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DIAGNOSTIC AND THERAPEUTIC APPROACH TO PARKINSON'S DISEASE: A SYSTEMATIC REVIEW

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ABSTRACT

Objective: To report the main aspects involving Parkinson's disease, including diagnostic and therapeutic methods. Methodology: This is a systematic review focused on understanding the essential aspects of Parkinson's disease. The research was guided by the question: "What are the main aspects that permeate the evolution of Parkinson's disease, as well as what are the diagnostic resources and therapeutic approaches used in clinical practice?" To find answers, searches were performed in the PubMed database using four descriptors combined with the Boolean term "AND". This resulted in 2,069 articles, of which 23 were selected for analysis. Results: Parkinson's disease (PD) is a progressive neurological disorder involving motor and non-motor symptoms, with diagnosis and treatment that require a multidisciplinary approach. The identification of clinical subtypes, such as the early or late form, and the profiles of tremor or postural instability, help to personalize the treatment. Levodopa is the standard treatment for most patients, although long-term use can cause complications. Conclusion: The future promises advances in precision medicine, improving the management of PD. The review highlights the need for more research to identify biomarkers, improve early diagnosis, and develop effective treatments.

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INTRODUCTION

Parkinson's disease (PD) is the second most common neurodegenerative disease, with a global prevalence of more than 6 million individuals. This number corresponds to an increase in prevalence over the last generation, making Parkinson's disease one of the leading causes of neurological disability. Between the years 1990 and 2016, the prevalence of PD increased significantly from 2.5 million to 6.1 million cases globally, representing a 2.4-fold increase compared to the initial number. This disease causes a progressive impairment that notably impacts the lives of patients, their families and caregivers, representing a high cost of treatment and interrupting their quality of life. Considering that the elderly population is expected to double by 2050, the number of PD patients is expected to increase accordingly (TOLOSA et al., 2021) (MULEIRO ALVAREZ et al., 2024) (GARCIA SANTA CRUZ; HUSCH; HERTEL, 2023).

Age is the most significant risk factor for developing Parkinson's disease, and men are more susceptible than women, with a prevalence rate of approximately. There is a strong genetic component to disease risk, with more than 90 genetic risk loci currently identified. In addition, several possibly modifiable environmental (e.g., pesticides, water pollutants) and behavioral (e.g., tobacco use, coffee, exercise, or head trauma) factors have been found to have a role in the pathogenesis of Parkinson's disease in different populations (TOLOSA et al., 2021).

PD symptoms occur due to the progressive loss of dopamine-producing neurons in the compact substantia nigra region of the brain. Symptoms usually occur gradually over several years, making diagnosis challenging. PD is traditionally characterized as a disorder of the motor system with four cardinal symptoms: bradykinesia (slowness of movement); rigidity (stiffness of the limbs and trunk); postural instability (impaired balance and coordination); and tremor (tremor in the hands, arms, legs and face). Although not as visible as these motor symptoms, non-motor symptoms are also experienced by many PwP as part of their disease. The most common non-motor symptoms of PD include constipation, urinary dysfunction, depression, psychosis, apathy, and sleep disturbances (CHURCH, 2021).

Advances in treatment are expected, but current approaches rely primarily on drug therapy as symptomatic therapy modulating neurotransmitters in the brain. Degeneration of nigrostriatal dopaminergic neurons is the most common pathological finding in PD patients. Therefore, dopamine replacement therapy is the fundamental treatment for PD patients. However, dopaminergic treatment for several years results in complications, such as the phenomenon of wear and tear, which motivated the development of symptomatic therapies.

In addition to medication, physical therapy can be employed as a complementary approach to improve cognitive function in individuals with dopamine deficits. Physical therapy focuses on improving mobility, balance, and coordination, which can positively impact cognitive abilities. In addition, alternative therapeutic pathways are being explored (MURAKAMI et al., 2023) GARCIA SANTA CRUZ; HUSCH; HERTEL, 2023).

This systematic review article aims to compile and evaluate the existing scientific evidence on Parkinson's Disease. The intention is to provide a comprehensive and up-to-date view, which not only synthesizes current knowledge about the condition, but also identifies gaps in research and directs future investigations and clinical practices. By offering an in-depth analysis of the evidence, this study aims to serve as a resource for health professionals, researchers, and academics, helping to optimize diagnostic and therapeutic approaches to this condition.

METHODOLOGY

This is a systematic review that seeks to understand the main aspects of Parkinson's Disease, as well as to demonstrate the main diagnostic and therapeutic methods used in the condition. For the development of this research, a guiding question was elaborated through the PVO (population, variable and objective) strategy: "What are the main aspects that permeate the evolution of Parkinson's Disease, as well as what are the diagnostic resources and therapeutic approaches used in clinical practice?"

