

## Review

# Study of Safety and Effectiveness of Levodopa in Patients with Parkinson's Disease

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## Abstract

Parkinson's disease is the second most prevalent neurodegenerative disease in the world. Although there are no treatments that can inhibit the neurodegenerative process itself, symptomatic treatments can enhance patients' quality of life. Dopamine replacement or augmentation treatments can partially or totally restore the dopaminergic neuronal degeneration that characterizes Parkinson's disease. Physicians most usually prescribe Levodopa, which is still the most potent oral dopaminergic medicine for Parkinson's disease. The purpose of this research is to review the available information about study of safety and effectiveness of levodopa in patients with Parkinson's disease. Levodopa is the gold standard for the treatment of Parkinson's disease since it is safe, effective and well tolerated among patients. It has been established that during the past 50 years the majority of Parkinson's symptoms improve in the average levodopa treated patient, most likely due to the striatal conversion of this amino acid into dopamine. Levodopa lessens morbidity and mortality, improves function and quality of life, and therefore lowers individual and community expenses. Levodopa, on the other hand, has a short half-life and is rapidly metabolized in the plasma, which results in variances, such as the wearing-off of action and uneven symptom relief as well as the onset of dyskinesias, both of which worsen as the disease progresses. Levodopa is often prescribed with other medications including carbidopa, pramipexole and others to lessen the side effects associated, further clinical research however can assist in developing strategies to make levodopa safer in long term use.

**Keywords:** *Parkinson's, disease, levodopa, safety*

## Introduction

Parkinson's disease (PD) is a neurodegenerative condition whose cardinal motor characteristics include bradykinesia, rigidity, postural instability, and resting tremor. Non-motor characteristics include depression and hyposmia. It is the most prevalent chronic neurodegenerative disease that affects motor behaviour, and its prevalence rises with age, from 2% in people over 65 years to 5% in people over 85 years. A small area located deep inside the human midbrain's core; the substantia nigra pars compacta, which contains dopaminergic pigmented neurons, is the hallmark of PD (1). The neuropathological indicators of PD are intracellular inclusions containing clusters of synuclein and neuronal death in the substantia nigra, which results in striatal dopamine insufficiency. The central and peripheral autonomic nerve systems contain more numerous cell types that are also involved, most likely beginning with the first stages of the disease. Although bradykinesia and other essential motor characteristics are required for clinical diagnosis, PD is also accompanied by a wide range of non-motor symptoms that increase overall disability (2).

Treatment objectives differ from individual to individual, underscoring the demand for individualized management. There is no need to put off symptomatic therapy in PD-related impairment. The most typical drug used as initial treatment is levodopa. A multidisciplinary team approach and an expanding arsenal of non-pharmacological therapies are necessary for optimal management, which should begin with diagnosis. There is currently no cure for PD but increasing knowledge about the genetic origins of the condition and the mechanisms underlying neuronal death has spurred the development of a number of intriguing treatment options (3). PD is characterized by the degradation of dopaminergic neurones, which can be partially or completely reversed by dopamine replacement or augmentation techniques. Levodopa, which continues to be the most effective oral dopaminergic medication for PD, is used most frequently by clinicians. Levodopa is not recommended for long-term usage due to concerns about its tendency to cause dyskinesias and motor irregularities. There are methods to postpone or lessen these issues, but the clinician must create the groundwork for them by choosing the medications for early treatment and the order in which they are introduced later. Combining levodopa with a catechol-O-methyl transferase inhibitor may increase the effectiveness and duration of the drug's effects. The

major objectives of therapy continue to be preserving good motor function and quality of life, and it is crucial that the course of treatment is individualized for each patient (4).

Levodopa the most efficient medication for PD decreases morbidity and mortality, improves function and quality of life, thus lowering the individual and community expenses. Levodopa, however, has a brief half-life and is rapidly metabolized in the plasma, which causes variations, including the wearing-off of action and inconsistent symptom alleviation as well as the emergence of dyskinesias, both of which get worse with the progression of the disease. Motor fluctuations are still an issue even though immediate-release and controlled-release formulations have been utilized successfully (5). Levodopa serves as the benchmark against which all other treatments must be measured. Most parkinsonian symptoms are alleviated by levodopa, and it also seems to lower mortality rates. Decarboxylase and catechol-O-methyl transferase enzymes both break down levodopa. To avoid peripheral dopamine build-up and its associated side effects, such as nausea and vomiting, it is frequently given in conjunction with a decarboxylase inhibitor. Recent research suggests that taking levodopa along with an inhibitor of catechol-O-methyl transferase can extend the time the medicine takes to take effect and can extend the time a patient's motor response lasts. However, using levodopa is also linked to both acute and long-term side effects that make treatment less effective (6). The purpose of this research is to review the available information about study of safety and effectiveness of levodopa in patients with PD.

