5–4.5 mg/day	Essential in kidney impairment
	Ropinirole	0.25 mg orally, 3 times/day	12–16 mg/day	Essential in kidney impairment
	Rotigotine	2 mg/day	2–6 mg/day	Unnecessary
MAO inhibitor	Selegiline	5 mg/day	5–10 mg/day	Using with caution in kidney and hepatic impairment
	Rasagiline	0.5 mg/day	0.5–1 mg/day	Essential in hepatic impairment
	Safinamide	50 mg/day	50–100 mg/day	Essential in hepatic impairment
NMDA antagonist	Amantadine	100 mg/day	200–300 mg/day	Essential in kidney impairment

MAO: Monoamine oxidase; NMDA: N-methyl-D-aspartate

One of the most common forms of motor fluctuation is known as "wearing off", which occurs when the effects of the medication diminish before the next dose is taken. This results in "off" episodes characterized by poor mobility.[49] Motor fluctuations include delay-on (delay in the initiation of levodopa's effect), on-off (unpredictable on-off states), and dose failure (the absence of effect from a previously effective levodopa dose).[68]

The second type of levodopa-related motor complication is LID. This condition is characterized by involuntary and excessive movements or postures that arise from the chronic pulsatile stimulation of striatal neurons due to external levodopa, which is prescribed for patients with PD. Approximately 90% of patients who have been treated with levodopa for more than five years will experience some form of dyskinesia. There are three main types of dyskinesia observed in these patients: peak-dose dyskinesia, diphasic (or biphasic) dyskinesia, and off-period dystonia. Peak-dose dyskinesia is the most common form, occurring when levodopa reaches maximum plasma and brain concentrations. It typically involves choreiform or stereotypic movements, predominantly affecting the upper body more than the lower body. Diphasic dyskinesia occurs during the transition between "on" and "off" states of medication. It usually manifests as stereotypic or bizarre movements in the lower limbs, such as cycling-like motions or movements resembling kicking a ball. Off-period dystonia primarily affects the lower limbs, can be painful, and is often observed in the early morning before the patient takes their first dose of levodopa.[50,69] Dyskinesia is more prevalent in women, patients with low body mass index (BMI), younger individuals, and those receiving higher cumulative doses of levodopa.[68,69] These unusual movements can cause social distress and lead to physical disabilities.