The searches were carried out through searches in the PubMed Central (PMC) databases. 4 descriptors were used in combination with the Boolean term "AND": Parkinson's Disease, Diagnosis, Motor Symptoms and Pharmacological Treatment. The search strategy used in the PMC database was: Parkinson's Disease AND Diagnosis AND Motor Symptoms and Parkinson's Disease AND Pharmacological Treatment. From this search, 2,069 articles were found, which were subsequently submitted to the selection criteria. The inclusion criteria were: articles in English, Portuguese and Spanish; published in the period from 2019 to 2024 and that addressed the themes proposed for this research, in addition, review, observational and experimental studies, made available in full. The exclusion criteria were: duplicate articles, available in the form of abstracts, that did not directly address the proposal studied and that did not meet the other inclusion criteria.

After associating the descriptors used in the searched databases, a total of 2,069 articles were found. After applying the inclusion and exclusion criteria, 23 articles were selected from the PubMed database, and a total of 17 studies were used to compose the collection.

RESULTS

Author	Major Contributions
Muleiro Alvarez et al., 2024 (Parte 1)	Common mutations in the LRRK2/PARK8 gene, especially among individuals aged 50 years and older. - R1441H, R1441G, R1441C and G2019S mutations cause loss of dopaminergic neurons and alter processes such as cytoskeletal function, lysosomal system, protein synthesis and vesicle transport. They regulate the inflammatory response and oxidative stress in microglia.
Muleiro Alvarez et al., 2024 (Parte 2)	DJ-1/PARK7, PARK6 and PARK2 genes protect dopaminergic neurons from oxidative stress. Mutation in any of these genes increases oxidative stress, predisposing to neurodegeneration. PINK1 regulates mitophagy and prevents the accumulation of toxic products. Mutation in PINK1 causes early-onset PD symptoms, with astrocytic gliosis and microgliosis.
Prajjwal et al., 2023	Dopamine deficiency caused by dysfunction of neurons in the substantia nigra. Excessive production of alpha-synuclein resulting in Lewy bodies. . Lewy bodies impair synaptic function and cause neuronal degeneration. Levodopa, despite increasing patient survival, has side effects such as dyskinesias and motor oscillations. Adverse reactions to levodopa include motor fluctuations and on-off complications. New extended-release formulation of levodopa-carbidopa showed reduction in "off" time compared to immediate-release.
Kilzheimer et al., 2019	PD is manifested by the selective loss of dopaminergic neurons, affecting motor and non-motor functions. Caudal and ventrolateral regions of the substantia nigra are most affected. Dopamine deficiency in these areas causes motor features characteristic of PD.
Tolosa et al., 2021 (Parte 1)	PD is characterized by a motor syndrome with bradykinesia, resting tremor, and rigidity. Motor syndrome causes progressive disability and affects quality of life. Non-motor symptoms (NMS) are frequent, including hyposmia, constipation, urinary dysfunction, orthostatic hypotension, memory loss, depression, pain, and sleep disturbances. - Cognitive decline and hallucinations are common causes of hospitalization in advanced PD. Clinical subtypes vary in age of onset, rate of progression, and response to treatment.
Tolosa et al., 2021 (Parte 2)	Empirically defined subtypes include early-onset PD and late-onset PD. Benign-shaky PD or dominant tremor has slower progression and less cognitive decline. A subtype of postural instability and gait disorder (PIGD) associated with rapid motor and cognitive decline.
Costa et al., 2023	Men have a higher incidence and mortality of PD than women. Women have a later onset and more benign progression, but have more symptoms such as depression and pain. Men have greater cognitive impairment and sexual dysfunction.
Muleiro Alvarez et al., 2024	Diagnostic criteria for PD include the presence of bradykinesia and at least one symptom such as resting tremor or limb stiffness. Supporting criteria for diagnosis include response to levodopa and occurrence of resting tremor. Immune system components in CSF, such as MCP-1 and YKL-40, are investigated as biomarkers in PD.
Motherless; Ozturk; East, 2022	Inflammatory markers such as MCP-1 and YKL-40 in CSF are correlated with motor progression in PD and cognitive impairment. High CSF C-reactive protein correlated with severity of motor and non-motor symptoms in PD and atypical parkinsonism.

