

## Advancements in the Treatment of Parkinson's Disease: Current Therapies and Emerging Innovations: A Review Article

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### ABSTRACT

Parkinson's disease (PD) is a progressive neurodegenerative disorder characterized by motor impairment including muscle imbalance and mask-like face along with dementia as a potential secondary symptom. Understanding changes with time in its etiology, diagnosis and treatment is vital for improving the treatment options for parkinsons disease. Current therapeutic strategies focus on symptomatic relief and neuroprotection. In this review, the data is gathered from various reputable sources like PubMed, Google Scholar, Scopus, The Lancet, Web of Science, Crossref, Embase etc. to deepen understanding of the disease, advancement in its treatment and to identify emerging trends in the treatment of Parkinson's disease. PD affects over 10 million people globally, with prevalence expected to double by 2040 due to aging populations. In India the prevalence range from 15-43% per 1,00,000 suggesting that India may have the highest absolute number of PD patients globally. The prevalence suggests the need for multidisciplinary approaches to address challenges and optimize care for PD patients.

**Keywords:** Parkinson's disease, dopamine depletion, deep brain stimulation, Neurodegeneration.

### INTRODUCTION

Parkinson's disease is a clinical syndrome that primarily affects movement control and various non-motor system. PD was first described by James Parkinson in 1817 publication, "An essay on shaking palsy".<sup>(1-6)</sup> The symptoms including tremors, bradykinesia (slowness), stiffness, sleep behaviour disorder are most common in these diseases<sup>(7)</sup>. PD is a progressive neurodegenerative disease that kills or weakens nerve cell. These cells are found in substantia nigra, a part of brain which is responsible for producing a chemical called dopamine. Dopamine is a chemical messenger that helps brain to make smooth and coordinated movements of muscles possible. When these cells weakens or lost, dopamine level decreases as result brain strives to control movements, leading PD. After Alzheimer's, Parkinson's is the second most common neurodegenerative disorder in the world, affecting people over the age of 60<sup>(8)</sup>.

Globally, over 8.5 million people were living with PD in 2019, expected to exceed 12 million by 2040 due to aging population<sup>(2)</sup>. In India, the prevalence of PD varies regionally. A survey conducted in Kolkata, Kashmir and Mumbai in 2006 reported a prevalence of 14.1-192 per 1,00,000, with 40-45% experiencing early-onset Parkinson's disease (EOPD) between age 22-49<sup>(3)</sup>. Male are more prone to PD than females at a ratio of 3:2, meaning men are 1.5 times more likely to develop PD than

women. PD poses a significant public health challenge, particularly with the aging global population<sup>(9)</sup>.

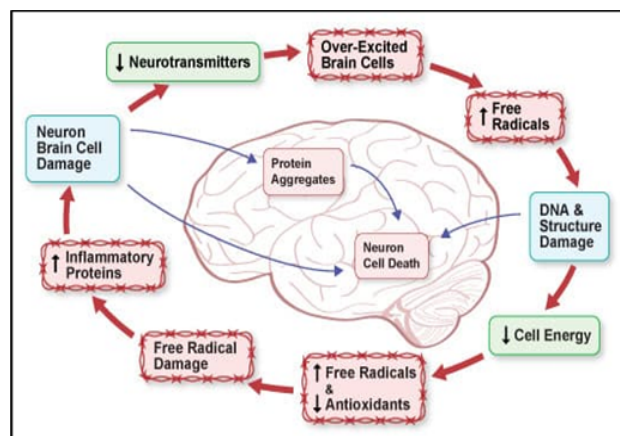


Fig. 1: Neurodegeneration in Parkinsons disease

Although treatments like levodopa and deep brain stimulation (DBS) have improved symptom management, they fail to hold the disease progression<sup>(10)</sup>. The innovations in therapies, including gene therapy, stem cell transplantation, immunotherapy, and precision medicine, offers new hope for modifying the course of PD<sup>(11)</sup>. This review aims to provide an updated overview of the pathophysiology, classification, and therapeutic

advancements in PD, while identifying emerging trends and gaps in current knowledge.

