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Conventional vs. Emerging Therapeutic Approaches in Parkinson's Disease: Challenges and Prospects

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Abstract

Parkinson's disease is a progressive neurodegenerative disorder that causes motor symptoms such as tremor, stiffness, bradykinesia, and postural instability, as well as a variety of non-motor consequences. Despite being the second most common neurodegenerative illness worldwide, effective disease-modifying medicines are still elusive. For decades, conventional therapy techniques such as levodopa, dopamine agonists, monoamine oxidase-B inhibitors, and deep brain stimulation (DBS) have served as the cornerstone of Parkinson's disease management. While these treatments relieve symptoms and enhance quality of life, their long-term efficacy is restricted by consequences like motor fluctuations, dyskinesias, and decreased responsiveness.

Recent advances in neuroscience have fueled the development of emerging therapies that aim to go beyond symptomatic relief. These include gene therapies targeting dopamine synthesis and α-synuclein aggregation, stem cell–based neuronal replacement strategies, novel neuroprotective agents, and precision medicine approaches. In addition, innovative drug delivery systems and non-invasive neuromodulation techniques are being explored to enhance treatment outcomes.

This review highlights the strengths and limitations of conventional therapies while critically evaluating the promise of emerging approaches. By comparing established practices with novel strategies, the paper underscores the evolving landscape of Parkinson's disease management and the potential for future interventions to achieve true disease modification.

Keywords: Parkinson's Disease, dyskinesia, Levodopa, Deep Brain Stimulation, Neurodegenerative

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1.0 Introduction

Parkinson's disease (PD), previously conceptualized primarily as a localized deficiency of striatal dopamine, is now acknowledged as a multifaceted, multisystem neurodegenerative disorder characterized by extensive cellular dysfunction, neuroinflammation, and failures in non-motor networks. Even after more than two centuries since its initial clinical description, PD continues to be incurable, with standard treatments providing only limited symptomatic relief (Muleiro Alvarez et al., 2024). It ranks as the second most prevalent neurodegenerative condition, impacting about 2–3% of those aged 65 and older (Blauwendraat et al., 2020). The condition occurs more often in men (52.5%) than in women (47.5%), and its frequency is greater in countries with a medium-to-high socio-demographic index (85.2%) compared to those with a low socio-demographic index (14.8%) (Poewe et al., 2017).

Introduced in the late 1960s, levodopa continues to be the gold standard. However, its prolonged use highlights the paradox of Parkinson's disease treatment. Initial advantages are ultimately compromised by motor complications and decreased responsiveness, exposing the fundamental shortcomings of symptomatic approaches. This therapeutic plateau has spurred initiatives to advance beyond dopamine-focused models and investigate treatments that address the disease at molecular, cellular, and circuit levels.

The evolving landscape is characterized by innovations such as CRISPR gene editing, α-synuclein immunotherapy, stem cell-derived dopaminergic neuron transplants, and adaptive closed-loop deep brain stimulation, all of which push the limits of traditional pharmacological approaches. These next-generation methods seek not just to control symptoms but to alter disease course, stop progression, or even reverse neurodegeneration goals that were once seen as speculative but are now more firmly based on translational research.

Nonetheless, the transition from traditional to next-generation treatments is laden with scientific, clinical, and ethical obstacles. Issues regarding delivery, safety, scalability, patient selection, and long-term effectiveness are still unanswered. Additionally, inequalities in access to innovative treatments risk expanding the worldwide treatment divide (Muleiro Alvarez et al., 2024).

This evaluation examines the changing treatment landscape in Parkinson's disease, comparing established pharmacological and surgical approaches with novel and experimental methods (figure 1). By analysing existing constraints, transitional challenges, and the potential of personalized, mechanism-based therapies, we seek to clarify the way ahead in transforming Parkinson's disease treatment in the 21st century.

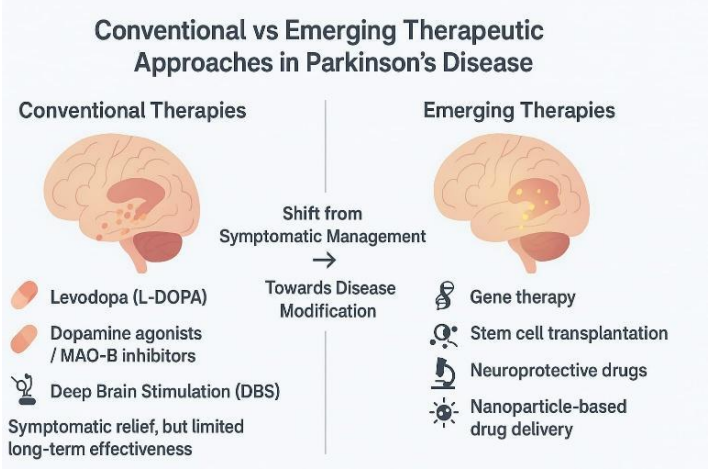

Figure 1: Paradigm Shift in Parkinson's Disease Therapeutics: From Symptomatic Management to Molecular Disease Modification.