Munhoz et al., 2024	Criteria for diagnosing PD include identification of parkinsonian syndrome and exclusion of alternative diagnoses. Supportive criteria include response to levodopa and long clinical course. Diagnosis of PD reached accuracy of up to 90% in the 1990s.
Church, 2021	Treatment of PD includes pharmacological dopamine replacement, mainly with carbidopa/levodopa. Complementary and alternative medicine (CAM) approaches and lifestyle modifications, such as aerobic exercise, offer therapeutic benefits.
and; Filed Under: 2020	Levodopa increased the survival of PD patients by more than 12 years in the post-levodopa era, compared with 9 years in the pre-levodopa era. Continued benefit of levodopa is associated with the maintenance of activity of daily living.
Dong-Chen et al., 2023	Levodopa has undesirable side effects such as motor oscillations and dyskinesias. New sustained-release formulations and continuous administration techniques are being developed to mitigate these effects.
Scanga; Lafontaine; Kaminska, 2023	Adverse reactions to the use of levodopa include motor fluctuations and "on-off" complications. New extended-release formulation of levodopa-carbidopa showed reduction in "off" time compared to immediate-release
Tension; Genre; Chen, 2022	Dopamine agonists and enzyme inhibitors, such as COMT and MAO-B inhibitors, are used as adjuncts to levodopa to relieve motor complications. MAO-B inhibitors, such as selegiline and rasagiline, are recommended as first-line therapies for early PD.
Murakami et al., 2023	Administration of rasagiline improves motor symptoms in patients with early- and advanced-stage PD. Safinamide extends the time of use and decreases downtime in PD patients with wear and tear phenomenon.

Nemade; Subramanian; Shivkumar, 2021 (Parte 1)	Dopamine (DA) agonists include ropinirole, pramipexole, rotigotine, and apomorphine, which are used primarily in the early stages of PD and as adjunctive therapies. Common side effects of AD include hallucinations, orthostatic hypotension, nausea, pedal edema, excessive daytime sleepiness, and impulse control disorders (ICDs). Reduction or cessation of AD can cause dopamine agonist withdrawal syndrome (DASA).
Nemade; Subramanian; Shivkumar, 2021 (Parte 2)	Amantadine used to treat dyskinesias due to its antiglutamatergic property. Side effects of amantadine include hallucinations and blurred vision. Amantadine extended-release formulations (ADS-5102 or GOCOVRI) reduce dyskinesias and "off" time in PD.
Adam et al., 2023	Deep brain stimulation (DBS) uses electrodes implanted in the brain to treat PD symptoms. DBS is more effective than medical therapy for severe PD and dyskinesias. DBS is advantageous for inconsistent and fluctuating responses to levodopa.

Source: Table created by the author

DISCUSSION

Parkinson's Disease (PD) has a multifactorial etiology, as it results from a combination of genetic, epigenetic, and environmental factors. Several genes contribute to the onset and progression of the disease. The most common mutations associated with PD occur in the LRRK2 or PARK8 gene, particularly among individuals aged 50 years and older. Several mutations have been described, the most common being R1441H, R1441G, R1441C, and G2019S, which cause loss of dopaminergic neurons while altering processes such as cytoskeletal function, lysosomal system, protein synthesis, and vesicle transport. They also play a role in regulating the inflammatory response and oxidative stress in microglia (MULEIRO ALVAREZ et al., 2024).

DJ-1 or PARK7, PARK6 and PARK2 are the genes responsible for protecting dopaminergic neurons from hydrogen peroxide, rotenone and mutant synucleins. Therefore, a mutation in any of the above will increase oxidative stress, predisposing the patient to an increase in neurodegeneration. Another associated gene is PINK1, a mitochondrial kinase that accumulates in damaged mitochondrial membranes, where it will recruit parkin to regulate mitophagy and stop the collection of toxic products that cause neuronal loss. A mutation in the aforementioned gene will cause symptoms and neuropathology

characteristic of early-onset PD, accompanied by astrocytic gliosis and microgliosis (MULEIRO ALVAREZ et al., 2024).

The main pathological cause of PD is a deficiency of dopamine in the brain. The dopamine-producing neurons in the brain are typically located in an area called the substantia nigra. Dysfunction of these cells, either through death or their inability to produce and secrete dopamine, will decrease the concentration of dopamine in the brain. This is due to the fact that dopamine in the substantia nigra is normally transferred to the basal ganglia, the area of the brain responsible for controlling movement (PRAJJWAL et al., 2023). This neuronal deterioration has been closely linked to the excessive production of alpha-synuclein, a 140-amino acid protein present in the presynaptic terminals of neurons. Predominantly located in the substantia nigra, thalamus, neocortex, and cerebellum, alpha-synuclein is crucial for vesicle fusion and movement, axonal transport, neurotransmitter release, and synaptic connectivity. However, post-mortem examinations of PD individuals have revealed that alpha-synuclein frequently folds incorrectly, resulting in its accumulation within intracytoplasmic inclusions known as Lewy bodies. These Lewy bodies are also found in other PD-related diseases. The intermediate molecules produced during this accumulation contribute to harmful effects that ultimately impair synaptic function and cause neuronal degeneration (MULEIRO ALVAREZ et al., 2024).