**1.1 Classification of Parkinson's disease:**

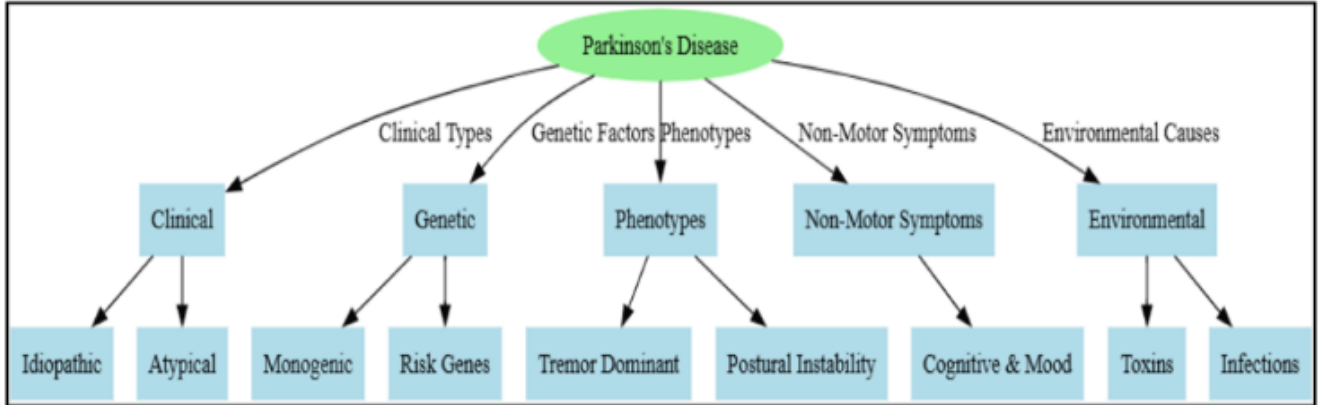
A comprehensive overview of PD classification is represented as follows organising important category extracted from peer review of the data collected.

**1.2 Pathophysiology<sup>(12-15)</sup>**

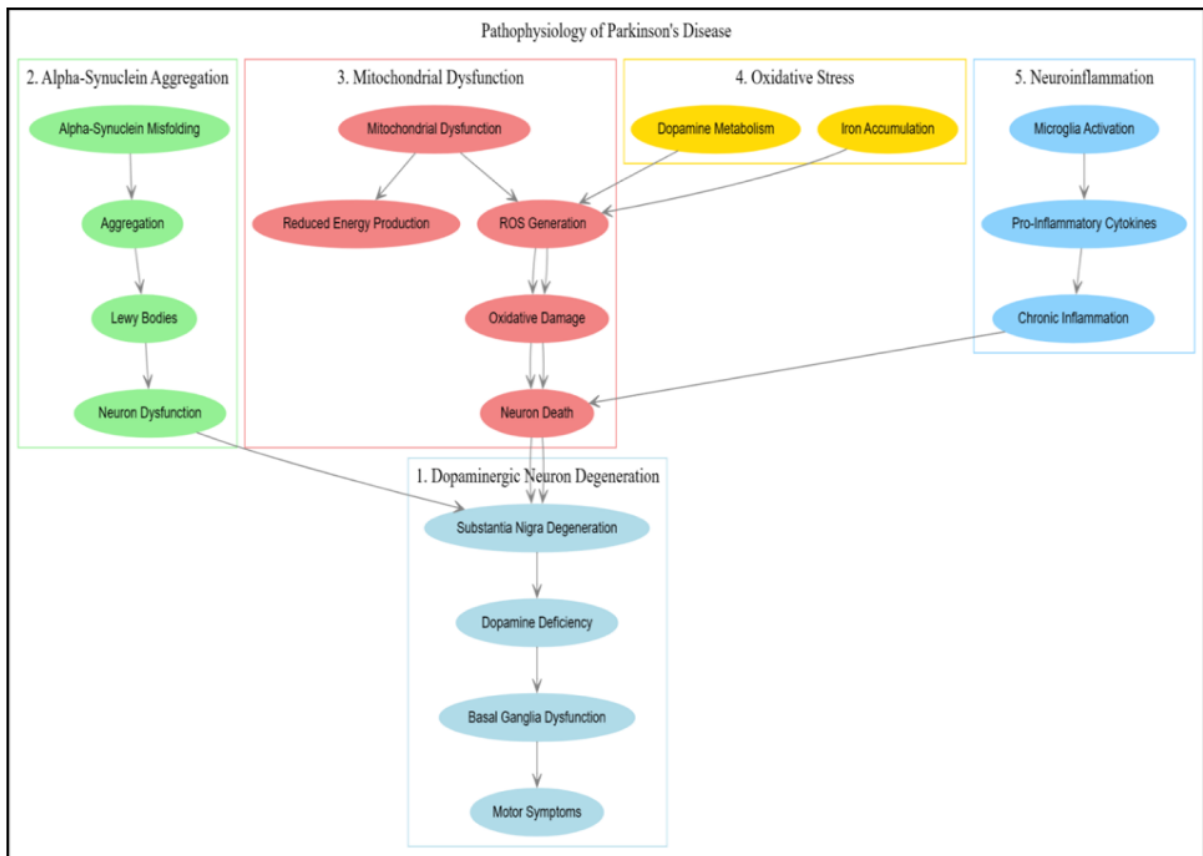
The pathogenesis of Parkinsons disease is complex and multifactorial, involving a combination of genetic,

