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CHAPTER 24

PHARMACOLOGICAL APPROACHES IN THE TREATMENT OF PARKINSON'S DISEASE: AN INTEGRATIVE REVIEW

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ABSTRACT

Parkinson's disease (PD) is a progressive neurodegenerative condition that affects movement, and its treatment involves medications, complementary therapies and, in specific cases, interventions such as deep brain stimulation, aiming to improve the patient's quality of life. From this perspective, the present study aimed to analyze pharmacological approaches in the treatment of PD, with emphasis on efficacy, safety, and impact on motor and non-motor symptoms. This was an integrative literature review, whose data searches were carried out in the PUBMED, SCIELO and LILACS databases. Initially, a total of 442 articles were located, and after screening and careful selection, about 08 articles were chosen to compose this review. A total of 4,764 individuals were evaluated, most of whom were male, aged between 50 and 70 years. Among the medications used, levodopa was most prominent, both in monotherapy and in combination with another drug. Studies show that levodopa, alone or in combination, is effective in motor symptoms, but does not impact the progression of the disease. Intrajejunal therapy and combination with selegiline offer additional benefits, while flavonoids may complement treatment. Isradipine, on the other

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hand, has not shown efficacy in the progression of the disease. It is concluded that the pharmacological approach to PD continues to be fundamental for the management of motor and non-motor symptoms, with levodopa being the pillar of treatment, complemented by combination therapies and new agents that offer additional benefits in certain contexts.

Keywords: Parkinson's disease. Pharmacological therapy. Combination treatment. Effectiveness.

INTRODUCTION

Parkinson's disease (PD) is a complex neurodegenerative condition, which is manifested by debilitating motor and non-motor symptoms, resulting from the progressive loss of dopaminergic neurons (LEVADA *et al.,* 2024). From a pathological point of view, PD is characterized by the degeneration of dopaminergic neurons in the substantia nigra pars compacta (SN), located in the midbrain, and by the presence of Lewy bodies, which are cytoplasmic inclusions that contain insoluble aggregates of alpha-synuclein. In addition, PD has a more widespread pathology, affecting other regions of the brain and also involving non-dopaminergic neurons, which contributes to the complexity and diversity of symptoms associated with the disease (SIMON; TANNER; BRUNDIN, 2020).

Most cases of PD probably have a multifactorial etiology, resulting from the interaction between environmental and genetic factors. Exposure to toxic chemicals and head trauma can increase the risk of developing PD, while certain lifestyle habits can contribute to reducing this risk (GOLDMAN *et al.,* 2019). In addition, genetic susceptibility factors may influence how environmental exposures affect disease. Age is considered the most relevant risk factor for the onset of the disease, and men are more susceptible than women, with an approximate prevalence rate of 3:2 (BLAUWENDRAAT; NALLS; SINGLETON, 2020).

The clinical diagnosis of PD is predominantly based on motor signs, including asymmetric and progressively slow resting tremor, cogwheel rigidity, and bradykinesia (TOLOSA *et al.,* 2021). However, it is also important to consider non-motor symptoms, which can appear years before motor deficits appear. These non-motor symptoms can include anosmia, constipation, depression, and sleep behavior disorders. In the advanced stages of the disease, other non-motor features may manifest, such as autonomic dysfunction, pain, and cognitive impairment (CHIA; TAN; CHAO, 2020).

Currently, the treatments available for PD focus on relieving symptoms, but cannot prevent the progression of the disease. Emerging therapies, such as stem cell-derived dopaminergic cell transplantation, show potential but face ethical challenges and limitations regarding cell availability. The reprogramming of astrocytes to replace lost neurons presents itself as a promising alternative, as well as approaches aimed at repairing mitochondrial dysfunctions and controlling inflammation. While cellular reprogramming brings hope, it is essential to carefully evaluate the potential long-term consequences before its widespread clinical implementation (WANG *et al.,* 2023).

