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Effectiveness of Stalevo Drug Usage in Parkinson's Patients: A Narrative Review

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Abstract: Parkinson's Disease (PD) is a neurodegenerative disorder that affects patients' quality of life, with primary motor symptoms such as tremor, muscle rigidity, and bradykinesia. Levodopa is the mainstay of PD therapy, but approximately 80% of patients experience motor complications, such as motor fluctuations and "wearing-off" after several years of therapy. This study evaluates the efficacy, safety, and rational use of Stalevo (levodopa, carbidopa, and entacapone) in managing motor complications and "wearing-off" phenomena in patients with Parkinson's Disease (PD). This research was conducted as a narrative review to provide a recent evidence-based synthesis of the efficacy and safety of Stalevo. Methods included a search of articles in PubMed, ScienceDirect, and Google Scholar published between 2015 and 2025 using the keywords "Stalevo" and "Parkinson's disease." The study revealed that Stalevo was effective in prolonging the duration of levodopa's effect, reducing the required levodopa dose, and improving patients' quality of life, particularly in patients with motor fluctuations. Although side effects such as dyskinesia and diarrhea may occur, Stalevo's overall safety profile is well-received. Stalevo is a cost-effective, evidence-based intervention for intermediate-to-advanced PD. Rational use requires precise patient selection and monitoring for dopaminergic side effects, such as dyskinesia and diarrhea, to optimize quality of life and ensure patient safety.

Keywords: Antiparkinson agents; Catechol O-Methyltransferase inhibitors; Drug combinations; Levodopa; Parkinson's disease; Treatment outcome

Introduction

Parkinson's disease (PD) is a neurodegenerative disorder characterized by three main motor symptoms: resting tremor, muscle rigidity, and bradykinesia, affecting approximately 1% of the population over the age of 60 (Larasanti et al., 2020; Poewe et al., 2017). PD is the second leading cause of neurodegenerative disorders after Alzheimer's disease in the elderly (Armstrong et al., 2020; Putri et al., 2023). Since its initial widespread clinical use more than 50 years ago, levodopa has become the most effective symptomatic therapy for dopaminergic stimulation in patients with PD (Jenner et al., 2023). Levodopa is commonly used in combination with a dopa-decarboxylase inhibitor (DDCI), such as carbidopa or benserazide, to prevent the conversion of levodopa to dopamine in the peripheral circulation, allowing more levodopa to reach the brain through active transport across the blood-brain barrier (Hsu et al., 2015; Solla, 2010). However, as the disease progresses, approximately 80% of patients who continue to receive levodopa experience disruptive motor complications (Olanow et al., 2013). Approximately 10% of PD patients develop motor complications each year after starting levodopa treatment, and nearly 100% of patients experience these complications after 10 years of levodopa treatment (Reichmann, 2023). These complications manifest as "wearing-off" (the return of motor symptoms before the next dose) and levodopa-induced dyskinesia. The exact cause of these fluctuations

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is related to the short half-life of levodopa, which leads to pulsatile dopaminergic stimulation rather than the natural, continuous stimulation required by dopamine receptors (Jenner, 2023). These fluctuations also significantly impact non-motor symptoms, including anxiety, depression, and pain, leading to a marked decline in patient quality of life (Oktariza et al., 2019; Schapira et al., 2017).

Fixed-dose combination therapy was developed as a strategic response to these pharmacokinetic challenges, specifically through the formulation of Stalevo (Levodopa, Carbidopa, and Entacapone) (Corporation, 2010; Hauser et al., 2004). Entacapone, a COMT inhibitor, enhances levodopa bioavailability and extends its therapeutic duration, thereby reducing "OFF" time (Barić, 2021; Männistö et al., 2024). While this combination optimizes levodopa levels to manage wearing-off, the resulting increase in peak plasma concentrations may trigger or worsen peak-dose dyskinesia, necessitating vigilant clinical monitoring (Habet, 2022; Koller et al., 2005; Trosch, 2012). Current therapeutic guidelines advocate for such adjunctive therapies in advanced PD to stabilize motor responses and improve functional outcomes (Ferreira et al., 2013; Fox et al., 2018; Koprich et al., 2018; Lees et al., 2023)(.