environmental, and aging-related factors. Among these, five mechanisms are widely recognized with experimental evidences, these are:

1. Dopaminergic neuron degeneration.
2. Alpha-synuclein aggregation.
3. Mitochondrial dysfunction.
4. Oxidative stress.
5. Neuroinflammation.



**Figure 2: Classification of Parkinson's Disease**



**Fig. 3: Pathophysiology of Parkinson's disease**

**Table 1: Emerging therapies for Parkinson's disease**

S. No.	Case Study	Patient (Age)	Symptoms /Challenges	Treatment Approach	Outcomes	References
1.	Levodopa and Carbidopa	John (67)	Resting tremors, bradykinesia; dyskinesias after 5–7 years of Levodopa usage.	Initial therapy with Levodopa + Carbidopa. Later, COMT inhibitor (Entacapone) added to reduce "on-off" fluctuations.	Improved motor control and ability to perform daily tasks. Dyskinesias managed by adjusting medication regimen.	Olanow, C. W., & Stocchi, F. (2018). <i>Movement Disorders</i> , 33(7), 859–866.
2.	Deep Brain Stimulation	Maria (58)	Severe motor fluctuations unresponsive to medications. No cognitive or psychiatric impairments.	Electrodes implanted in the subthalamic nucleus (STN) to regulate abnormal motor signaling.	60% reduction in "off" episodes, improved motor control, reduced medication dosage, and fewer side effects	Weaver, F. M., Follett, K., et al. (2009). <i>JAMA</i> , 301(1), 63–73.
3.	Tai Chi and Physical Therapy	Raj (62)	Postural instability, frequent falls.	12-week Tai Chi program focused on controlled, slow movements and stability exercises.	Balance improved by 50%, fewer falls, and enhanced confidence in mobility.	Li, F., Harmer, P., et al. (2012). <i>New England Journal of Medicine</i> , 366(6), 511–519.
4.	Speech Therapy	Linda (70)	Hypophonia (low voice volume), difficulty communicating in noisy environments	Enrolled in LSVT LOUD program with voice exercises over four weeks to strengthen vocal output.	Vocal loudness improved by 8–10 decibels, allowing better communication.	Ramig, L. O., Sapir, S., et al. (2008). <i>The Lancet Neurology</i> , 7(10), 880–890.
5.	Nutritional Therapy	Ahmed (65)	Chronic constipation, fatigue, low energy levels.	Dietitian recommended antioxidant-rich foods, omega-3 fatty acids, and reduced processed/refined foods.	Improved digestion and energy, better symptom control.	Mischley, L. K., Lau, R. C., & Bennett, R. D. (2017). <i>Oxidative Medicine and Cellular Longevity</i> .
6.	Psychological Therapy	Emily (55)	Depression, social withdrawal, reduced engagement in hobbies.	Cognitive Behavioral Therapy (CBT) and participation in a Parkinson's support group.	Anxiety reduced, coping skills improved, resumed painting, and experienced enhanced mood and social interaction.	Dobkin, R. D., et al. (2011). <i>American Journal of Psychiatry</i> , 168(10), 1066–1074.
7.	Neural Grafting	Experimental Trial	Advanced Parkinson's disease with severe motor symptoms.	Dopaminergic neurons from embryonic tissue transplanted into the striatum.	Long-term motor improvement; some patients developed graft-induced dyskinesias requiring further refinement.	Barker, R. A., Barrett, J., et al. (2013). <i>The Lancet Neurology</i> , 12(1), 84–91.
8.	Biomarkers for Early Diagnosis	50 year old male	No symptoms yet; family history of Parkinson's disease.	Biomarker testing revealed elevated alpha-synuclein levels in cerebrospinal fluid.	Early neuroprotective intervention (exercise, diet changes) potentially delayed symptom onset.	Mollenhauer, B., et al. (2011). <i>Archives of Neurology</i> , 68(5), 635–641.