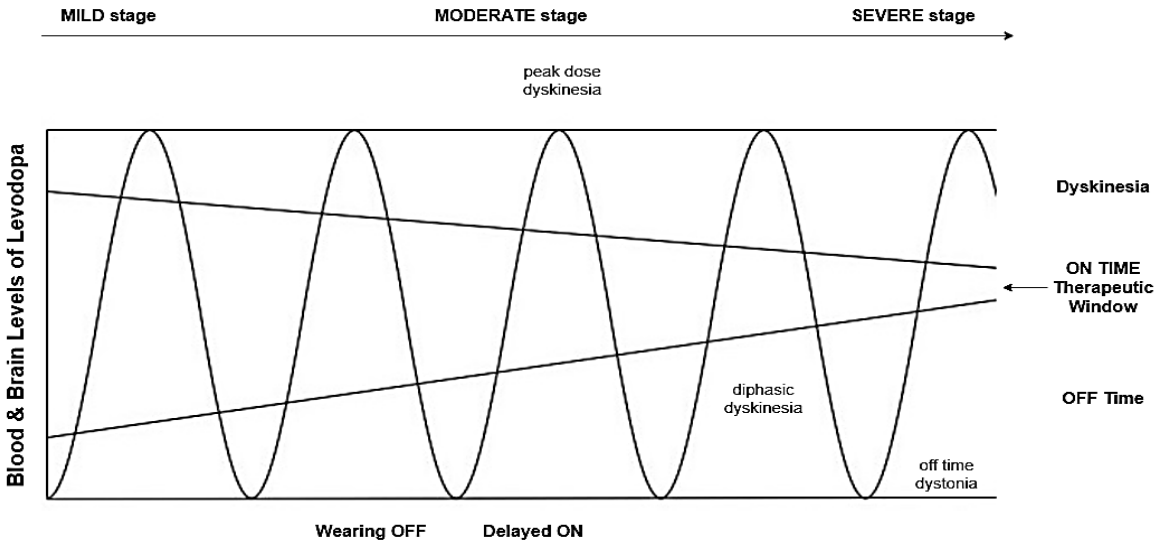


Figure 3. Motor complications of levodopa: fluctuations and dyskinesia

To manage motor complications, it is recommended that levodopa dosing be rescheduled. This can involve using smaller, more frequent doses or switching to ER formulations to achieve smoother plasma concentrations. However, some studies have shown that CR and ER formulations of levodopa may worsen or intensify dyskinesias.[68] Adjunctive therapies such as COMT inhibitors (entacapone, opicapone) and MAO-B inhibitors (rasagiline, safinamide) are used to prolong "on" periods and reduce "off" time; however, they can sometimes worsen dyskinesia.[50] For sudden "off" episodes, using subcutaneous apomorphine injections or inhaled levodopa can provide quick relief.[70] Amantadine, particularly its ER forms, and clozapine may have anti-dyskinetic effects. Amantadine effectively reduces LID without significantly worsening PD symptoms, although tolerance may develop over time, and cognitive side effects can occur.[50,67] Zonisamide, levetiracetam, foliglurax, mavoglurant, and Sarizotan are currently being investigated as new medications for treating dyskinesia.[50,71]

It is important to note that several non-motor complications associated with dopaminergic medications can also occur with levodopa treatment. However, these complications are generally milder in comparison to those seen with other dopaminergic therapies.

Non-motor complications of treatment: Psychosis can develop as a complication of PD treatments, particularly with the use of dopaminergic and anti-cholinergic medications. These medications may also worsen existing psychosis. The psychogenic effects of levodopa are less common compared to those of dopamine agonists and anticholinergic drugs. ICDs—such as pathological gambling, hypersexuality, and binge eating—are primarily associated with dopamine agonists. The main strategy for treating ICDs involves the gradual reduction or discontinuation of the medication responsible for the disorder. It is crucial to taper off dopamine agonists slowly to prevent dopamine agonist withdrawal syndrome (DAWS). DAWS can lead to symptoms such as anxiety, sensory disturbances, depression, and/or worsening Parkinson's symptoms. For individuals experiencing DAWS, reintroducing dopaminergic medications along with behavioral therapy is recommended for effective treatment.[72] Autonomic complications, such as OH, are common and can be caused or worsened by dopaminergic medications. Notably, the autonomic side effects of levodopa are less frequent than those associated with dopamine agonists. Management of OH includes lifestyle changes, such as increasing salt and fluid intake and using compression stockings. If necessary, pharmacologic treatments like midodrine, fludrocortisone, or droxidopa may be used.[73] Constipation is a significant issue that can be worsened by anticholinergics and disease-related dysautonomia. Treatment emphasizes dietary fiber, proper hydration, and the use of laxatives when necessary.[73] Gastroparesis may affect the absorption of levodopa and should be taken into account for patients experiencing unpredictable motor fluctuations.[73] Cognitive impairment and dementia can be worsened by anticholinergic drugs and high doses of dopaminergic medications. Sleep issues, such as insomnia and EDS, can also be side effects of PD treatments.

Pharmacotherapy of non-motor symptoms: Non-motor symptoms of PD are diverse, including mood disturbances, cognitive impairment, sleep dysfunction, autonomic instability, and sensory abnormalities. Current treatments are primarily off-label and supported by varying levels of evidence derived from similar neurological or psychiatric disorders.[67] The recommendations summarized in table 2 follow the latest MDS guidelines. However, as research advances, these treatment protocols may be significantly revised.[67]

Current evidence suggests that venlafaxine is the preferred first-line medication for treating depression in patients with PD.[54] The first-line treatment for RBD is melatonin. If the patient does not respond to melatonin, clonazepam can be used as a second-line option.[74] Furthermore, rivastigmine has the strongest evidence for cognitive symptom relief and is currently the first-line treatment.[75] Psychosis can manifest as visual hallucinations or delusions, affecting as many as 60% of patients with PD.[76] A systematic approach is recommended for managing psychosis, which includes the following steps:

1. Investigate any underlying medical conditions that could trigger or exacerbate psychosis (such as respiratory or urinary infections, dehydration, electrolyte imbalances, etc.).