2.0 Conventional Therapeutic Approaches

2.1 Pharmacological Therapy

2.1.1 Levodopa and Carbidopa

Levodopa remains the primary treatment for symptomatic management of PD because it can restore the striatal dopamine levels and reactivate basal ganglia function. As dopamine itself cannot cross the blood-brain barrier (BBB), oral levodopa is administered as a metabolic precursor which is transported through the large amino acid transporter and then broken down by aromatic L-amino acid decarboxylase (AADC) enzyme within dopaminergic neurons to form dopamine. This newly synthesized dopamine activates postsynaptic D1 and D2 receptors, restoring the physiological balance between dopaminergic and cholinergic signaling , thereby alleviating bradykinesia, stiffness, and other motor impairments. Due to a significant amount of levodopa being metabolized before it accesses the brain, it is co-administered with carbidopa. Carbidopa is a peripheral decarboxylase inhibitor that cannot penetrate the BBB; it effectively blocks the peripheral conversion of levodopa, maximizing its bioavailability and uptake into the brain. This combination allows for the use of lower doses and improves adverse effects like nausea, vomiting, orthostatic hypotension, and cardiac arrhythmias. It is generally well tolerated and has proven to be particularly well accepted in the initial phases of the disease.

However, in the long run, this therapy causes complications such as motor fluctuations, dyskinesias from levodopa and neuropsychiatric symptoms such as hallucinations, disorientation and vivid dreams. Despite these restrictions, this combination of treatment continues to be the foundation of modern clinical care because of its effectiveness in controlling motor symptoms and improving patients' quality of life (Dhall et al., 2016).

To bridge the gap between traditional oral therapies and invasive, device-aided systems, recent clinical literature has highlighted the therapeutic role of next-generation oral formulations. Stocchi et al. (2026) evaluated the clinical utility of IPX203, a novel oral modified-release capsule that combines immediate-release granules with targeted, extended-release pellets. By utilizing a specialized formulation that includes enteric and mucoadhesive coatings, this system optimizes absorption within the proximal small intestine to deliver both a rapid onset of action and highly sustained plasma levels. Clinical evidence indicates that this design significantly reduces daily 'OFF' time, maximizes 'Good ON' periods, and extends symptom relief well into the following morning without requiring the invasive surgical procedures typical of advanced infusion pumps or deep brain stimulation.

2.1.2 Dopamine agonists

Dopamine agonists represent a class of synthetic compounds that directly stimulate postsynaptic dopamine receptors, bypassing the requirement for presynaptic enzymatic conversion. When utilized as an initial monotherapy, they delay the necessity of introducing levodopa, thereby minimizing the long-term risk of levodopa-induced dyskinesias and motor fluctuations—a strategy particularly vital for younger patients. Dopamine agonists are chemically categorized into ergoline (ergot-derived) and non-ergoline derivatives. When a person takes a dopamine agonist in a form of a tablet, patch or injection, the drug is absorbed into the blood and travels through the circulation. Because these drugs are designed to cross the blood–brain barrier, they move from the blood into the brain. Once inside the brain, they spread to areas involved in movement control, mainly the striatum. There, the drug molecules bind to dopamine receptors (mainly D2 and D3 receptors) on nerve cells and activate them, just like natural dopamine would. This activation sends signals to restore the balance between the direct and indirect movement pathways, which improves symptoms such as slowness, stiffness, and tremor (Borovac, 2016). The commonly used drugs are Pramipexole and Ropinirole (Isaacson et al., 2023).

