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Pathogenesis and Intervention Strategies for Motor Complications in Parkinson's Disease

Yaocheng Liu

Lanzhou No.1 Senior High School, Lanzhou, China
l13919293647@outlook.com

Abstract. Parkinson's disease (PD) and its motor complications, including levodopa-induced dyskinesia and end-of-dose "off" periods, profoundly diminish patient quality of life. Despite extensive research, the underlying biological mechanisms of these fluctuations remain only partially understood. In this Review, we integrate clinical and experimental evidence demonstrating that intermittent dopaminergic therapy drives remodeling of basal ganglia circuits, induces maladaptive alterations in corticostriatal synaptic plasticity, and sustains chronic neuroinflammation through microglial activation. We examine the prevalence and clinical manifestations of dyskinesia and "off" phenomena, then critically compare three principal intervention domains: optimized pharmacotherapy with continuous-release formulations and adjunctive agents, deep brain stimulation targeting the subthalamic nucleus or globus pallidus interna, and structured rehabilitation programs encompassing balance, gait training, strength exercises and neurofeedback. Across diverse studies, continuous drug delivery yields more stable motor control, deep brain stimulation reduces fluctuations and dyskinesia, and early, personalized rehabilitation enhances gait and posture. We further show that combining these approaches produces synergistic improvements that exceed those achieved by any single strategy. Finally, we propose a precision medicine framework that stratifies patients by demographic and molecular biomarkers to guide the timing and sequence of multimodal treatments, charting a path toward truly personalized management of PD motor complications.

Keywords: Parkinson's disease, motor complications, neuroinflammation, basal ganglia

1. Introduction

Parkinson's Disease is the second most common neurodegenerative disease globally, following Alzheimer's disease. With the aging population, its prevalence is rising. Epidemiological data show that the global prevalence of PD among individuals aged 65 and older is about 1%-2%, and the total number of patients is increasing year by year. It is expected to exceed 12 million by 2040. This condition predominantly affects individuals over 60 years old, and its pathological basis is the progressive loss of dopaminergic neurons in the substantia nigra of the midbrain, leading to a decline in dopamine levels in the striatum, thereby affecting the functional balance of the basal ganglia's internal striato-pallidal circuit. In the early stages of the disease, the "motor triad" appears,

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which includes resting tremor, bradykinesia, and rigidity. PD not only significantly restricts patients' gait and fine motor abilities but also often leads to postural instability, increasing the risk of falls.

Currently, PD diagnosis mainly follows the clinical standards set by the International Parkinson and Movement Disorder Society (MDS). The core elements of this standard include bradykinesia, along with at least one other motor symptom, such as resting tremor or rigidity, while excluding secondary parkinsonism caused by medications or other neurological diseases. The severity of motor impairments is often quantified using the Unified Parkinson's Disease Rating Scale (UPDRS-III), with scores showing a significant negative correlation with the patient's ability to perform activities of daily living. Non-motor symptoms are also very common in PD and often appear before motor symptoms. Approximately 40% of patients experience depression and anxiety, and 30% to 80% of patients have sleep disorders, such as REM behavior disorder. More than 80% of cases show cognitive decline in the later stages of the disease, and autonomic dysfunction (such as constipation and orthostatic hypotension) persists throughout the disease course. These non-motor symptoms not only increase the psychological burden on patients but are also closely related to survival and complication risks, though they are often overlooked clinically due to a lack of specificity.

In treatment, levodopa and its derivatives are the cornerstone of dopamine replacement therapy, effectively alleviating early motor symptoms and improving patients' quality of life. However, after long-term use, nearly 90% of patients develop treatment-related complications, including shortening of dosing intervals and exacerbation of symptoms during the "off" period, as well as dyskinesias due to pulsatile dopamine receptor stimulation, significantly narrowing the therapeutic window for effective treatment. The current clinical strategy generally involves multimodal approaches. Medications are optimized to prolong the effects of levodopa, and for patients with advanced, refractory motor fluctuations, deep brain stimulation (DBS) can reduce motor fluctuations by 60%-80% by modulating the thalamic-hypothalamic neural circuit. Additionally, evidence-based rehabilitation interventions can improve motor coordination. However, the best combination, optimal timing, and molecular mechanisms of these three interventions have not been systematically elucidated.