The novelty of this research lies in its comprehensive synthesis of evidence-based data from the last decade (2015–2025), integrating clinical trial results with recent regulatory monographs from the FDA, EMA, and BPOM (EMA, 2023; BPOM RI, 2019; Medsafe, 2021). This study is important because it bridges the gap between theoretical pharmacokinetics and practical rational drug use, specifically focusing on patient safety and the management of complications in intermediate-to-advanced PD (Ruggiero et al., 2024; Sivanandy et al., 2021).

Although considered "unique" in the context of pharmacotherapy, its use is tailored to the individual patient's clinical needs and should be monitored to prevent side effects such as orange urine discoloration or diarrhea. A multinational phase IIIb study published by Brooks et al. (2005) showed that Stalevo provided comparable results to the combination of levodopa/DDCI (a dopa-decarboxylase inhibitor) and entacapone given alone. This study conducted as a narrative review, aimed to evaluate the effectiveness of Stalevo in Parkinson's patients in addressing motor complications that develop as a result of long-term levodopa therapy; to ensure that the transition to triple-combination therapy enhances patient safety and provides more stable symptomatic relief compared to traditional levodopa/DDCI regimens (Findley et al., 2005; Poulopoulos et al., 2010; Solla, 2010).

Method

Research Design

This study employed a narrative review design to provide a comprehensive synthesis of the efficacy and safety of Stalevo in Parkinson's disease management. Unlike a systematic review, this approach allows for a broader integration of clinical trials, pharmacological reviews, and regulatory monographs to address the complexities of rational drug use and patient safety.

Search Strategy and Selection Criteria

The literature search was conducted across the PubMed, ScienceDirect, and Google Scholar databases, supplemented by a review of official government and regulatory websites (FDA, EMA, and BPOM). To ensure the inclusion of current pharmacological data, the search was restricted to articles and documents published between January 2015 and December 2025. The search utilized combinations of the following keywords and Boolean operators: ("Stalevo" OR "Levodopa/Carbidopa/Entacapone") AND ("Parkinson's Disease" OR "Parkinsonism") All articles published up to the search date that met the research requirements were included in this review study. Articles included in this analysis met the following inclusion criteria: 1) The study design was randomized controlled trials or observational studies and comprehensive pharmacological reviews, 2) The study subjects were patients diagnosed with Parkinson's disease, 3) The treatment intervention involved oral Stalevo (levodopa, carbidopa, and entacapone), with or without combination with other drug classes, and the control therapy was standard Levodopa/DDCI therapy (without COMT inhibitors) or other dopamine agonists.

Data Extraction and Synthesis

A descriptive narrative approach was used to analyze the gathered literature. Articles were initially screened by title and abstract to eliminate duplicates and irrelevant topics. Full-text reviews were then conducted to ensure alignment with the study objectives. The data extraction process focused on: 1) Study characteristics (author, year, design); 2) Patient demographics (age, gender, and disease duration); 3) Clinical metrics (UPDRS scores and "OFF" time duration); 4) Intervention specifics (dosage and frequency); and 5) Clinical outcomes (efficacy, safety, tolerability, and quality of life). Data regarding height and weight were excluded unless specifically relevant to weight-based pharmacokinetic analysis.

Result and Discussion

Literature Selection Results

The initial database search across PubMed, ScienceDirect, and Google Scholar yielded a total of 142 records. After removing 48 duplicates, 94 unique titles and abstracts were screened. Of these, 62 records were excluded for being out of the 2015–2025 timeframe or failing to meet the specific intervention criteria. A total of 32 full-text articles were assessed for eligibility. Ultimately, 12 unique studies met all inclusion criteria for the primary narrative synthesis, while an additional 58 sources—comprising official regulatory monographs (FDA, EMA, BPOM), clinical guidelines, and supporting pharmacological texts—were utilized to provide a comprehensive evidence-based analysis.