## Methodology

This study is based on a comprehensive literature search conducted on August 22, 2022, in the Medline and Cochrane databases, utilizing the medical topic headings (MeSH) and a combination of all available related terms, according to the database. To prevent missing any possible research, a manual search for publications was conducted through Google Scholar, using the reference lists of the previously listed papers as a starting point. We looked for valuable information in papers that discussed the information about the study of safety and effectiveness of levodopa in patients with PD. There were no restrictions on date, language, participant age, or type of publication.

## Discussion

Levodopa a dopamine precursor is an effective and well-tolerated medication used to treat PD. Since it has a longer half-life and a higher availability to the brain, oral levodopa has been used extensively for more than 40 years. It is frequently used in conjunction with a dopa-decarboxylase inhibitor, which lessens numerous treatment problems. Treatment for early-stage PD depends on how severe the symptoms are; if more symptomatic relief is needed, levodopa or dopamine agonists are typically the best options. In some cases, levodopa introduction should be explored early on, either as a monotherapy or in conjunction with other medications, because maintaining employment or physical activity is a significant goal for younger people. The emergence of different treatment-related complications and outcomes, including response variations, dyskinesia, and psychological issues, may eventually place a cap on the clinical usage of levodopa. Intermittent dopamine-replacement medication supply to the brain is linked to motor difficulties. Levodopa, carbidopa, and entacapone combined in a single tablet with a range of levodopa dose strengths provides flexibility and helps regulate response swings. Transdermal levodopa patches, oral pro-levodopa, and duodenal infusion of a levodopa/carbidopa are recent innovations in levodopa therapy that aim to achieve continuous delivery of the medication. The most effective dopaminergic therapy for PD is still levodopa (7).

### *Literature evidence for safety and efficacy of levodopa*

Zhao stated in his meta-analysis findings that for early-stage PD patients, levodopa-alone therapy may be more effective in relieving motor symptoms than levodopa-sparing therapy, and the motor benefit of levodopa-alone therapy may increase over time. Sparing therapy may carry a lower chance of wearing off and dyskinesia, although long-term outcomes may not differ between the two groups. In general, levodopa alone therapy may benefit early PD patients more than levodopa sparing methods. Although, contradictory clinical and imaging results necessitate more research (8). Current research suggests that regular levodopa administration should enhance long-term symptomatic effectiveness and may postpone or prevent motor problems. Levodopa dosage or dosing schedule changes, switching to a different levodopa formulation, and the use of adjunct therapies like catechol-O-methyl transferase inhibitors, dopamine agonists, and monoamine oxidase-B inhibitors are just a few of the therapeutic options available to improve

therapeutic outcomes. Early symptom recognition and the start of successful treatment are essential for managing wearing-off (9).

Levodopa, which can replenish dopamine in the brain and enhance extrapyramidal function, is the cornerstone of treatment for PD patients. However, prolonged levodopa use can result in negative side effects as the on-off phenomena, dyskinesia, and wearing off phenomenon. Some individuals may also experience permanent, irreversible conditions. A dopamine receptor agonist called pramipexole is used to treat the clinical signs and symptoms of adult idiopathic PD. In other words, pramipexole can be administered alone or in combination with levodopa for PD patients when levodopa effectiveness gradually declines, or on-off fluctuations occur along the course of the disease. For the treatment of clinical symptoms in PD patients, pramipexole and levodopa combination therapy is preferable to levodopa monotherapy. Additionally, pramipexole and levodopa combination therapy has a superior safety profile than levodopa monotherapy (10). Paolini et al. stated that long-term research findings show that levodopa-related motor complications will eventually affect all patients. Pramipexole and other dopamine agonists appear to have a decreased incidence of dyskinesia and wearing off after first treatment. But only younger patients and those with minor and manageable clinical symptoms can be considered to benefit from this method. When compared to levodopa therapy, dopamine agonists and other levodopa-sparing drugs such monoamine oxidase B inhibitors and catechol-O-methyl transferase inhibitors are effective but insufficient to control severe motor abnormalities. Levodopa's potential neurotoxic effects are also a source of concern due to the drug's increased creation of reactive oxygen species. However, no strong evidence regarding the neurotoxicity of levodopa has yet been offered. Instead, it appears that levodopa encourages the regeneration of dopaminergic neurons and increases the sprouting of striatal dopaminergic terminals in rodents treated with 6-hydroxydopamine, suggesting a potential moderating influence on the course of the disease (11).