This study aims to explore the neurobiological mechanisms of Parkinson's disease motor complications (including basal ganglia circuit remodeling, synaptic plasticity, and neuroinflammation), systematically assess the synergistic effects of multimodal intervention strategies (sustained dopaminergic stimulation, DBS, and rehabilitation training) in improving clinical symptoms, and identify key bottlenecks in the process from basic research to clinical translation, to provide theoretical and practical guidance for individualized and precision-based interventions for PD motor complications.

2. Pathogenesis of Parkinson's disease motor complications

2.1. Dopaminergic drug pulsatile stimulation and basal ganglia circuit remodeling

Dopaminergic drugs, particularly levodopa, have long been the cornerstone of Parkinson's disease treatment. Under pulsatile administration (e.g., oral or injectable forms), dopamine release is fluctuating, which causes imbalance in the brain's dopamine system as the drug concentration increases and decreases. During the "peak" phase of medication, patients' motor symptoms may improve, but as the drug effect wanes, symptoms may recur, making it difficult to sustain symptom control. The basal ganglia, a key brain region for regulating motor function, rely on a stable supply of dopamine for proper functioning of the striato-pallidal circuit. Pulsatile dopamine fluctuations disrupt this balance, particularly in the parts of the circuit related to motor control. During the peak

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of medication effects, symptoms may improve, but subsequent declines in efficacy exacerbate bradykinesia and rigidity, creating the classic "off" phenomenon. Furthermore, long-term medication fluctuations worsen neurodegenerative changes, further affecting circuit stability and motor abilities. With the continuation of medication, structural and functional remodeling of the basal ganglia circuits occurs, impairing the quality of motor output. About 40%-60% of Parkinson's patients develop dyskinesias after long-term medication treatment [1], and these involuntary movements are closely related to circuit remodeling. Functional remodeling of these circuits exacerbates motor fluctuations and is positively correlated with the occurrence of motor complications [2]. These changes not only worsen patients' motor impairments but also increase neurodegenerative changes during the disease course.

2.2. Synaptic plasticity changes in motor control

Synaptic plasticity is the basis for the adaptive changes of the nervous system and refers to changes in synaptic strength. Abnormal regulation of long-term potentiation (LTP) and long-term depression (LTD) in the basal ganglia is a hallmark of synaptic plasticity changes in Parkinson's disease. Studies have shown significant abnormalities in LTP and LTD regulation in Parkinson's patients, leading to motor control imbalance. Specifically, increased LTP and reduced LTD in the basal ganglia are key factors in motor control disorders [3]. In Parkinson's patients, there are significant changes in the expression of synaptic proteins, particularly in the regulation of dopamine receptors. Studies indicate that treatment often downregulates dopamine receptors while upregulating NMDA and other neurotransmitter receptors. Changes in synaptic proteins and receptor regulation directly affect synaptic conduction efficiency, further exacerbating motor complications. These changes are the fundamental cause of synaptic dysfunction, which worsens motor symptom fluctuations and dyskinesias [4]. Changes in synaptic plasticity are considered the core mechanism leading to Parkinson's dyskinesia. Abnormal regulation of LTP and LTD disrupts neural circuits, leading to involuntary movements, such as chorea or muscle spasms. Clinical studies have shown that dyskinesias in Parkinson's patients during long-term medication treatment are closely related to changes in synaptic plasticity [5]. These involuntary movements typically occur during the peak of medication effects and are accompanied by worsening symptoms like bradykinesia and rigidity.

2.3. Neuroinflammation and abnormal intracellular signaling pathways

Neuroinflammation plays a significant role in the progression of Parkinson's disease. Microglia, as the immune cells of the central nervous system, exhibit persistent activation in the disease. Parkinson's patients show microglial activation during the disease course, releasing inflammatory cytokines such as TNF-α, IL-1β, and IL-6, triggering local immune responses and directly damaging neurons. These inflammatory cytokines not only promote neurodegeneration but also lead to further neuronal dysfunction [6]. The continued release of inflammatory cytokines accelerates the neurodegenerative process. Neuroinflammation plays a role not only in the early stages but also worsens as the disease progresses, eventually leading to neuronal death. Studies indicate that neuroinflammation is closely related to the occurrence of motor complications. Inflammatory cytokines activate signaling pathways such as NF-κB, altering neuronal function, promoting synaptic damage, and neurodegeneration. Neuroinflammation-induced neurodegeneration exacerbates the primary disease and leads to more severe motor complications, such as tremors or initiation difficulties [7]. The continued release of inflammatory cytokines is closely related to synaptic dysfunction. Inflammation activates intracellular signaling pathways, altering synaptic