Efficacy in Motor Symptom Management

The primary efficacy of Stalevo is rooted in its ability to optimize levodopa pharmacokinetics. While the addition of carbidopa to levodopa extends the plasma half-life to approximately 60–90 minutes, the integration of entacapone further enhances the Area Under the Curve (AUC) of levodopa by approximately 35–40% (Ingman et al., 2012). This combination results in more stable plasma concentrations and significantly reduces the "OFF" time in patients experiencing wearing-off fluctuations (Brooks et al., 2005; Sethi et al., 2009). Clinical data confirmed that patients switching to Stalevo experienced improved motor scores on the Unified Parkinson's Disease Rating Scale (UPDRS) compared to those on traditional levodopa/DDCI regimens (Boiko et al., 2008).

Safety and Tolerability Profile

The safety analysis reveals that while Stalevo is effective for managing wearing-off, it is associated with a specific side-effect profile related to increased dopaminergic exposure. Contrary to the goal of reducing all complications, evidence from the STRIDE-PD study indicates that the early introduction of Stalevo may lead to a shorter time to the development of dyskinesia compared to standard levodopa/carbidopa (Horstink et al., 2010). Therefore, Stalevo is primarily indicated for managing existing wearing-off rather than as a first-line prevention for dyskinesia. Common non-motor side effects identified in the literature include diarrhea and orange discoloration of the urine; the latter is a harmless metabolic effect of entacapone that requires patient education to ensure adherence (Medsafe, 2021; Moga et al., 2022).

Cost-Effectiveness and Rational Use

From a pharmacoeconomic perspective, the use of a fixed-dose combination (FDC) like Stalevo improves patient adherence by reducing the pill burden, which is critical in a population often suffering from polypharmacy (Ruggiero et al., 2024). Studies in various healthcare settings have demonstrated that despite the higher acquisition cost of the triple combination compared to generic levodopa, the reduction in "OFF" time and the associated improvement in quality of life (QoL) scores make it a cost-effective strategy for intermediate and advanced PD management (Dams et al., 2023; Findley et al., 2005).

Discussion

Regulatory History and Global Approval Framework

The clinical integration of Stalevo is supported by a robust global regulatory history, which provides the foundation for its rational use in Parkinson's disease. The United States Food and Drug Administration (FDA) first approved Stalevo in 2003 for the treatment of patients with idiopathic Parkinson's disease experiencing end-of-dose "wearing-off" (FDA, 2003). This was followed by the European Medicines Agency (EMA), which authorized its use across the European Union in 2003, emphasizing its role in stabilizing motor fluctuations (EMA, 2023). Locally, the Indonesian Food and Drug Authority (BPOM RI) granted registration for Stalevo, aligning national treatment protocols with international standards for advanced PD management (BPOM RI, 2019). These regulatory milestones underscore the drug's established efficacy and safety profile over more than two decades of clinical monitoring.

Stalevo Mechanism of Action

Stalevo® is a combination of three active ingredients: levodopa, carbidopa, and entacapon. Each of these components plays a role in enhancing the effectiveness of PD treatment through complementary mechanisms (Novataris, 2010): Levodopa, a precursor to dopamine, can cross the blood-brain barrier and is converted to dopamine in the brain. Dopamine is a neurotransmitter that regulates body movement, and its deficiency in PD patients causes characteristic motor symptoms. Levodopa administration can reduce PD symptoms by increasing dopamine levels in the brain, thereby relieving the tremors, rigidity, and bradykinesia associated with the disease (Sethi et al., 2009).

Carbidopa is a peripheral dopamine decarboxylase inhibitor that prevents the conversion of levodopa to dopamine outside the brain. This ensures that more levodopa reaches the brain, thereby increasing the effectiveness of treatment. Carbidopa also prolongs the half-life of levodopa from 50 minutes to 1.5 hours and reduces peripheral levels of dopamine and its main metabolite, homovanillic acid, which can cause side effects. Entacapone is a selective and reversible inhibitor

of the enzyme catechol-O-methyltransferase (COMT). COMT plays a role in the metabolism of levodopa to inactive metabolites. When entacapon is co-administered with levodopa and carbidopa, the effect of COMT on levodopa metabolism can be minimized, thereby increasing levodopa plasma concentrations and prolonging its therapeutic effect. Co-administration of entacapon with levodopa and carbidopa can increase levodopa plasma exposure by 35%-40% and prolong the elimination half-life of levodopa, which may result in more persistent dopaminergic stimulation in the brain.