PD is a progressive neurodegenerative disease that manifests in the selective loss of dopaminergic neurons beginning in the early stages of the disease and affects a range of motor and non-motor functions. This loss is most prominent in the substantia nigra pars compacta, from which important afferent projections to the basal ganglia originate. Within the substantia nigra, the caudal and ventrolateral layers that project into the dorsal putamen of the striatum are usually most affected. Successive dopamine deficiency, particularly in this area, is likely the cause of the development of characteristic motor characteristics (KILZHEIMER et al., 2019).

The clinical hallmark of Parkinson's disease is a motor syndrome characterized by bradykinesia, resting tremor, and rigidity, as well as changes in posture and gait. Motor disorders cause progressive disability with impairment in activities of daily living and reduced quality of life. Although classic motor symptoms occur early and are the mainstays of current diagnostic criteria, the development of postural instability and increased gait difficulties, as well as dysphagia and dysarthria, drive the progression of motor disability (TOLOSA et al., 2021).

The main characteristic, bradykinesia, is the decrease in velocity, amplitude, or slow movement in movements made continuously, which becomes evident over time. It can also

be present in the voice and face (hypomimia). However, limb bradykinesia must be present to establish the diagnosis. Increased and persistent resistance to passive movement, specifically in the joints, is known as stiffness. This is different from spasticity because it is independent of speed. In clinical practice, it can be difficult to establish differences, but remembering that spasticity is only seen in rapid movements can help. Postural instability is usually seen in the advanced stages of the disease and is correlated with the severity of the disease. It is described as the tendency to fall and imbalance. It can be evaluated with the traction test, where the doctor stands behind the patient and slightly lifts the shoulders forward or backward. This maneuver tests the ability to maintain balance and is positive when there is ineffective balance (PRAJJWAL et al., 2023).

The presence of tremor remains an important criterion for the clinical diagnosis of Parkinson's disease (PD) since its first meticulous description by James Parkin-son in 1817. Tremor is defined as an involuntary rhythmic oscillatory movement of a body part, usually as a result of alternating contractions of agonist and antagonist muscles. The classic presentation of tremor in PD is an asymmetric 4–6 Hz resting tremor of the distal extremities, which may be elicited or exacerbated by active movement of other parts of the body (e.g., tremor in the hands while walking), cognitive tasks, or stress. Resting tremor usually subsides with voluntary movement of the affected body part (e.g., lifting an affected hand), but may recur in posture or during movement after a delay. This re-emergent tremor is in the same frequency range as the resting tremor and the tremor severity in the two situations is usually correlated. The average latency for a resting tremor to resurface with tonic muscle activation is about 9 seconds, with a wide inter-individual range of 1 to more than 30 seconds. The tremor can also affect the legs during the standing position, where it has been called 'pseudo-orthostatic' (PIRKER et al., 2023).

Tremor is also one of the most obvious clinical signs of PD, a feature present in approximately 70% of patients and was recorded in about 77% of patients at some stage during the course of PD in a pathological clinical study and can be distressing even when its severity or impact on motor function is limited. The pathophysiology of PD tremor remains incompletely understood, and in contrast to bradykinesia and rigidity, its severity is not related to the overall degree of nigrostriatal dopaminergic denervation (PIRKER et al., 2023).

Although Parkinson's disease is defined as a movement disorder, it is associated with a variety of non-motor symptoms (NMS) in virtually all patients, including hyposmia, constipation, urinary dysfunction, orthostatic hypotension, memory loss, depression, pain, and sleep disturbances. While the classic motor signs of Parkinson's disease are linked to

nigral degeneration and striatal dopamine depletion, NMS are likely related to neurodegeneration of other structures, including the peripheral autonomic nervous system. NMS are frequent in the early stages, and although intense and disruptive for some patients, observational studies indicate that they are mild in most cases, increasing in severity with the duration of the illness. NMS in the course of Parkinson's disease cause a significant burden, reduce quality of life, and are a determining factor of the overall cost of care. Particularly, cognitive decline and hallucinations are a common cause of hospitalization and institutionalization in advanced Parkinson's disease (TOLOSA et al., 2021).

Parkinson's disease is surprisingly heterogeneous with respect to age of onset, clinical presentation, rate of progression, and response to treatment. Several clinical subtypes of Parkinson's disease have been proposed. In addition, the discovery of genetically defined forms of the disease, which may differ from classic Parkinson's disease in a number of clinical variables, challenged the unitary view of Parkinson's disease and opened the door to a biological definition of subentities within the spectrum of Parkinson's disease. Approaches to subtyping Parkinson's disease have used empirical evaluations of individual clinical features or the more objective and hypothesis-free methodology of hierarchical cluster analysis and other forms of machine learning. Clinical features that were used for subtyping with either approach included age of onset (early onset versus late onset), predominant motor phenotype (cases with dominant tremor versus cases without tremor), motor complications in response to chronic levodopa, non-motor features (particularly autonomic dysfunction, cognitive dysfunction, and RBD), as well as the rate of progression (TOLOSA et al., 2021).