Pharmacological approaches to the treatment of PD primarily include the use of levodopa and dopamine agonists, which help relieve motor symptoms by replacing or

stimulating dopamine (CATTANEO; JOST, 2023). Emerging therapies, such as GLP-1 receptor agonists (e.g., liraglutide and exenatide), have been investigated due to their neuroprotective potential, including reducing inflammation and toxic protein accumulation (NOWELL *et al.,* 2023; CATTANEO; JOST, 2023). Other antidiabetic agents, such as metformin and PPARγ agonists, are also being studied, aiming to combat both the motor and cognitive symptoms of PD, exploring mechanisms such as reducing oxidative stress and improving mitochondrial function (NOWELL *et al.,* 2023).

Given the complexity of PD and its growing impact on public health, investigating effective treatments that can modify its progression is crucial. PD significantly affects the quality of life of patients, also bringing challenges to health systems. Exploring new approaches, such as cell therapies and the use of antidiabetic drugs, is promising, although it still requires rigorous studies to prove safety and efficacy. This research is justified by the need for therapeutic strategies that not only relieve symptoms, but also influence the course of PD, bringing lasting benefits to patients.

From this perspective, the present study aimed to analyze pharmacological approaches in the treatment of PD, with emphasis on efficacy, safety, and impact on motor and non-motor symptoms, in order to provide a comprehensive and up-to-date view of the advances and limitations of the main drugs used.

METHODOLOGY

It is an integrative literature review, which consists of a research method that allows for a comprehensive and systematic analysis of scientific studies, promoting the characterization and dissemination of knowledge (DANTAS *et al*., 2022).

The search strategy of this research was based on the PICO strategy, defined as follows: **P (Patients):** Patients diagnosed with Parkinson's Disease; **I (Intervention):** Pharmacological treatments; **C (Comparison):** Other treatments (e.g., surgical, non-pharmacological); **O (Results):** Efficacy in controlling symptoms, safety and adverse effects.

Based on the PICO strategy, the following guiding question was defined: "What are the most effective and safe pharmacological approaches for the control of motor and non-motor symptoms in Parkinson's Disease, according to recent scientific literature?"

The selection of studies was carried out in the *Medical Literature Analysis and Retrieval System Online* (MEDLINE/PUBMED), SCIELO and Latin American and Caribbean Literature on Health Sciences (LILACS) databases. The search for articles was carried out using the following descriptors, in Portuguese: "Parkinson's Disease", "Pharmacological

Treatment", and in English: "Parkinson Disease"; "Drug Therapy". Based on the Descriptors in Sciences and Health (DeCS) and Medical Subject Headings (MESH) and with the help of the Boolean operators "AND" and "OR". During the searches, the following combination of descriptors was used: "Parkinson Disease and Drug Therapy".

Complete articles, accessible online and free of charge, in Portuguese and English, that deal with pharmacological approaches in the treatment of Parkinson's Disease, with a focus on the efficacy and safety of drugs, published in the last 5 years, were included. Editorials, letters to the reader, reflective studies, abstracts, duplicate articles, theses, dissertations, manuals, and studies that did not correspond to the theme or objective of the review were excluded.

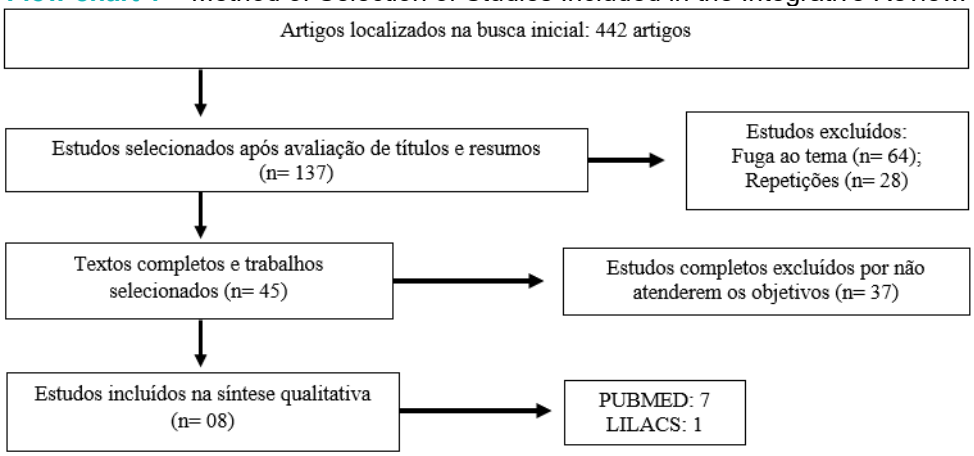
After collecting data in the databases, the titles and abstracts were read, and among the studies selected after this process, the full articles were read, and from these, the studies eligible for analysis were chosen. The study was carried out respecting the researched literature, with no changes in the results found to the benefit of this research.