Pramipexole is classified as a non-ergoline aminobenzothiazole compound that selectively agonizes the dopamine D2-like receptor subfamily, which includes the D2, D3, and D4 receptor subtypes. Pramipexole is a unique compound in its therapeutic potential because it has D3-preferring properties. The D3 receptor target has implications in both motor and psychiatric symptoms of Parkinson's disease, restless leg syndrome, and bipolar and unipolar depression. It

compensates for dopamine deficiency in the nigrostriatal pathway (motor control) and mesolimbic system (motivation, reward) (Wilson et al., 2020). Approved by the FDA in 1997, it can be used alone or with other drugs for PD. For younger patients, pramipexole is often recommended as first-line monotherapy to delay motor complications caused by long-term levodopa use. In older patients, however, it is used cautiously because of stronger side effects. In advanced PD, it is often combined with levodopa to reduce “off” periods (Singh et al., 2023). Reported side effects include nausea, dizziness, sleep disturbances, constipation, fatigue, and hallucinations. In advanced disease, additional issues like orthostatic hypotension, worsening dyskinesia, confusion, memory problems, gait changes, and urinary frequency may occur (Mu et al., 2025).

Ropinirole also acts on D2-like receptors (D2, D3, D4). It works through G-protein-coupled receptors, inhibiting adenylyl cyclase and calcium channels while activating potassium channels. This action increases “on” time and reduces “off” time in PD, making it useful both early and late in the disease. It is also effective for restless leg syndrome and can improve sleep disturbances and nighttime symptoms in PD. Common side effects include nausea, headache, daytime drowsiness, and swelling in the legs and Neuropsychiatric side effects may include hallucinations, confusion, and impulse-control disorders (Rewane et al., 2024).

A major breakthrough in selective receptor targeting came to light in early 2026 with the long-term clinical data for Tavapadon. Unlike traditional dopamine agonists that stimulate receptors broadly and cause widespread side effects, Tavapadon is highly selective, focusing almost exclusively on the D1 and D5 receptor subtypes. Data from the TEMPO-4 phase III trials highlighted a remarkable 'levodopa-sparing' quality: over 90% of patients with early-stage disease were able to manage their symptoms successfully for a full year without needing to start or ramp up traditional levodopa therapy. This offers a highly practical strategy for postponing the onset of motor fluctuations and dyskinesias that inevitably complicate standard, long-term care. (Fernandez et al., 2026)

2.1.3 MAO-B inhibitors

Monoamine oxidase-B (MAO-B) inhibitors, including selegiline, rasagiline, and safinamide, are essential treatments for Parkinson’s disease (PD) that function by blocking the MAO-B enzyme that degrades dopamine, thus boosting dopaminergic function and enhancing motor control. There are two MAO isoenzymes: MAO-A and MAO-B. Historically, they have been utilized as standalone treatment in early PD or as supplementary options to levodopa in later stages to extend its effects and minimize “off” intervals. Recent developments, however, have emphasized their potential surpassing symptom management, indicating possible neuroprotective effects via antioxidant, anti-apoptotic, and anti-inflammatory pathways. Safinamide specifically exhibits a dual mechanism by influencing both dopamine and glutamate function, providing a wider therapeutic range. Even with these improvements, issues like inconsistent long-term neuroprotective results and differing patient reactions restrict their widespread use. Recent studies are concentrating on combining MAO-B inhibitors with gene therapy, nanocarrier drug delivery methods, and tailored treatment approaches to improve brain bioavailability and possibly reduce the pace of disease advancement. Consequently, MAO-B inhibitors continue to serve as a crucial bridge between traditional symptomatic treatment and advancing neuroprotective strategies in Parkinson's disease (Tan et al., 2022).

2.1.4 COMT inhibitors

COMT inhibitors are medications used in Parkinson's disease to prolong the therapeutic effects of levodopa and reduce "end-of-dose wearing-off" symptoms (Muranova et al., 2023). Catechol-O-Methyltransferase (COMT) is an enzyme that is found in the liver, intestines, and brain. It breaks catecholamines (dopamine, epinephrine, norepinephrine) and levodopa by adding a methyl group to them. When levodopa is taken orally, a significant fraction undergoes peripheral metabolism into the inactive metabolite 3-O-methyldopa (3-OMD) in the periphery (before reaching the brain). COMT inhibitors like Entacapone, Tolcapone, and Opicapone prevent this methylation reaction. As a result, less levodopa is converted to 3-OMD, resulting in more active levodopa and higher levodopa levels in the blood for a longer period. This enables more levodopa to get across the BBB and into the brain, increasing dopamine levels in the striatum. They are always used in combination with levodopa and carbidopa to help lower levodopa dosages and motor fluctuations.[1] Common side effects include nausea, exacerbation of levodopa-related dyskinesia, diarrhea, abdominal pain and urine discoloration (orange yellow) (Brooks,2004).