**Table 2: Emerging therapies for Parkinson's disease**

S.No	Therapy	Example	Description & Mechanism	Outcomes
1.	Gene Therapy	AAV2-GDNF	Uses an adeno-associated viral (AAV) vector to deliver Glial cell line-derived neurotrophic factor (GDNF), which promotes dopamine neuron survival.	Showed modest improvement in motor symptoms and dopamine function, but challenges remain with targeted delivery and long-term efficacy. <sup>36</sup>
		AAV-AADC	Uses an AAV vector to introduce the Aromatic L-amino acid decarboxylase (AADC) gene into the putamen, enabling more efficient conversion of levodopa into dopamine.	Phase I/II trial demonstrated significant motor improvement (UPDRS scores) and reduced levodopa dosage requirements over three years. <sup>37</sup>
2.	Stem Cell Therapy	iPSC-derived neurons	Induced pluripotent stem cells (iPSCs) from a patient's own skin cells are reprogrammed into dopaminergic neurons and transplanted into the brain.	Clinical trial participants showed improvement in motor function, with PET scans confirming survival and integration of transplanted neurons. <sup>38,39</sup>
		CIRM trials	Embryonic stem cells differentiated into dopamine-producing neurons and transplanted into PD models.	Stem cells survived and produced dopamine, but challenges such as graft integration and immune response need further research. <sup>38,39</sup>
3.	Immunotherapy	BIIB054 (sinapanemab)	A monoclonal antibody designed to bind to alpha-synuclein aggregates, preventing their toxic accumulation in the brain.	Phase II trials confirmed safety and tolerability, but motor benefits were limited, requiring further optimization. <sup>40,41</sup>
		AFFITOPE PD01A	A vaccine designed to stimulate the immune system to produce antibodies against alpha-synuclein, aiming to reduce neurodegeneration.	Initial trials showed reduced alpha-synuclein levels in cerebrospinal fluid, but long-term efficacy remains under investigation. <sup>40,41</sup>
4.	CRISPR/Cas9-based Gene Editing	LRRK2 mutation correction	CRISPR/Cas9 used to correct mutations in the LRRK2 gene, which is linked to familial Parkinson's disease and increased kinase activity.	Edited neurons showed reduced alpha-synuclein accumulation, suggesting potential neuroprotection. <sup>42</sup>
		PINK1/Parkin gene repair	PINK1 and Parkin genes regulate mitochondrial quality control; CRISPR has been used to restore their function in preclinical models.	Improved mitochondrial function and reduced neuronal degeneration in laboratory models of PD. <sup>42,43</sup>
5.	RNA-based Therapies	Ionis ASOs	Antisense oligonucleotides (ASOs) target overactive LRRK2 gene expression, reducing its harmful impact on neurons.	Early clinical trials showed safety and potential disease-modifying effects. <sup>26</sup>
		RNAi therapy	Uses RNA interference (RNAi) technology to block alpha-synuclein production, preventing toxic accumulation.	Animal models demonstrated reduced alpha-synuclein aggregates and improved motor function. <sup>44</sup>
6.	Neuroprotective Therapy	Nilotinib	A leukemia drug that enhances autophagy, helping clear toxic proteins like alpha-synuclein.	Modest motor improvements and increased dopamine metabolites in cerebrospinal fluid in early trials. <sup>27,45</sup>
		Urolithin A	A natural compound that boosts mitochondrial function, protecting neurons from degeneration.	Preclinical studies showed improved mitochondrial health and reduced neurodegeneration. <sup>45</sup>