After collecting data in the research databases, the titles and abstracts were read. Among the studies selected at this stage, the articles were read in full, from which those eligible for analysis were chosen. This data was organized into tables, and the search strategy represented in the flowchart.

Based on the search strategy, a total of 442 complete articles were initially found, which were screened and evaluated. After reviewing the titles and abstracts, 305 articles were discarded because they did not meet the eligibility criteria and 137 articles were selected for content analysis. In the end, only 08 studies met all the criteria and were incorporated into this review, as shown in flowchart 1.

Subsequently, after the critical analysis of the selected articles, carried out by an independent researcher, the works were classified by author, year of publication, objective, type of study and sample size.

Flow chart 1 – Method of Selection of Studies Included in the Integrative Review.



Source: Authors, 2025.

RESULTS

Based on the search strategy and after selection and analysis of the eligibility criteria, about 08 studies met all the criteria and were incorporated into this review. Table 1 presents the methodological characteristics of the included studies. It is important to note that most of the searches were obtained from the Pubmed database (83.3%) and consisted of Randomized Clinical Trial studies (50.0%).

Table 1. Methodological characteristics of the studies included in the integrative review.

Author/ Year	Study Type	Periodic	Database
Verschuur et al., 2019	Randomized Clinical Trial	N Engl J Med	PUBMED
Popa et al., 2020	Study Retrospective	Medicine	PUBMED
Simuni et al., 2020	Randomized Clinical Trial	Annals of Internal Medicine	LILACS
Jiang et al., 2020	Systematic Review and Meta-analysis	Aging Clin Exp Res	PUBMED
Mehta et al., 2021	Randomized Clinical Trial	Neurol Ther	PUBMED
Wang et al., 2022	Retrospective Cohort Study	Eur J Neurol	PUBMED
Santos-García et al., 2023	Randomized Clinical Trial	Parkinsonism Relat Disord	PUBMED
González-May et al., 2024	Systematic Review	Nutr Res	PUBMED

Source: Authors, 2025.

Chart 1 shows the characteristics of the treatments performed in the included studies. It is verified that 4,764 individuals were evaluated, most of whom were male, aged between 50 and 70 years. Among the medications used, levodopa was most prominent, both in monotherapy and in combination with another drug.

Table 1. Characteristics of Parkinson's treatments used in the studies.

Author/ Year	Sample	Treatment Used	Dosage and Treatment Time
Verschuur et al., 2019	No: 445 Gender: 69.8% men Age: 65 years old	Levodopa Carbidopa Placebo	Levodopa Dose: 100mg – 3 times/day Carbidopa Dose: 25 mg – 3 times/day Duration: 40 weeks

Popa et al., 2020	No: 61 Gender: 68.9% men Age: 70.4 years	Levodopa-Carbidopa (Intestinal Gel) Levodopa-Carbidopa (oral)	NR
Simuni et al., 2020	No: 336 Gender: 68.0% men Age: 62 years	Isradipine Placebo	Dose: 5 mg - 2 times/day Duration: 36 months
Jiang et al., 2020	No.: 2.008 Gender: NR Age: 50 to 66 years old	Levodopa Selegiline + Levodopa	Selegiline Dose: 1 to 10 mg Levodopa dose: 300 to 750 mg Duration: 2 to 60 months
Mehta et al., 2021	No: 196 Gender: 54.0% Age: 64.2 years	Amantadine (Gocovri ®) Placebo	Dose: 274 mg – 1 time/day Duration: 12 weeks
Wang et al., 2022	N: 1.526 Gender: 53.0% men Age: 69.0 years	Amantadine (Gocovri ®) Levodopa	NR
Santos-García et al., 2023	N: 63 Gender: 68.3% men Age: 63.9 years	Levodopa	NR
González-May et al., 2024	No: 129 Gender: NR Age: 69 years old	Flavonoids	Dose: 2.6 to 10.7 mg of flavonoids