Entacapone is a short-acting peripheral COMT inhibitor that is administered with each dosage of levodopa/carbidopa. It is generally well tolerated (Habet,2022). Tolcapone inhibits COMT both peripherally and centrally, increasing its potency; nonetheless, its usage is limited due to the danger of lethal liver toxicity, requiring constant liver function monitoring (Artusi et al., 2021). Opicapone is a novel, long-lasting COMT inhibitor that can be administered once each day and has a lower risk profile than tolcapone (Opicapone for Parkinson's Disease, 2023). Overall, COMT inhibitors improve the duration and consistency of levodopa activity, making them particularly beneficial in the later stages of Parkinson's.

2.1.5 Anticholinergics

Anticholinergic medications, such as trihexyphenidyl and benztropine, are among the initial pharmacological therapies developed for Parkinson's disease (PD). Their main method consists of antagonizing muscarinic acetylcholine receptors in the basal ganglia, thus reinstating the fragile equilibrium between dopamine and acetylcholine. This aids in reducing tremors, muscle tightness, and stiffness, providing symptomatic relief especially advantageous for younger individuals with tremor-dominant PD (Jankovic et al., 2008).

In traditional therapy, anticholinergics have served a supplemental function, primarily targeting tremors when dopaminergic treatments such as levodopa are not as effective. Nonetheless, their clinical application has diminished because of considerable side effects, including memory loss, confusion, dry mouth, blurred eyesight, constipation, and urinary retention, which pose issues for older individuals or patients with cognitive vulnerabilities. As a result, their prescription has become more targeted and frequently restricted to symptom patterns (Smith et al., 2012).

In the developing therapeutic environment, increased research attention aims at improving the safety and accuracy of anticholinergic treatment. Contemporary methods involve precise drug delivery systems, CNS-specific formulations, and dosage optimization techniques designed to enhance central effectiveness while reducing peripheral side effects. Additionally, recent research indicates that cholinergic impairment may play a role not just in motor symptoms but also in non-motor aspects of PD, including sleep issues and cognitive deterioration. This has created opportunities for creating next-generation anticholinergic drugs that offer both motor and cognitive advantages (Jankovic et al., 2008).

Consequently, although traditional anticholinergics are currently employed with care, they still symbolize a significant conceptual link between standard symptomatic treatment and new precision therapies. Their changing role demonstrates continuous attempts to enhance Parkinson's treatment by restoring neurochemical balance and customizing pharmacological approaches. A comprehensive summary of these conventional pharmacological mechanisms, benefits and side effects is presented in Table 1.

Table 1: Overview of Conventional Pharmacological Strategies in Parkinson's Disease Management

Therapy	Mechanism of Action	Examples	Major Benefits	Limitations/Side Effects
Levodopa + Carbidopa	Restores dopamine levels in brain	Levodopa, Carbidopa	Most effective for motor symptoms	Dyskinesia, motor fluctuations, hallucinations
Dopamine Agonists	Direct stimulation of dopamine receptors	Pramipexole, Ropinirole	Delay levodopa use, reduce "off" time	Sleep attacks, hallucinations, impulse-control disorders
MAO-B Inhibitors	Prevent dopamine breakdown	Selegiline, Rasagiline, Safinamide	Improves motor control	Limited long-term efficacy
COMT Inhibitors	Extend levodopa activity	Entacapone, Tolcapone, Opicapone	Reduces wearing-off effects	Diarrhea, hepatotoxicity

Anticholinergics	Restore dopamine-acetylcholine balance	Trihexyphenidyl, Benztropine	Effective against tremors	Cognitive impairment, dry mouth

2.2 Non-Pharmacological Conventional Therapies

2.2.1 Deep Brain stimulation

Deep Brain Stimulation (DBS) is a non-drug conventional treatment that has emerged as a fundamental approach in managing advanced Parkinson's disease (PD), especially for patients who do not respond sufficiently to medication. This surgical method entails the accurate placement of electrodes in targeted motor control areas of the brain typically the subthalamic nucleus (STN) or the globus pallidus interna (GPi). These electrodes link to a neurostimulator (like a pacemaker) placed under the chest skin, which sends carefully adjusted electrical impulses to regulate irregular neuronal activity. DBS effectively reduces core motor symptoms like tremor, rigidity, and bradykinesia, while also minimizing medication-related motor fluctuations by reestablishing balance in the basal ganglia-thalamocortical circuit.