Empirically defined subtypes include early-onset Parkinson's disease or late-onset Parkinson's disease, usually defined by onset age limits below 40 or 50 years and characterized by slower progression, preserved cognition, and increased risk of developing motor complications in response to levodopa. Benign-shaky Parkinson's disease or Parkinson's disease with dominant tremor are two terms that have been used to describe the clinical predominance of resting tremor over other motor symptoms and this clinical subtype has been associated with slower progression and less cognitive decline compared to other clinical presentations. Clinical presentations with prominent postural instability and gait disturbance have been classified as a subtype of postural instability and gait disorders (PIGD) characterized by a rapid decline in motor function as well as cognition. Problems with empirically defined subtypes include the fact that patients who initially present with

shaky or non-shaky motor signs of Parkinson's disease may change categories with longer follow-up (TOLOSA et al., 2021).

Being a man is a risk factor as well as a worse prognosis factor. Men have a higher incidence of PD and a slightly higher mortality than women. The presentation and age of onset of the disease also differ between the sexes. Women have a later onset of motor symptoms and a more benign progression. However, symptoms such as fatigue, depression, anxiety, constipation, pain, hypo/anosmia, hyperhidrosis, and propensity for severe dysphagia are more common and severe in women. However, the higher incidence of depression, anxiety, and pain in women is not specific to PD. Women are also more likely to develop postural instability, motor complications, and hallucinations due to iatrogenic symptomatic therapy. Men have greater cognitive impairment, greater sexual dysfunction, severe REM sleep disorders, association with impulse control disorder, and severe drooling (COSTA et al., 2023).

Due to the non-motor symptoms that often precede motor manifestations, almost 10% of patients are misdiagnosed with other pathologies. The Parkinson's and Movement Disorders Society has established specific criteria to improve diagnostic accuracy. According to its recommendations, the diagnosis of PD requires the presence of bradykinesia and at least one of the following symptoms: resting tremor (4–6 Hz) or stiffness of the limbs. In addition, it is crucial to consider exclusion criteria to eliminate PD as a diagnosis and to meticulously evaluate alarming data that may indicate potential signs of other pathologies (MULEIRO ALVAREZ et al., 2024). Step 1 for diagnosis consists of identifying parkinsonian syndrome. Bradykinesia is a mandatory criterion for the syndrome, and is defined as "slowness in the onset of voluntary movement, with progressive reduction in the speed and amplitude of repetitive actions". This definition of bradykinesia was a powerful ally in differentiating bradykinesia from slowness in other conditions, such as dystonia, altered mental states, and depression. Step 2 was the exclusion of findings that could point to alternative diagnoses, including findings in history (gradual decline, repeated head injury, encephalitis, or treatment with dopamine receptor-blocking agents at onset), neurological examination (oculogyric seizures, supranuclear gaze palsy, cerebellar signs, Babinski's signs), or disease course (early severe dysautonomia or dementia, unilateral disease after 3 years). And finally, step 3 was the presence of support criteria. (MUNHOZ et al., 2024).

Supporting criteria are: occurrence of resting tremor, unilateral onset with continuous asymmetry, evidence of progression, consistent response to levodopa (>70%), levodopa-induced chorea, response to levodopa for more than 5 years, long clinical course (>10

years). The Criteria became the most widely used criteria for diagnosing PD in subsequent years, and by the 1990s, the clinical accuracy of PD diagnosis had increased significantly to as much as 90% (MUNHOZ et al., 2024).

Immune system components in CSF have been investigated as biomarkers in PD. A shift from classical monocytes (CD14+/CD16-) to non-classical monocytes (CD14+/CD16+) was observed in PD. Two indicators are promising in this area. They are monocyte chemoattractant protein-1 (MCP-1) and chitinase-like protein-3-1 (YKL-40). Increased CSF MCP-1 levels were observed in PD and MSA compared to controls. Although these markers are diagnostically inadequate, they have been correlated with motor progression in PD. YKL-40 was found to be associated with cognitive impairment in PD and showed inconsistent results in the PD, atypical parkinsonism, and control groups. Another inflammatory marker, C-reactive protein, was found high in CSF in PD syndromes and atypical parkinsonism and correlated with the severity of motor and non-motor symptoms in these patients. Although many inflammatory markers have been studied in PD, they have failed to achieve statistical significance due to their limited effect (ÖKSÜZ; ÖZTÜRK; DOĞU, 2022).

In addition to detailed questioning and accurate physical evaluation, several resources help in the diagnosis of PD. Imaging techniques, such as dopamine transporter single-photon emission computed tomography (DAT-SPECT) and structural magnetic resonance imaging (MRI), are commonly used due to their specificity. MRI, in particular, provides distinctive features useful for identifying atypical parkinsonism, including neuromelanin imaging (NMI), which detects changes in the substantia nigra pars compacta and locus coeruleus (MULEIRO ALVAREZ et al., 2024).