2. Streamline the patient's medication regimen by stopping or reducing the doses of non-PD medications that possess anticholinergic effects (e.g., oxybutynin, tolterodine, clidinium-c, etc.).

Table 2. Treatments for non-motor symptoms of Parkinson's disease (PD)

Sign/symptom	Pharmacologic category	Drug	Clinical efficacy
Depression	Dopamine agonists	Pramipexol	Effective
		Rotigotine	Under investigation
	MAO-B inhibitors	Rasagiline, selegiline, moclobemide	Under investigation
	Tricyclic antidepressants	Nortriptyline, amitriptyline, desipramine	Probably effective
	SSRIs/SNRIs	Citalopram, sertraline, paroxetine, fluoxetine	Probably effective
		Venlafaxine	Effective
	Others	Atomoxetine	Under investigation
	Complementary	Omega-3 fatty acids	Under investigation
Psychosis	Anti-psychotics	Clozapine	Effective
		Pimavanserin	Effective
		Quetiapine	Probably effective
Apathy	Dopamine agonists	Piribedil	Probably effective
		Rotigotine	Under investigation
	AChE inhibitors	Rivastigmine	Probably effective
ICD	NMDA antagonists	Amantadine	Under investigation
	Anti-narcotics	Naltrexone	Under investigation
Dementia/cognitive disorder	AChE inhibitors	Donepezil, Galantamine	Probably effective
		Rivastigmine	Effective
	NMDA antagonists	Memantine	Under investigation
Orthostatic hypotension	Various	Fludrocortisone, midodrine, droxidopa	Probably effective
Insomnia	Dopaminergic	Levodopa	Under investigation
	Dopamine agonists	Rotigotine	Probably effective
		Piribedil	Under investigation
	Hypnotics	Eszopiclone	Probably effective
		Melatonin	Probably effective
Daytime sleepiness	Psychoactive	Modafinil	Probably effective
		Caffeine	Under investigation
Urinary dysfunction	Anti-muscarinic	Solifenacin	Probably effective
Fatigue	MAO-B inhibitors	Rasagiline	Probably effective
	Psychoactive	Methylphenidate, modafinil	Under investigation
Sexual dysfunction	PDE5 inhibitors	Sildenafil	Effective
Constipation	Various	Prebiotics and probiotics	Effective
		Macrogol, lubiprostone	Probably effective
		Abdominal massage	Under investigation
Anorexia and/or drug-induced nausea/vomiting	Dopamine D2 receptor antagonists	Domperidone	Probably effective
Drooling	Various	Botulinum A and B toxins	Effective
		Glycopyrrolate	Probably effective
		Ipratropium bromide spray	Under investigation
Pain	Dopamine agonists	Rotigotine	Under investigation
	Opioids	Oxycodone, ER naloxone	Probably effective

AChE: Acetylcholinesterase; ER: Extended-release; ICD: Impulse control disorder; MAO: Monoamine oxidase; NMDA: N-methyl D-aspartate; PDE5: Phosphodiesterase-5; SNRI: Serotonin and norepinephrine reuptake inhibitors; SSRI: Selective serotonin reuptake inhibitors

3. Simplify PD treatment by discontinuing or lowering the dosages of medications in the following sequence: a) anticholinergics, b) amantadine, c) MAO-B inhibitors, d) dopamine agonists, e) COMT inhibitors, and f) dose reduction of levodopa.