Historically, DBS has been applied as a final intervention for individuals experiencing severe motor complications or dyskinesias triggered by levodopa. A primary benefit is the capacity to modify stimulation parameters, enabling healthcare providers to tailor treatment for the best symptom management while minimizing side effects. Moreover, the therapy is reversible and flexible, offering lasting advantages without permanently changing brain matter. Nonetheless, it necessitates thorough preoperative evaluation, comprising assessments of motor function, cognitive ability, emotional state, and neuroimaging, to confirm patient eligibility and surgical accuracy. (Bucur et al., 2023; Hariz et al., 2022).

To advance this precision, modern hardware has evolved to utilize directional leads that allow for highly focused electrical current delivery. However, to deal with the sheer complexity of calibrating these complex systems**,** 2026 clinical guidelines have increasingly adopted Image-Guided Programming (IGP). By feeding a patient's pre-surgical MRI and post-surgical electrode data into mapping software like Illumina 3D or Stimview XT, clinical teams can look right into the patient's unique basal ganglia structure in real time. Instead of relying on hours of exhausting, trial-and-error adjustment by the bedside, doctors can visualize the electrical field and steer current precisely into the dorsolateral subthalamic nucleus. This optimizes motor symptom management almost instantly while sparing patients from unintended stimulation side effects (Umemura et al., 2026).

In summary, Deep Brain Stimulation continues to be a key standard treatment connecting traditional symptom control and the upcoming phase of personalized neuromodulation. Through providing lasting motor enhancement and diminished reliance on medication, DBS exemplifies how technology-based neurotherapies can transform the realm of PD.

2.2.2 Physiotherapy

Physiotherapy is critical in Parkinson's disease because stiffness, slow movement, and poor balance make daily tasks challenging. Regular physiotherapy helps patients maintain flexibility, strengthen weak muscles, improve posture, and learn to walk more safely. Stretching, resistance training, treadmill training, dance, and balancing exercises can all help lower the chance of falling. Overall, physiotherapy helps patients maintain their independence for longer periods of time (Radder et al., 2020).

2.2.3 Speech therapy

Parkinson's disease often causes speech issues such as a soft voice, slurred or unclear words, and trouble swallowing (dysphagia). Speech therapy aims to improve these difficulties. Therapists utilize voice exercises to improve speech louder and clear as well as to teach breathing control and pronunciation. They teach safe swallowing practices to prevent choking in people with swallowing issues. Furthermore, modern therapies such as Lee Silverman Voice Treatment (LSVT) are specifically designed to help Parkinson's patients improve their voice and communication. This significantly boosts confidence and quality of life (Ramig et al., 2018). Table 2 outlines the clinical purpose, distinct benefits, and primary limitations of these non-pharmacological modalities.

Table 2: Overview of Conventional Non-Pharmacological Strategies in Parkinson's Disease Management

Therapy	Purpose	Benefits	Limitations
Deep Brain Stimulation (DBS)	Electrical modulation of motor circuits	Reduces tremor and dyskinesia	Expensive, invasive
Physiotherapy	Improve mobility and balance	Reduces falls, improves posture	Requires long-term commitment
Speech Therapy	Improve speech and swallowing	Better communication and quality of life	Variable effectiveness

3.0 Limitations of Conventional Therapies

Despite decades of clinical use, conventional therapies for Parkinson's disease are primarily palliative rather than curative. Current treatments such as levodopa, dopamine agonists, MAO-B inhibitors, COMT inhibitors, anticholinergics, physiotherapy and speech therapy, give effective symptom relief but have significant limits. Prolonged levodopa treatment results in motor fluctuations and dyskinesias, whereas dopamine agonists and MAO-B inhibitors frequently cause psychiatric or gastrointestinal adverse effects and lose effectiveness over time. COMT inhibitors such as entacapone, tolcapone, and opicapone just prolong the effect of levodopa without providing any direct benefit and they may cause diarrhea, hepatotoxicity or increase treatment complexity. Anticholinergics, while effective for tremor, are restricted by cognitive and systemic side effects, particularly in elderly patients. Non-pharmacological therapies such as physiotherapy and speech therapy offer only partial and transitory relief and necessitate a long-term commitment. Even Deep Brain Stimulation (DBS), while useful for motor symptoms, is intrusive, expensive and not suitable for all patients. Most importantly, none of these treatments stop or reverse the underlying neurodegeneration, emphasizing the critical need for additional disease-modifying techniques (Dumbhare et al., 2023).

4.0 Emerging Therapeutic Approaches

4.1Neuroprotective and Disease Modifying Therapies

4.1.1 Gene Therapy

Gene therapy is a promising disease-modifying technique in Parkinson's disease (PD), aiming to address the underlying neurodegeneration rather than simply treating symptoms. Several strategies have been devised, each focusing on a unique feature of the condition.