The traditional approach to treating PD typically begins with a pharmacological dopamine replacement strategy. The first line for such therapy is daily oral carbidopa/levodopa or a dopamine agonist. Some medications extend the lifespan of endogenous dopamine. Along with or as an alternative to dopamine replacement, complementary and alternative medicine (CAM) and integrative medicine approaches are used by many to improve brain health. Lifestyle modifications may provide therapeutic benefits, as different forms of strenuous aerobic exercise are neuroprotective, in addition to the overall quality of life (QoL) benefits offered by frequent and regular exercise (CHURCH, 2021).

Dopamine has the chemical structure of 3,4-dihydroxyphenethylamine and is a member of the catecholamine and phenethylamine molecular families. Like other neurotransmitters, dopamine transmits messages throughout the central nervous system

(CNS). Dopamine is a derivative of the amino acid tyrosine (Tyr), where the enzyme tyrosine hydroxylase converts Tyr to levodopa (DOPA). From there, DOPA decarboxylase removes carbon dioxide from DOPA to produce dopamine. Because PD is first and foremost a dopamine deficiency disorder, dopamine replacement remains the standard therapeutic goal. The combination of levodopa with carbidopa, an aromatic L-amino acid decarboxylase inhibitor, provides the most significant amount of symptomatic relief with the fewest adverse side effects in the treatment of PD. The addition of carbidopa prevents the conversion of levodopa (i.e., DOPA) to dopamine in peripheral tissues, allowing for successful transport of levodopa into the CNS. Interestingly, the blood-brain barrier allows levodopa access to the CNS but denies dopamine and carbidopa entry. There are several formulations for carbidopa/levodopa tablets. Alternatively, Duodopa is a continuously infused carbidopa/levodopa intrajejunal gel. In addition, subcutaneous infusion of carbidopa/levodopa is under evaluation. The main side effects of carbidopa/levodopa are the development over time of dyskinesia and fluctuating periods of 'on-off' efficacy (CHURCH, 2021).

Levodopa had a major impact on the treatment of PD, as patient survival increased by more than 12 years at a 15-year follow-up in the post-levodopa era, compared with 9-year survival in the pre-levodopa era. Although the advent of levodopa did not normalize the mortality rate compared to patients without PD, the relative increase in survival was attributed to the significant clinical improvement in the first 4 to 6 years after initiation of levodopa. The continued benefit of levodopa observed thereafter was associated with continued maintenance of activity of daily living (SY; FERNANDEZ, 2020).

Although it is a classic treatment for PD, levodopa (L-DOPA) has several undesirable side effects, including motor response oscillations and drug-induced dyskinesias. Presynaptic and postsynaptic mechanisms are involved in the development of these motor complications, which eventually arise from non-physiological stimulation of the pulsatile striatum DA receptor. The main cause of maladaptive neuronal responses is discontinuous drug administration, due to the short half-life of L-DOPA, as well as variability in gastrointestinal absorption and blood-brain barrier transport. To address these challenges, new L-DOPA sustained-release formulations and continuous administration techniques are continuously being developed. This includes intestinal administration via percutaneous endoscopic gastrojejunostomy tubes and subcutaneous administration via mini-pumps (DONG-CHEN et al., 2023).

Adverse drug reactions that occur with the advancement of PD include motor fluctuations and recurrent symptoms due to the "on-off" phenomenon. After taking

levodopa, patients will be in the "on" phase when symptoms are relieved, but due to its short half-life, its effects begin to wear off after a few hours and patients go through the "off" phase when symptoms can become unpredictably more severe. Common "on" complications include a delay in the onset of symptomatic relief or a less potent symptom relief response than usual with medication intake. To address this problem, the frequency of levodopa may be increased, or other classes of drugs may be added. A new extended-release levodopa-carbidopa formulation showed efficiency in reducing off time compared to the immediate-release formulation (PRAJJWAL et al., 2023) (SCANGA; LAFONTAINE; KAMINSKA, 2023). Levodopa-induced dyskinesia is a common but physiologically complex complication in PD, occurring in 3%45 to 94% of PD patients. Levodopa-induced dyskinesia occurs when dopamine concentrations reach their maximum in the brain, termed peak dose dyskinesia, which occurs in a dose-dependent manner and also depends on the methods of administration of the drug (LANGA; LAFONTAINE; KAMINSKA, 2023).