Legend: NR: not reported. Source: Authors, 2025.

The reviewed studies show that levodopa, alone or in combination with other medications, is effective in controlling motor symptoms, but does not alter the progression of Parkinson's disease. Intrajejunal therapy improves motor fluctuations in advanced stages, whereas combination with selegiline is more effective than monotherapy. The response to levodopa remains consistent in the long term, and flavonoids, present in foods such as cocoa, can complement treatment, reducing motor symptoms and the risk of progression. Isradipine, however, has not shown benefits in the progression of the disease. Amantadine has been shown to be effective in improving dyskinesia, depressed mood, and daytime sleepiness.

Chart 2 shows the main observations found after analyzing the treatments performed in the studies included in this review.

Table 2. Effects of treatments used in the studies included in the integrative review.

Author/ Year	Treatment Effects
Verschuur et al., 2019	Treatment with levodopa at a dose of 100 mg three times daily in combination with carbidopa at a dose of 25 mg three times a day had no disease-modifying effect, either beneficial or harmful.
Popa et al., 2020	Continuous intrajejunal infusion of levodopa-carbidopa intestinal gel ensures a clinically significant reduction in motor fluctuations compared to oral therapy in advanced Parkinson's disease.
Simuni et al., 2020	Long-term treatment with immediate-release isradipine did not slow the clinical progression of early-stage Parkinson's disease.
Jiang et al., 2020	Selegiline + Levodopa combination therapy is superior to Levodopa monotherapy for the improvement of clinical symptoms in patients with Parkinson's disease. In addition, the safety profile of Selegiline + Levodopa combination therapy is comparable to that of Levodopa monotherapy.

Mehta et al., 2021	In addition to significant improvements in dyskinesia and OFF time with Gocovri, study participants also experienced improvement in depressed mood and daytime sleepiness.
Wang et al., 2022	Early treatment with amantadine may delay the onset of levodopa-induced dyskinesia.
Santos-García et al., 2023	There was a median response to levodopa, stable, and in fact, more than 70% of patients showed a good response after a 4-year follow-up.
González-May et al., 2024	Higher consumption of total flavonoids and their subclasses, anthocyanins, or foods rich in them (apples, red wine, blueberries, and strawberries) reduce the risk of developing Parkinson's disease and its mortality.

Source: Authors, 2025.

DISCUSSION

The reviewed studies present complementary and, in some cases, divergent perspectives on the management of Parkinson's disease (PD), addressing aspects related to the efficacy of different interventions, safety, and impact on disease progression.

Verschuur *et al.* (2019) and Simuni *et al.* (2020) investigated treatments with a potential PD progression-modifying effect, but both studies found no evidence to do so. Verschuur *et al.* (2019) evaluated levodopa, combined with carbidopa, in patients with early PD, showing significant improvement in motor symptoms in the initial phase of treatment, but with no impact on disease progression after 80 weeks. Similarly, Simuni *et al.* (2020) did not identify neuroprotective benefits with long-term use of isradipine, suggesting that the doses employed may have been insufficient. These findings reinforce that, although effective in symptomatic management, these interventions do not significantly alter the course of PD.

On the other hand, Santos-García *et al.* (2023) demonstrated that the efficacy of levodopa in relieving motor symptoms remains consistent in the long term, even in patients with motor fluctuations. This study highlighted the stability of the clinical response to levodopa, corroborating its importance as a therapeutic basis and reinforcing the need to consider its efficacy before the indication of invasive treatments, such as deep brain stimulation.