4.1.1.1Dopamine Synthesis Enhancement: This cutting-edge approach aims to biochemically restore the striatum's autonomous, long-term capacity for dopamine biosynthesis. In contrast to oral pharmacological agents that cause highly fluctuating, non-physiological pulsatile stimulation, gene therapy provides stable, continuous neurotransmitter production. This process utilizes replication-deficient viral vectors, primarily engineered Adeno-Associated Viruses (AAV, specifically serotypes like AAV2), to deliver cDNA cassettes encoding the critical rate-limiting enzymes of the dopamine synthesis pathway: tyrosine hydroxylase (TH), aromatic L-amino acid decarboxylase (AADC), and GTP cyclohydrolase 1 (GCH1) (Taxman et al., 2010).

4.1.1.2 α-Synuclein-Targeted Therapy: Tools like RNA interference (RNAi), which utilize short hairpin RNAs (shRNAs) or small interfering RNAs (siRNAs) are engineered into a viral vector (often an Adeno-Associated Virus, or AAV). Upon delivery into neurons, these RNAi molecules selectively bind to the

complementary *SNCA* mRNA transcripts, guiding them into the RNA-induced silencing complex (RISC) for degradation, effectively silencing the SNCA (α-synuclein) gene. This mechanism reduces toxic protein accumulation, protects neurons, and may slow disease progression (Szunyogh et al., 2025).

4.1.1.3 Glutamic acid decarboxylase (GAD): This method involves inserting the GAD gene into an overactive brain area, such as the subthalamic nucleus (STN). GAD produces GABA, an inhibitory neurotransmitter that helps to decrease abnormal neuronal activity and restore equilibrium in Parkinson's motor circuits (Serva et al., 2022).

4.1.1.4 Neurotrophic Factor-Based Therapy: To protect and repair dopaminergic neurons, gene therapy delivers neurotrophic factors such as GDNF (glial cell line-derived neurotrophic factor), neurturin, and BDNF (brain-derived neurotrophic factor). These proteins bind to neuronal receptors, activating intracellular signaling pathways that promote cell survival, inhibit apoptosis, and improve synaptic plasticity (Kim et al., 2024).

The most common viral vectors are **adeno-associated virus (AAV) and lentiviruses** for stable integration and bigger gene delivery and adenoviruses also being utilized on occasion. Nonviral vectors such as plasmids, liposomes and nanoparticles are being investigated experimentally. Stereotactic surgery or convection-enhanced infusion are typically used to deliver the drug directly into the striatum or substantia nigra, resulting in targeted and localized gene expression (Kumar et al., 2025).

4.1.2 Stem cell therapy

The fundamental concept is to surgically transplant new cells into the brain's striatum that can survive, integrate, and begin releasing dopamine to replace the deteriorated neurons in the substantia nigra. This has the potential to improve motor symptoms such as tremor, stiffness, and slowness while also reducing the need for or reliance on typical pharmacological therapy such as L-DOPA (Morizane,2023).

Dopaminergic neurons used in transplantation are generally derived from embryonic stem cells (ESCs) and induced pluripotent stem cells (iPSCs). ESCs are pluripotent cells derived from early embryos that can differentiate into dopaminergic neurons; nonetheless, they present ethical concerns and risk immunological rejection. iPSCs, which are reprogrammed from adult somatic cells, provide a patient-specific, morally acceptable source that reduces the risk of immune response and allows for individualized therapy. Additional sources, such as neural stem cells and dental pulp stem cells, are also being studied, however they are less progressed in clinical development (Jeon et al., 2025).

Transplanted stem cells undergo differentiation into dopaminergic neuron precursors and are subsequently incorporated into the patient's striatum. These cells produce and release dopamine, which compensates for neuron loss and restores basal ganglia connectivity. Neurotrophic support from transplanted cells may also improve the survival and function of surviving host neurons (Mokhtari et al., 2025).

Early trials with fetal ventral mesencephalic tissue showed long-term motor improvement in some patients, although problems such as graft-induced dyskinesia were observed. Recent research has revealed that ESC-derived dopaminergic precursors can improve motor function, but tumorigenicity and standardization remain drawbacks. Autologous iPSC-derived therapies are currently being tested in clinical studies, and they promise to provide safer, more tailored treatment options. Immune rejection, tumor development and ethical issues are all significant challenges of this method (Wang et al., 2020).