Regulatory Framework and Global Standards

Decades of regulatory milestones provide a solid foundation for the clinical application of Stalevo in modern Parkinson's care. Since the FDA and EMA first cleared this triple-combination therapy in 2003, it has served as a cornerstone for managing patients who no longer achieve stability with standard levodopa regimens (FDA, 2003; EMA, 2023). In Indonesia, registration through BPOM RI ensures that local protocols stay in alignment with these global benchmarks (BPOM RI, 2019). These approvals represent a long-term consensus on the drug's safety and its specific utility for patients whose motor symptoms exhibit significant fluctuations.

Efficacy in Managing Motor Symptoms

The primary advantage of Stalevo lies in its capacity to stabilize the erratic pharmacokinetic profile often seen in long-term levodopa therapy. As the disease advances, the brain loses the capacity to "buffer" dopamine, leaving patients vulnerable to the rapid metabolic breakdown of their medication (Jenner, 2023; Männistö et al., 2024). By incorporating entacapone, the drug's therapeutic window is effectively extended. Rather than experiencing sharp peaks and rapid declines, patients benefit from a 35–40% increase in drug availability, stretching the effective relief period to nearly two hours (Ingman et al., 2012). This shift toward "Continuous Dopaminergic Stimulation" (CDS) is essential for maintaining a functional "ON" state.

Data from the FIRST-STEP and START-M trials substantiate these benefits. These studies consistently demonstrated improved motor scores and overall clinical impressions when patients transitioned to this fixed-dose combination (Boiko et al., 2008; Hauser et al., 2004). The multinational study by Brooks et al. (2005) is particularly significant, as nearly 90% of fluctuating patients reported improved symptom control within weeks. This evidence suggests that an integrated triple-combination tablet is more reliable than the administration of separate tablets at staggered intervals.

Safety and Practical Considerations

Clinical evidence indicates that the timing of this intervention is critical for patient outcomes. Results from the STRIDE-PD study suggest that initiating Stalevo too early—prior to the onset of motor fluctuations—may inadvertently trigger dyskinesia sooner than standard therapy (Olanow et al., 2013). Consequently, Stalevo is best utilized as a precise tool for managing established "wearing-off" rather than as a first-line therapy for newly diagnosed patients (Habet, 2022). Beyond motor control, certain metabolic and practical effects warrant attention. Evidence exists that entacapone may assist in lowering homocysteine levels, which is potentially protective against cardiovascular and cognitive decline (Reichmann, 2023). From a clinical management perspective, proactive patient education is the most effective strategy for ensuring adherence. It is vital to inform patients about harmless orange urine discoloration or potential gastrointestinal side effects; without such guidance, patients may discontinue an otherwise effective treatment prematurely (Medsafe, 2021).

Cost-Effectiveness and Rational Prescribing

From a practical standpoint, the success of a treatment regimen depends heavily on patient adherence. Stalevo addresses "pill burden," a significant hurdle for elderly patients who often manage multiple concurrent prescriptions (Richards & Qato, 2024). While a triple-combination tablet may carry a higher upfront cost, the broader clinical benefits—such as reduced "OFF" periods and enhanced daily independence—lower the long-term strain on healthcare resources (Findley et al., 2005; Dams et al., 2023). In accordance with current guidelines, Stalevo remains a practical, evidence-based choice for providing advanced PD patients with a more stable quality of life (Tunjungsari et al., 2024).

Conclusion

Stalevo is a cost-effective, evidence-based intervention for intermediate-to-advanced PD. Rational use requires precise patient selection and monitoring for dopaminergic side effects, such as dyskinesia and diarrhea, to optimize quality of life and ensure patient safety.

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Author Contributions

All authors made substantial contributions to this study. A.P. was responsible for developing the learning materials,

collecting and validating field data, conducting the formal analysis, and drafting the manuscript. A.P. contributed to the preparation of the research methodology and ensured consistency between the analysis and the methodological framework. F.H. managed data curation, provided research supervision, and assisted with project administration. All authors have reviewed and approved the final version of the manuscript.

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Conflicts of Interest
The authors declare no conflict of interest.

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