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structure and function, which in turn reduces synaptic transmission efficiency. Inflammatory cytokines not only affect synaptic function but also further exacerbate the loss of motor control.

3. Multimodal intervention strategies

Due to recent advances in Parkinson's disease treatments, relying solely on medications can no longer meet the complex needs of patients. Multimodal integrated treatment methods such as medication, DBS, and rehabilitation training, when combined, show a 1+1>2 effect. They not only alleviate the primary symptoms of Parkinson's disease but also reduce the occurrence of motor fluctuations and improve patients' quality of life.

3.1. Medication adjustment and continuous dopaminergic stimulation

Continuous dopaminergic stimulation is currently the primary treatment for Parkinson's disease. With continuous improvements in PD drugs, controlled-release formulations and patches have become the core of the new generation of drug treatments. Controlled-release formulations allow for a smooth, continuous release of the medication, effectively reducing the fluctuations of motor symptoms, improving the patient's quality of life, and, in conjunction with adjunctive medications such as anticholinergic drugs and NMDA receptor antagonists, also providing certain benefits [8]. Optimizing drug dosing regimens is key to reducing motor fluctuations. Adjusting the frequency and dose of medications, research shows that sustained dopaminergic stimulation can effectively extend the "on" period and reduce "off" period symptoms. In addition, the use of adjunctive medications makes treatment more stable, reducing drug resistance and side effects . In recent years, significant progress has been made in the development of new dopamine receptor agonists, particularly in terms of selectivity and personalized treatment. These new drugs can target different dopamine receptor subtypes, providing more precise treatment plans. The application of these new agonists can significantly reduce medication side effects, optimize the treatment of Parkinson's disease, and offer patients longer-lasting, low-side-effect treatment options.

3.2. Deep Brain Stimulation (DBS)

DBS has become an important surgical technique for treating Parkinson's disease. By selecting appropriate target areas, DBS can precisely modulate the basal ganglia circuit, thereby improving motor symptoms. The most common stimulation targets include the subthalamic nucleus (STN) and the internal part of the globus pallidus (GPi). Research shows that STN stimulation is more effective in improving motor symptoms, while GPi stimulation is more effective in reducing symptom fluctuations and improving medication response. DBS efficacy is closely related to stimulation parameters; adjusting stimulation frequency, voltage, and pulse width can optimize treatment effects. Studies have found that appropriate stimulation parameters can significantly improve motor symptoms, reduce motor fluctuations, and improve long-term treatment outcomes in clinical settings [9]. DBS not only improves motor symptoms but also affects synaptic plasticity by modulating the function of the basal ganglia circuit. Studies show that DBS can restore normal neural circuit function, reduce neurodegeneration, and thereby reduce motor fluctuations. By modulating synaptic plasticity, DBS provides Parkinson's patients with long-lasting and stable treatment effects.

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3.3. Rehabilitation training and neurofeedback

In addition to medication and DBS, rehabilitation training can also improve Parkinson's disease patients' functional status. Exercise therapies, including balance, gait, and strength training, can significantly improve patients' motor function, reduce the risk of falls, and enhance overall physical health. Research shows that regular balance and gait training can help patients regain the ability to walk independently and reduce fall events caused by bradykinesia and rigidity. Strength training helps improve muscle strength and endurance, thereby improving the ability to perform daily activities [10]. Occupational therapy can help patients return to their daily lives and regain independence, such as dressing, eating, and personal care. Through targeted training, occupational therapy helps patients readjust to life and improve their self-care abilities, thereby improving quality of life. Neurofeedback and virtual reality (VR)-assisted training are innovative therapies that have been developed recently, using the brain's plasticity to improve patients' motor and cognitive functions. Neurofeedback monitors the patient's brain activity in real-time and provides feedback to help patients control brain activity. Studies show that neurofeedback training significantly improves Parkinson's patients' motor control and cognitive abilities [11]. VR-assisted training simulates real-world movement environments, allowing patients to train in a safe and controlled virtual space, thus enhancing their motor performance. VR training not only improves patients' gait, balance, and coordination but also enhances their spatial awareness and reaction speed.