The persistent roadblock of host-versus-graft immune rejection is also being solved through a fascinating new development: 'hypoimmune' pluripotent stem cell platforms. By using precise gene editing to knock down major histocompatibility complex (MHC) classes I and II while overexpressing the CD47 signalling molecule, researchers have essentially engineered allogeneic dopaminergic precursors that can hide from the host's immune system. This 'off-the-shelf' cell design prevents the patient’s body from destroying the newly transplanted cells, successfully removing the clinical requirement for toxic, full-body immunosuppressant drugs (Kim et al., 2025).

4.3 Immunotherapy

Parkinson's disease is caused by a combination of dopamine-producing neuron loss, brain inflammation, and aberrant α-synuclein protein build-up. These protein aggregates spread throughout brain cells, exacerbating the condition. Immunotherapy uses the body's defense

system or specially produced antibodies to eliminate toxic α-synuclein and reduce inflammation. Immunotherapy aims to delay or stop disease progression, providing hope beyond conventional symptom-relieving drugs.

There are two types of immunotherapies: Active and Passive Immunotherapy. In active immunotherapy, short peptides are used which are then modified so that when injected as a vaccine, the patient's immune system recognizes them as foreign, and the body makes antibodies to target real α-synuclein aggregates in the brain to clear or reduce them. The common examples are PD01A and PD03A. Early-phase clinical trials of active immunotherapies such as PD01A, PD03A, and UB-312 have shown these treatments are generally safe and well tolerated, with robust antibody responses and some evidence of target engagement. In passive immunotherapy, lab-produced monoclonal antibodies are directly administered to patients. These antibodies can bind extracellular α-synuclein and promote its clearance via microglia or prevent its uptake into healthy neurons. Passive immunotherapies using monoclonal antibodies, such as prasinezumab and cinpanemab, have shown good safety and tolerability in phase II trials, but did not meet primary efficacy endpoints for slowing disease progression (Alfaidi et al., 2025).

Lately, the focus of immunotherapy has broadened significantly. Rather than simply trying to clear away toxic α-synuclein aggregates, researchers are now looking at ways to manage widespread neuroinflammation and systemic immune dysfunction. Next-generation vaccine designs and dendritic cell-based therapies are currently being studied to see if they can clear out pathological proteins while simultaneously restoring a healthy immune balance. Furthermore, convincing evidence now shows that chronic brain inflammation and an aging immune system (immunosenescence) are key drivers behind why the disease worsens. These discoveries highlight why tailoring immunomodulatory treatments to individual patient profiles could be the key to unlocking true disease-modifying therapies (Busot et al., 2026).

5.0 Novel drug delivery system

Many drugs, including dopamine, neurotrophic factors, and even gene or immunotherapy treatments, have difficulties crossing the blood-brain barrier (BBB), making treatment for PD a significant issue. This limits their efficacy and frequently requires high systemic doses, which might result in side effects. Novel drug delivery systems are being developed to improve drug penetration into the brain, offer sustained release, and target affected areas more precisely.

5.1 **Nanoparticle-Based Delivery:** Engineered lipid-based, polymer-based, or metallic nanoparticles can transport levodopa, dopamine agonists or neuroprotective compounds across the blood-brain barrier. They prevent medications from deterioration, increase absorption and allow for regulated release, which reduces dose frequency and adverse effects.

5.2 Liposomes and Solid Lipid Nanoparticles (SLNs): Liposomes and Lipid nanoparticles imitate natural cell membranes, allowing for safe delivery of therapeutic substances into the brain. They can be modified with surface ligands to target dopaminergic neurons, resulting in more precise delivery.

5.3 Intranasal Delivery: The nasal route bypasses the BBB via the olfactory and trigeminal pathways. Intranasal delivery of dopamine, stem cells, or growth factors has showed promise in preclinical and early clinical trials, offering a non-invasive and direct route to the brain (Saraswathi et al., 2025).

5.4 Hydrogels and Implantable Systems: These scaffolds or microcapsules can encapsulate stem cells, neurotrophic factors, or drugs into the striatum. This method ensures local, long-term therapeutic effects while reducing systemic toxicity (Yang et al., 2021).

5.5 Exosome-Mediated Delivery: Exosomes are natural vesicles secreted by cells that can cross the BBB. They are being explored as carriers for siRNA, miRNA, or proteins targeting α-synuclein aggregation, offering a biocompatible and precise delivery option (Zhu et al., 2025).