4. Initiate treatment with clozapine, quetiapine, or pimavanserin. Other typical or atypical antipsychotic medications are not considered safe enough for use in patients with PD for the management of psychosis.[77]

Treatment of motor symptoms in advanced PD:

Advanced PD refers to a stage where the disease either does not respond effectively to the optimal adjustments of oral medication or where the response leads to significant disabling motor complications. A straightforward definition of advanced PD can be summarized as the 5-2-1 criterion. At this point, even when the patient is given the correct doses of levodopa at least five times a day, they would experience a minimum of two hours of "off" symptoms daily and one hour of dyskinesia. The management of advanced PD involves carefully reorganizing the oral levodopa schedule, utilizing rescue treatments like the apomorphine pen or inhalable levodopa forms, or implementing device-aided therapies (DATs). The primary options for DAT available today include deep brain stimulation (DBS), continuous subcutaneous apomorphine infusion (CSAI), and continuous levodopa injection into the small intestine [levodopa-carbidopa intestinal gel (LCIG)]. Each of these treatment options aims to provide more continuous dopaminergic stimulation, which can substantially decrease fluctuations and dyskinesia.[55]

Apomorphine, a strong dopamine agonist, is delivered subcutaneously via either intermittent injections (pen) or continuous infusion through a pump. Typically, candidates for this treatment include patients who previously benefited from levodopa but now face inadequate control due to disease progression or malabsorption.[72] Prior to starting treatment, an apomorphine challenge test must be conducted in a specialized environment. Once the test is successfully completed, apomorphine administration can be performed at home by patients or their caregivers under physician oversight. Continuous access to medical support is crucial because of the potential side effects and the intricacies involved in administration.[72] The details regarding DBS and LCIG will be elaborated upon in the "surgical interventions" section.

Continuous subcutaneous infusion of foslevodopa/foscarbidopa is a promising non-invasive alternative to intestinal levodopa delivery for advanced PD. As prodrugs of levodopa and carbidopa, these agents offer excellent chemical stability and solubility, enabling effective symptom control and reducing motor fluctuations in patients. While long-term efficacy and safety are still being studied, this method marks a significant advancement in treatment.[78]

Stem-cell-based therapy: Current PD treatments mainly alleviate symptoms by restoring dopamine but do not slow disease progression. In contrast, stem-cell therapies show promise for replacing lost neurons and advancing our understanding of the disease. However, challenges such as tumor risk and immune rejection remain. These therapies aim to restore nerve function rather than just relieve symptoms. While early trials suggest feasibility, safety concerns and ethical issues persist. Currently, stem-cell therapies are experimental and not part of standard treatment, but ongoing research may clarify their future role in managing PD.[79]

Non-pharmacological treatment

Rehabilitative care, surgical procedures, and a range of other non-pharmacological treatments will be explored in this section.

Rehabilitative strategies are vital in managing PD. By utilizing specialized techniques like the Lee Silverman Voice Treatment (LSVT) BIG, trained physiotherapists can significantly improve movement symptoms, decrease the risk of freezing and falls, and enhance the QoL in patients with PD.[80] Using methods such as LSVT LOUD, speech therapists can improve not only patients' verbal communication but also assist those suffering from dysphagia, which can be life-threatening if left untreated.[73,81] Clinical psychologists are capable of identifying cognitive and psychological challenges and offering cognitive rehabilitation alongside non-pharmacological treatments for psychiatric issues. Occupational therapists can aid patients in utilizing their current abilities to manage the challenges associated with their disabilities. Additionally, social workers and trained nurses are crucial in meeting medical needs, particularly when access to the primary physician is unavailable.[82]

The effectiveness of minimally-invasive stimulation methods, such as repetitive transcranial magnetic stimulation (rTMS) and transcranial direct current stimulation (tDCS), in alleviating PD symptoms (except for depression) is still under examination and has yet to be established as standard treatment options. Transcranial temporal interference electrical stimulation (tTIS) and transcranial focused ultrasound (tFUS) represent two promising non-invasive brain stimulation techniques that may benefit patients with PD. Further research is underway to assess these two innovative methods.[83] Non-pharmacological approaches for addressing psychiatric issues, including cognitive behavioral therapy (CBT) and electroconvulsive

therapy (ECT), may be utilized as symptomatic treatments under the supervision of qualified psychiatrists and psychologists.