Long-term use of levodopa may induce motor complications such as motor fluctuations ('wear and tear'; 'on-off') and dyskinesia. Dopamine agonists (DAs) or enzyme inhibitors, including catechol-O-methyl-transferase (COMT) inhibitors and monoamine oxidase B (MAO-B) inhibitors, are commonly applied as adjuncts to levodopa to relieve motor complications. Commonly used COMT inhibitors, such as entacapone and opicapone, inhibit the degradation of levodopa in the periphery, while MAO-B inhibitors penetrate the blood-brain barrier, inhibit central MAO activity in the CNS, and thus reduce dopamine degradation (TAN; JENNER; CHEN, 2022).

According to the Guidelines for Parkinson's in Adult Disease published by the National Institute for Health and Care Excellence (NICE) in 2017, MAO-B inhibitors are recommended as first-line therapies for patients with early PD whose motor symptoms are not affecting their quality of life. For PD patients with dyskinesia or motor fluctuations, MAO-B inhibitors may be selected as adjuncts to levodopa. Treatments for the motor symptoms of PD from the International Parkinson and Movement Disorder Society. The 2018 Evidence Based Medicine Review recommends the use of the MAO-B inhibitor selegiline and rasagiline as effective monotherapy for early PD. However, it appears that rasagiline is clinically effective as an adjunct to AD therapy for early/stable PD, but safinamide is ineffective as an adjunct to AD (TAN; JENNER; CHEN, 2022).

MAOI-Bs work by inhibiting the degradation of levodopa, thus aiming to prolong and increase its impact on dopaminergic neurotransmission (MULEIRO ALVAREZ et al., 2024). Currently approved MAO-B inhibitors include irreversible inhibitors, such as selegiline and rasagiline, and the reversible inhibitor, safinamide (TAN; JENNER; CHEN, 2022).

Administration of rasagiline as a single agent at a dose of 1 mg/day improves motor symptoms in patients with early-stage PD, and addition of 0.5 or 1 mg/day of rasagiline significantly shortens downtime and improves motor symptoms in patients with advanced-stage PD with motor complications under treatment with oral levodopa. Safinamide extends the time of use and decreases downtime in PD patients with wear phenomenon not accompanied by problematic dyskinesia and also improves motor symptoms over time (MURAKAMI et al., 2023).

Although MAOI-Bs improve motor symptoms, their effectiveness is somewhat lower compared to levodopa; however, they carry a reduced risk of inducing dyskinesia. Consequently, PD patients often undergo treatment involving multiple classes of drugs to maximize benefits and minimize adverse effects. As the disease progresses, the brain's ability to store excess dopamine decreases, resulting in a decreased response to medications and necessitating higher doses over time (MULEIRO ALVAREZ et al., 2024).

Catechol-O-methyltransferase (COMT) is present in both the central nervous system (CNS) and peripheral tissues. It plays a role in accelerating the conversion of levodopa to 3-O-methyl-DOPA (3-OMD), thereby decreasing levodopa levels. 3-OMD competes with levodopa for transport across the blood-brain barrier and conversion to dopamine in the CNS, potentially exacerbating motor symptoms. COMT inhibitors (COMT-Is) work by increasing levodopa levels in the CNS directly and reducing the presence of its competitor, 3-OMD. By enhancing the dopaminergic effects of levodopa, COMT-Is may induce adverse CNS effects such as somnolence, confusion, dyskinesia, hallucinations, and depression, as well as gastrointestinal problems such as diarrhea and colitis. Currently, three COMT inhibitors are approved by the FDA as adjunctive treatments for PD. Tolcapone was the first COMT inhibitor to receive FDA approval, in 1998. It effectively inhibits the function of COMT both peripherally and centrally. However, due to its association with liver failure, tolcapone is rarely used nowadays and is only recommended as an adjunctive therapy for patients with predominant motor symptoms who have not responded adequately to conventional treatments (MULEIRO ALVAREZ et al., 2024).

Entacapone was the second COMT inhibitor approved by the FDA in 2003. It works by decreasing the peripheral metabolism of levodopa, thereby increasing its bioavailability and prolonging its action. Opicapone, the third COMT inhibitor to be approved, works by inhibiting the peripheral metabolism of levodopa. This action extends the half-life of levodopa and increases its ability to deliver dopamine to the brain, thereby improving motor symptoms. However, there is currently no evidence in the literature to support its ability to

slow the progression of PD. Abrupt discontinuation of opicapone can lead to withdrawal symptoms such as confusion and hyperpyrexia (MULEIRO ALVAREZ et al., 2024).

Dopamine agonists (DA) exert their action by stimulating dopaminergic receptors. The agonists currently used are non-ergot derivatives, namely ropinirole, pramipexole, rotigotine, and apomorphine. AD is primarily used in the early stages of PD and as adjunctive therapies. Ropinirole and pramipexole are also available in extended-release (ER) formulations. Ropinirole ER is more effective compared to its immediate-release (IR) formulation. Although pramipexole ER still has the benefits of more convenient dosing, no difference was observed in tolerability compared to the IR formulation. Rotigotine is administered via a transdermal patch. Compared to ropinirole and pramipexole, it also has some action on D1 receptors, which may confer some additional benefit (NEMADE; SUBRAMANIAN; SHIVKUMAR, 2021).