6.0 Regenerative and Restorative Approaches

6.1 CRISPR/Cas9 based gene editing

Gene editing using CRISPR/Cas9 is one of the most advanced regenerative and restorative approaches in the effort to create therapies that modify diseases for Parkinson's disease (PD). In contrast to traditional therapies that mainly alleviate symptoms by increasing dopamine levels or adjusting neuronal function,

CRISPR/Cas9 technology seeks to address the fundamental genetic and molecular issues that lead to neuronal degeneration. This groundbreaking genome-editing technology employs a Cas9 nuclease enzyme, directed by a synthetic RNA strand, to accurately identify and alter segments of the DNA. In Parkinson's disease, this method can be utilized to correct mutations in crucial genes like LRRK2, PARKIN, PINK1, and SNCA (α-synuclein), which are involved in mitochondrial malfunction, protein clumping, and loss of dopaminergic neurons.

From a regenerative perspective, CRISPR/Cas9 provides the capability to reprogram or safeguard dopaminergic neurons by reinstating normal gene expression and inhibiting neurotoxic activities. It additionally paves the way for cell-based treatments, where patient-derived induced pluripotent stem cells (iPSCs) can undergo genetic correction prior to their differentiation into healthy dopaminergic neurons and subsequent transplantation back into the brain. This method shows potential for reconstructing the impaired nigrostriatal pathway, effectively tackling both the origin and effects of PD at a molecular scale.

Nonetheless, despite its impressive potential, various obstacles impede its clinical application. Issues like unintended gene modifications, immune system reactions, challenges in delivering treatments across the blood-brain barrier, and ethical dilemmas need to be addressed to guarantee safety and accuracy. Current studies are investigating advanced CRISPR variants such as base editors and prime editors, which provide improved precision and reduced DNA interference, along with nanocarrier delivery systems for effective and precise gene correction in neural tissues.

Essentially, gene editing using CRISPR/Cas9 represents a fundamental change from managing symptoms to restoring genetics in Parkinson’s disease. Through facilitating accurate DNA repair and possible neuronal regeneration, it represents the future of individualized, therapeutic interventions (Saraswathi et al., 2025).

6.2 Lifestyle and Complementary Interventions

6.2.1 Nutraceuticals

Nutraceuticals are food-derived substances that have neuroprotective properties and can complement standard Parkinson's disease treatments. Coenzyme Q10 (CoQ10) has been shown to support mitochondrial function and help reduce oxidative stress, while omega-3 fatty acids may offer neuroprotective benefits by calming inflammation in the brain. Polyphenols such as resveratrol and curcumin protect neurons from α-synuclein aggregation and oxidative stress. These agents can slow down disease development, boost neuronal health, and improve general brain function. Although preclinical studies show promise, most nutraceuticals still require large-scale clinical trials to identify appropriate dose, efficacy, and long-term safety in PD patients. Nutraceuticals are generally considered safe, but they can interfere with PD medications. For example, high protein intake can inhibit the absorption of levodopa, and certain supplements like Iron or Vitamin B6 can also affect drug absorption. Healthcare providers often recommend a general Mediterranean-style diet for PD patients, which is rich in fruits, vegetables, whole grains and healthy fats (Jiménez-Jiménez et al., 2022; Muleiro Alvarez et al., 2024).

7.0 Conclusion

To summarize, Parkinson's disease management necessitates a delicate balance between short-term symptom relief and long-term disease modification. Conventional medicines are still necessary for daily symptom control, while new therapeutics provide hope for neuroprotection, neuronal repair, and delaying disease progression. Integrating these treatments, together with supportive strategies such as neurorehabilitation and nutraceuticals, can improve quality of life today while potentially altering the disease's trajectory tomorrow. Future research should focus on personalized combination therapies, early intervention, and improved delivery methods, with the goal of achieving a holistic, patient-centered approach that tackles both symptoms and the underlying disease.

Author’s contribution: AA: Data curation, Literature study, Analysis, Writing original draft, Illustrations. MJHR: Analysis, Writing original draft. AS: Conceptualization, Supervision, Reviewing & editing the original draft. All authors approved the final version.

Author Declaration Statements

Declaration: The authors hereby declare that the manuscript submitted for consideration is an original work and has not been published or submitted elsewhere for publication. The authors take full responsibility for the integrity, accuracy, and ethical compliance of the work presented in the manuscript.

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- Any potential conflicts of interest, whether financial or non-financial, have been fully disclosed. – ~~**Yes**~~ **/ Not Applicable**√
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- Necessary ethical approvals have been obtained from the relevant institutional or regulatory bodies for studies involving human participants, animals, or sensitive data, wherever applicable. – ~~**Yes**~~ **/ Not Applicable**√

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8.0 References

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