Surgical interventions: Surgical interventions for the brain consist of both lesional and non-lesional approaches. Lesional procedures—such as thalamotomy, pallidotomy, and, less frequently, subthalamotomy—cannot be conducted bilaterally and are associated with permanent side effects. Currently, DBS stands as the most significant neurosurgical method for advanced PD cases. It is thought that DBS modifies the activity frequency of circuits responsible for PD motor symptoms, thereby alleviating these symptoms. The primary targets for implanting the leads are the subthalamic nuclei (STN) and globus pallidus internus (GPi). In cases of severe tremor, stimulating the posterior subthalamic area (PSA) or the ventralis intermedius (VIM) nucleus of the thalamus might be considered.

Candidates for DBS should: a) meet the criteria for clinically established PD;[36] b) have been diagnosed with PD for at least four years (though this may be shortened in the future); c) demonstrate a notable response to levodopa during the "on" phase (except for tremor, which may respond to DBS despite poor levodopa responsiveness); and d) experience motor fluctuations and/or dyskinesia. Exclusion criteria include: a) severe cognitive dysfunction; b) depression or significant psychiatric disorders; c) other comorbid conditions; d) surgical contraindications; and e) pronounced cerebral lesions visible on MRI. Furthermore, the patient must possess a stable social status, maintain realistic expectations, and have access to a multidisciplinary team for post-DBS surgery support. While there are no strict age restrictions for DBS, many facilities discourage its use for individuals older than 75 years. Moreover, the presence of significant midline symptoms (such as speech difficulties, dysphagia, freezing, and falls during the "on" phase), which typically do not respond well to levodopa, is often regarded as a contraindication for DBS at most centers.[84] Thus, DBS should be performed exclusively in institutions where specialists experienced in movement disorders and functional neurosurgery are available. Additionally, it is essential to have facilities that minimize surgical complications and provide access to skilled physiotherapists, speech therapists, occupational therapists, and psychologists.

Another surgical alternative for PD is LCIG. This approach involves the continuous administration of a specific mixture of CD/LD into the duodenum or proximal jejunum via a percutaneous endoscopic gastrostomy (PEG) or a percutaneous endoscopic jejunostomy (PEJ). This option may be appropriate for patients with advanced disease and a previously good response to levodopa who experience movement fluctuations or drug-induced dyskinesia that cannot be managed even with optimal combined oral treatments. The primary complications associated with LCIG include PEG/PEJ-related issues, such as peritonitis, as well as nutritional concerns like vitamin deficiencies. A medical team proficient in PEG/PEJ management should be available to instruct patients on how to adjust the levodopa injection pump and provide necessary guidance. Furthermore, this treatment is suitable for patients with mild cognitive and psychiatric challenges for whom DBS may be inappropriate.[85]

Conclusion

The diagnosis of PD, the most prevalent cause of parkinsonism, primarily depends on clinical observations. MRI, PET scans, and other imaging techniques assist in excluding alternative diagnoses in parkinsonian patients who do not fully meet the clinical criteria for PD. Despite having been recognized for over two hundred years, there remains no cure for PD. However, in recent decades, there has been an increase in clinical trials assessing various therapeutic strategies and medications as symptomatic or disease-modifying treatments for PD. While existing symptomatic treatments for motor and non-motor symptoms are effective in reducing disease burden and enhancing patients' QoL, significant gaps remain in the diagnosis and treatment of PD. Consequently, further research is required to establish objective diagnostic metrics and develop effective disease-modifying treatments. Immunotherapy targeting intracellular or extracellular phosphorylated α-synuclein (during its cell-to-cell, prion-like propagation) represents a primary focus of future studies.

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