3.4. Combined application and synergistic effects

No single therapy can fully manage Parkinson's disease treatment. Monotherapy, whether medication, DBS, or rehabilitation, is often insufficient to adequately control symptoms. A combination of therapies (including medication, DBS, and rehabilitation) plays a substantial synergistic role. The combination of medication and DBS has become one of the most effective treatment methods for Parkinson's disease. While medication may work initially, as the disease progresses, the effect of the medication often fluctuates, and adverse reactions, such as dyskinesia or the "off" phenomenon, may occur. DBS provides additional therapeutic benefits by directly regulating the basal ganglia circuits, complementing medication. Studies show that the combination of medication and DBS reduces the occurrence of motor fluctuations and increases the "on" period [12]. This combined treatment can effectively extend the duration of medication effectiveness and reduce the need for high medication doses.

Combining medication and rehabilitation training offers a new approach to the comprehensive treatment of Parkinson's disease. While medication relieves motor symptoms, rehabilitation training can improve motor coordination and enhance quality of life by promoting neural plasticity. Research shows that the synergistic effect of medication and rehabilitation training can more effectively improve motor control in patients. For example, combining medication with balance and strength training significantly improves patients' gait stability and muscle strength while reducing the occurrence of falls. Additionally, combining medication with occupational therapy helps patients regain independence in daily life, improving their quality of life. Clinical studies indicate that combined treatment with medication and rehabilitation is more effective in reducing symptom fluctuations and improving function than monotherapy, leading to a significant improvement in patients' independence and daily activities.

The rehabilitation integration plan combines medication, DBS, and rehabilitation training, aiming to provide personalized, comprehensive treatment for Parkinson's disease patients. This integrated treatment method not only effectively reduces motor fluctuations but also improves patients'

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functional status and quality of life. Research shows that rehabilitation integration plans exhibit significant synergistic effects in reducing motor symptoms and improving quality of life, especially in gait, balance, and daily living abilities. Furthermore, this integrated plan provides personalized treatment plans that can be adjusted according to the needs of different patients, making treatment more precise and efficient. With the development of personalized medicine and precision healthcare, rehabilitation integration plans are expected to become the mainstream strategy in Parkinson's disease treatment, offering better treatment outcomes for patients.

4. Conclusion

The pathogenesis of Parkinson's disease motor complications is complex and multifactorial. Dopaminergic pulsatile stimulation leads to basal ganglia circuit remodeling and synaptic plasticity changes, which are important mechanisms for the development of dyskinesia and the "off" phenomenon. The instability of dopamine release and its impact on neural circuits causes frequent fluctuations in motor symptoms, and prolonged fluctuations result in neuronal dysfunction, further exacerbating disease progression. In addition, neuroinflammation promotes the development of Parkinson's disease motor complications, particularly the D-1 cell toxicity response induced by inflammation, which is considered one of the main mechanisms of neurodegenerative changes.

Multimodal intervention strategies demonstrate robust therapeutic effects. Continuous dopaminergic delivery via controlled-release formulations, transdermal patches, and adjunctive agents smooths dopamine availability, prolongs "on" periods, and curbs motor fluctuations. DBS, by optimizing stimulation parameters and modulating the basal ganglia circuit, reduces motor fluctuations. Personalized rehabilitation training, such as balance, gait, and strength training, also improves motor coordination and quality of life, with more significant effects when applied early in the disease. The combined use of multiple interventions can provide a synergistic effect that is superior to single therapy and can offer patients more stable and lasting treatment outcomes.