Jiang *et al.* Wang et al. (2020) broadened this discussion by showing that the combination of levodopa with selegiline offers additional advantages over levodopa monotherapy, with a more significant reduction in motor and non-motor symptoms, and overall Parkinson's Disease Rating Scale scores. These findings suggest that combined strategies can enhance therapeutic benefits without compromising treatment safety.

In contrast to traditional pharmacological approaches, González-May *et al.* Wang et al. (2024) explored the role of polyphenols in PD management, noting modest improvements in motor symptoms and potential benefits in disease progression due to the

antioxidant and neuroprotective properties of these compounds. However, the impact on non-motor symptoms, quality of life, and mood was limited, and adverse events such as nausea and dizziness were more frequent with curcumin and licorice interventions.

Finally, Popa *et al.* (2020) highlighted the clinical superiority of intrajejunal gel (LCIG) administration of levodopa-carbidopa compared to the oral route in patients with advanced PD. The group treated with LCIG showed a significant reduction in motor fluctuations, dyskinesia, and wearing-off episodes, demonstrating greater stability in motor symptoms and improvement in functionality. However, anxiety disorders were more prevalent in this group, signaling the need for careful monitoring.

Mehta *et al.* (2021) and Wang *et al.* (2022) explored the effects of amantadine in different PD contexts, highlighting its potential impact on motor and non-motor symptoms. Mehta *et al.* (2021) evaluated the effects of extended-release amantadine (Gocovri) on non-motor PD symptoms, using Part I of the MDS-UPDRS. Patients randomized to receive Gocovri or placebo had, at baseline, symptoms such as sleep problems, daytime sleepiness, pain, and fatigue, significantly affecting quality of life. The analysis revealed that in addition to improving dyskinesia and reducing OFF time, Gocovri also improved specific non-motor symptoms, such as depressed mood and daytime sleepiness. These results suggest a relationship between the reduction of motor complications and the improvement of non-motor symptoms, indicating comprehensive benefits of the drug in the management of PD.

On the other hand, Wang *et al.* (2022) investigated the association between early amantadine use and late onset of levodopa-induced dyskinesia in patients with early-stage PD. Comparing amantadine with other agents such as anticholinergics and MAO-B inhibitors, the results indicated that the use of amantadine significantly delayed the onset of dyskinesia in analyses performed at 6 and 12 months, with adjusted hazard ratios of 0.65 and 0.64, respectively. These data suggest that early treatment with amantadine may be more effective than other symptomatic drugs in preventing motor complications related to levodopa use.

Both studies highlight the therapeutic potential of amantadine, both in reducing motor symptoms and improving non-motor aspects of PD. In addition, they reinforce the need for additional studies to deepen the understanding of the mechanisms by which amantadine influences these symptoms and to validate its applications in the clinical management of PD.

Overall, studies indicate that while levodopa remains the therapeutic mainstay for PD, combination approaches, such as with selegiline or LCIG, and complementary

interventions, such as polyphenols, may offer additional benefits. However, the absence of disease-progression-modifying impact in investigated interventions underscores the need for further studies, especially those exploring different doses, duration of treatment, and therapeutic combinations.

CONCLUSION

The reviewed studies highlight important advances in the management of Parkinson's disease (PD), while also highlighting limitations in the current ability to modify disease progression. Levodopa remains the most effective therapeutic mainstay, with sustained efficacy over time, both alone and in combination with other agents such as selegiline or in advanced formulations such as intrajejunal gel. Amantadine has also shown significant benefits, including improvement of motor and non-motor symptoms and the potential to delay levodopa-induced dyskinesia.

However, alternative strategies, such as the use of polyphenols, showed more modest results and limiting adverse effects. In addition, investigated interventions with neuroprotective potential, such as isradipine and levodopa in early stages, have not demonstrated an impact on modifying PD progression.

These findings reinforce the need for further research on combined approaches, innovative therapies, and adjustments in doses and durations of treatments. Although symptomatic management of PD has progressed, achieving interventions that effectively modify the course of the disease remains a central challenge.

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