Zadikoff et al. concluded that patients who needed 2000 mg/day of levodopa-carbidopa intestinal gel displayed a safety profile equivalent to the drug's known safety and tolerability with comparable therapeutic improvements. Higher adverse events were seen; however, they were within the range for levodopa-carbidopa intestinal gel. Advanced PD patients who require very high dosages of levodopa benefit from continuous administration of

levodopa-carbidopa intestinal gel (12). Findings of an interim analysis concluded that levodopa-carbidopa intestinal gel is well-tolerated, effective and reliable treatment among patients of PD (13). Results of a clinical trial double-blind study showed that Levodopa-carbidopa intestinal gel exposure lasted an average of 4.1 years. The general rate of discontinuation was 34%. Despite the fact that 94% of patients reported experiencing an adverse event, this number gradually dropped over time, and 53% of patients reported a major adverse event. 37% of patients in this extension trial needed percutaneous endoscopic gastrostomy tube replacement, while 54% needed jejunal tube replacement during the research period. The majority of individuals received only levodopa. From the start of the levodopa-carbidopa intestinal gel infusion through the study's end point, patients-maintained decreases in off time and increases in mean on time without dyskinesia ( $P < 0.001$ ). Assessments of quality of life and activities of daily living showed considerable gains that maintained throughout the research (14). Antonini et al. concluded in his findings that over the course of 24 months, levodopa-carbidopa intestinal gel reduced motor fluctuations, non-motor symptoms, and decreased quality of life while maintaining tolerability within the bounds of the recognized safety profile (15).

Poewe et al. described that levodopa, which has been used clinically for more than 40 years, continues to be the gold standard for PD medication symptomatic effectiveness. Dopamine replacement with levodopa is linked to the best improvement in motor function when compared to other dopaminergic treatments. However, the emergence of numerous forms of motor response oscillations throughout the day as well as drug-induced dyskinesias frequently make long-term levodopa therapy challenging. Drugs that lengthen the half-lives of levodopa or dopamine, such as entacapone or monoamine oxidase inhibitors, can reduce motor fluctuations. Controlling dyskinesia, however, continues to be very difficult. As a result, many neurologists are now hesitant to recommend levodopa therapy (16). Improved clinical outcomes are observed when the carbidopa/levodopa dosage exceeds the 800 mg threshold. Patients taking less or more than 800 mg of carbidopa/levodopa showed no appreciable differences in their motor, mood, or quality-of-life scores, albeit there was a slight lengthening of the duration of the dyskinesia without an aggravation of its pain or disability. Depressive symptoms and quality-of-life indicators significantly improved in PD patients who exceeded the 800 mg cut-off between two consecutive

clinic visits, and there was no worsening of motor fluctuations or dyskinesia in these patients (17).

Fahn et al. stated that based on the clinical evidence, levodopa either delays the progression of PD or has a lasting impact on the disease's symptoms. In contrast, the neuroimaging data imply that levodopa either modifies the dopamine transporter through its pharmacologic effects or speeds up the loss of nigrostriatal dopamine nerve terminals. Levodopa may have long-term impacts on PD; however, these implications are still unknown (18). Stocchi et al. concluded in his study that in individuals with advanced PD, continuous levodopa infusion is linked to fewer motor complications than the medication's traditional oral version. Pharmacokinetic studies show that relatively high plasma levodopa concentrations have no negative effects on motor complications and that reduced motor problems are associated with avoiding low plasma levodopa trough levels. Author further suggested that a comparable decrease in motor problems would occur if levodopa/carbidopa were to be given orally in a way that mimics the pharmacokinetic pattern of the infusion (19).

Orally administered levodopa, despite its limitations in the treatment of PD, can be considered a standard therapy due to its effects on disability and discomfort as well as its affordability. It has been established that during the past 50 years majority of Parkinson's symptoms improve in the average levodopa-treated patient, most likely due to the striatal conversion of this amino acid into dopamine. Fundamental uncertainties about its whole mechanism of action and the development of adverse responses yet persist. For a better understanding of the pharmacology of prolonged levodopa usage, a number of clinical phenomenology elements such as dyskinesias and the long-duration anti-Parkinsonian response continue to be a difficulty. Due to its uneven absorption and significant dose-to-dose fluctuation in plasma concentrations, the pharmacokinetics of levodopa seem to predict some of the issues that may arise during chronic administration. It is likely that a number of new pharmaceutical strategies will increase the consistency of levodopa anti-Parkinsonian dopamines impact because they are directed at the special physiology of its uptake (20). Despite the occurrence of common side effects of levodopa in long term use, it is practically the drug of choice for the treatment of PD although further research involving clinical trials can aid in developing strategies for combating the side effects associated with levodopa therapy also population-based clinical studies and trials

can contribute to literature since the available studies are limited.

## Conclusion

Levodopa is the gold standard for the treatment of PD. It is a safe, effective and well tolerated medication among the patients of PD. However, its long-term use is associated with certain common side effects research in future can significantly contribute to increasing the safety index of levodopa by addressing side effects.

## Disclosure

### Statement

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### Ethical consideration

Non-applicable.

### Data availability

Data that support the findings of this study are embedded within the manuscript.

### Authors' contribution

All authors contributed equally to the drafting, writing, sourcing, article screening and final proofreading of the manuscript.

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