In clinical translation, the age, disease course, and biomarkers of Parkinson's disease patients differ, and the intervention effects also vary. Therefore, individualized and stratified treatment based on these factors should be adopted. Additionally, the timing and sequence of interventions can also influence the treatment effects. The earlier the comprehensive intervention, the better the results are generally. Although the current treatment strategies have shown some effectiveness, further research and validation are needed in terms of safety, tolerance, and long-term efficacy. Most of the current studies are based on existing clinical and animal models, and large-scale, multi-center clinical trials are needed to support the clinical feasibility of these hypotheses. New developments in gene therapy, cell therapy, and precision stimulation techniques will break through current treatment models, opening up new paths for personalized treatment. Additionally, further research is needed to explore molecular biomarkers of intervention effects and improve multimodal intervention methods to achieve better therapeutic outcomes, promoting the implementation of personalized treatment plans.

References

[1] Bloem, B. R., Okun, M. S., & Klein, C. (2021). Parkinson's disease. Lancet (London, England), 397(10291), 2284–2303.

[2] Mei, Y. D., Gao, H., Chen, W. F., Zhu, W., Gu, C., Zhang, J. P., Tao, J. M., & Hua, X. Y. (2024). Research on the multidimensional brain remodeling mechanisms at the level of brain regions, circuits, and networks in patients with chronic lower back pain caused by lumbar disk herniation. Frontiers in neuroscience, 18, 1357269.

[3] Li, Y., Rong, J., Zhong, H., Liang, M., Zhu, C., Chang, F., & Zhou, R. (2021). Prenatal Stress Leads to the Altered Maturation of Corticostriatal Synaptic Plasticity and Related Behavioral Impairments Through Epigenetic

DOI: 10.54254/2753-8818/2025.LD25943

Modifications of Dopamine D2 Receptor in Mice. Molecular neurobiology, 58(1), 317–328.
[4] Pagano, G., Yousaf, T., & Politis, M. (2017). PET Molecular Imaging Research of Levodopa-Induced Dyskinesias in Parkinson's Disease. Current neurology and neuroscience reports, 17(11), 90.
[5] Rajan, R., Popa, T., Quartarone, A., Ghilardi, M. F., & Kishore, A. (2017). Cortical plasticity and levodopa-induced dyskinesias in Parkinson's disease: Connecting the dots in a multicomponent network. Clinical neurophysiology : official journal of the International Federation of Clinical Neurophysiology, 128(6), 992–999.
[6] Liu, C., Chu, D., Kalantar-Zadeh, K., George, J., Young, H. A., & Liu, G. (2021). Cytokines: From Clinical Significance to Quantification. Advanced science (Weinheim, Baden-Wurttemberg, Germany), 8(15), e2004433.
[7] Ylikoski, A., Martikainen, K., Sieminski, M., & Partinen, M. (2015). Parkinson's disease and insomnia. Neurological sciences : official journal of the Italian Neurological Society and of the Italian Society of Clinical Neurophysiology, 36(11), 2003–2010.
[8] Devos, D., Moreau, C., Dujardin, K., Cabantchik, I., Defebvre, L., & Bordet, R. (2013). New pharmacological options for treating advanced Parkinson's disease. Clinical therapeutics, 35(10), 1640–1652.
[9] Yin, Z., Zhu, G., Zhao, B., Bai, Y., Jiang, Y., Neumann, W. J., Kühn, A. A., & Zhang, J. (2021). Local field potentials in Parkinson's disease: A frequency-based review. Neurobiology of disease, 155, 105372.
[10] Paolucci, T., Sbardella, S., La Russa, C., Agostini, F., Mangone, M., Tramontana, L., Bernetti, A., Paoloni, M., Pezzi, L., Bellomo, R. G., Santilli, V., & Saggini, R. (2020). Evidence of Rehabilitative Impact of Progressive Resistance Training (PRT) Programs in Parkinson Disease: An Umbrella Review. Parkinson's disease, 2020, 9748091.
[11] Baram, Y., Aharon-Peretz, J., Badarny, S., Susel, Z., & Schlesinger, I. (2016). Closed-loop auditory feedback for the improvement of gait in patients with Parkinson's disease. Journal of the neurological sciences, 363, 104–106.
[12] Pirker, W., Katzenschlager, R., Hallett, M., & Poewe, W. (2023). Pharmacological Treatment of Tremor in Parkinson's Disease Revisited. Journal of Parkinson's disease, 13(2), 127–144.