The most common side effects of AD include hallucinations, orthostatic hypotension, nausea, pedal edema, excessive daytime sleepiness, and impulse control disorders (ICD). These side effects are more common with AD than with levodopa. Patients and caregivers should be advised about ICDs (hypersexuality, pathological gambling, compulsive shopping) prior to initiation and monitored thereafter at each visit. Although reducing or ceasing AD works to improve these symptoms, some patients may have a dopamine agonist withdrawal syndrome (SAAD). This is characterized by anxiety, panic, agoraphobia, fatigue, dysphoria, and suicidal ideation. These symptoms do not resolve with the addition of levodopa and resumption of the agonist may be the only solution (NEMADE; SUBRAMANIAN; SHIVKUMAR, 2021).

Amantadine has long been used for symptomatic improvement of PD. However, this symptomatic benefit has limited value in early PD Amantadine is often used to treat dyskinesias due to its antiglutamatergic property. It is also thought to block dopamine reuptake, stimulate the release of endogenous stored dopamine, and have a mild anticholinergic effect. Amantadine may cause side effects such as hallucinations and blurred vision (due to corneal edema, a rare ophthalmic emergency). Its dose needs to be adjusted in patients with renal impairment. An extended-release formulation (ADS-5102 or GOCOVRI) has been approved for the treatment of levodopa-induced dyskinesias in PD. It is administered orally daily at bedtime. Concentration increases slowly during sleep, reaches peak concentration in the morning with sustained levels during waking hours. At the recommended daily dose of 274 mg HS, it results in a plasma concentration of amantadine 1.4 to 2 times higher during the day compared to IR formulations. It is available in 68.5 mg and 137 mg capsules. In a phase 3, randomized, double-blind clinical trial, it was

shown to significantly reduce dyskinesias and "off" time. Another ER OSMOLEX ER formulation was approved for the treatment of PD, but the approval was based only on bioavailability studies comparing it to Amantadine IR (NEMADE; SUBRAMANIAN; SHIVKUMAR, 2021).

Deep brain stimulation (DBS) treatment is a surgical method used to treat Parkinson's disease by stimulating the brains of patients. During this surgery, electrodes are implanted in specific parts of the brain to treat the symptoms of Parkinson's disease. DBS is a treatment that employs nanotechnology-based electrodes to treat Parkinson's disease. These electrodes create electrical impulses in the brain to regulate the abnormal impulses induced by Parkinson's disease. This technique has been approved by the Food and Drug Administration as a viable therapy for severe cases of Parkinson's disease. Deep brain stimulation surgery is more effective than drug therapy for Parkinson's disease. Some people have problems with their DBS operation, which requires surgeons to address the problem. Deep brain stimulation is often used in individuals with severe Parkinson's disease who do not respond to drug therapy. DBS is advantageous for dyskinesias that do not improve with medication adjustments, as well as for inconsistent and fluctuating responses to levodopa. Parkinson's disease-related involuntary movements are surgically treated in deep brain regions involved in motor regulation (ADAM et al., 2023).

CONCLUSION

Based on the extensive review presented, it is possible to conclude that Parkinson's disease (PD) is a progressive neurological condition that encompasses a wide range of motor and non-motor manifestations. Early diagnosis of PD is a challenge, as many non-motor symptoms may precede classic motor manifestations. The standardization of diagnostic criteria, such as those defined by the Parkinson and Movement Disorders Society, has improved diagnostic accuracy and reduced common errors. Imaging techniques and biomarkers, although promising, are not yet robust enough for diagnostic use alone, but they can be useful in differentiating atypical parkinsonism

Regarding treatment, levodopa therapy remains the gold standard for most patients, providing significant improvement in motor symptoms and positive impact on survival. However, prolonged use can lead to motor complications such as efficacy fluctuations and dyskinesias, which has motivated the development of extended-release formulations and continuous infusions. In addition, dopamine agonists and enzyme inhibitors, such as MAO-B and COMT inhibitors, are often used as adjuncts to improve therapeutic response and mitigate adverse effects of levodo

New strategies, such as deep brain stimulation, offer promising alternatives for more advanced cases that are resistant to pharmacological treatment. With the advancement of technologies and therapies based on precision medicine, there is an expectation that, in the future, the management of PD may become even more effective, improving quality of life and potentially delaying the progression of PD. This review highlights the continued need for future investigations to identify specific biomarkers, enhance early diagnosis, and develop new therapeutic approaches that are effective in minimizing complications and improving patients' experience throughout PD progression.

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