7.	Gut Microbiome Modification	Fecal Microbiota Transplantation (FMT)	Transfers gut microbiota from healthy donors to PD patients to restore microbial balance and reduce inflammation.	Case studies showed significant motor improvements, supporting the gut-brain axis hypothesis. <sup>46</sup>
		Probiotic therapy	Specific bacterial strains, like Lactobacillus and Bifidobacterium, are being tested to reduce neuroinflammation and improve gut-brain interactions.	Early trials show potential modulation of inflammation and improved gut function in PD patients. <sup>13,46</sup>
8.	Wearable Technology & AI	Kinetigraph	A wearable device that monitors tremor, bradykinesia (slow movements), and dyskinesia (involuntary movements) to help clinicians optimize treatment.	Provides real-time symptom tracking, allowing better medication adjustment. <sup>46,47,48</sup>
		AI-based drug discovery	Uses artificial intelligence to analyze large datasets and identify potential neuroprotective compounds.	Helps in faster identification of new drugs and treatment targets. <sup>47,48</sup>
9.	Emerging Drugs	Ambroxol	A respiratory drug repurposed for PD that increases glucocerebrosidase (GCase) activity, reducing toxic protein accumulation.	Phase II trials showed decreased alpha-synuclein levels, suggesting potential disease-modifying effects. <sup>33</sup>
		Istradefylline	An A2A receptor antagonist that enhances dopamine function and reduces motor symptoms.	Approved in Japan; trials in other regions suggest improved motor control when used with levodopa. <sup>34</sup>
		Exenatide (GLP-1 receptor agonist)	Originally a diabetes drug, it reduces inflammation and may have neuroprotective effects in PD.	Trials showed improved motor function and reduced neuroinflammation in PD patients. <sup>48</sup>

## 2. MANAGEMENT OF PARKINSON'S DISEASE

### 2.1. Existing Therapies<sup>(16)</sup>

The existing therapies till date are depicted as given in figure 4.

The table 1 depicted presents a comprehensive summary of decades of progress in PD treatment. For example, levodopa, which was introduced in the 1960s, is still the main method of treating PD, and improvements in its use have been documented as of 2018. Deep brain stimulation (DBS), which gained approval in the 1990s, proved its efficacy in reducing motor fluctuations in studies conducted around 2009. Non-medical treatments like Tai Chi and speech therapy, which became popular in the 2000s, showed significant results in studies published in 2012 and 2008. Nutrition and psychological therapy have also now become an important part of overall PD treatment, with studies published in 2017 and 2011. Innovative treatments like neural grafting and new diagnostic tools like biomarkers reflect research conducted in the 2010s.

### 2.2 Emerging therapies

Parkinson's disease (PD) is a complex neurological disorder that affects millions of people worldwide. While conventional therapies such as levodopa are helpful in managing symptoms, they are unable to stop disease progression. Recent years evidents, revolutionary advances in gene therapy, stem cell transplantation,

immunotherapy and precision medicine have reshaped the medical field. Technologies such as CRISPR gene editing and RNA-based therapies offer unprecedented control over disease pathways, while innovations in wearable technology and AI-driven drug discovery optimize personalized care<sup>(15-17)</sup>. A comprehensive overview of these emerging therapies is as follows:

#### i. Gene Therapy

Gene therapy for Parkinson's disease (PD) aims to correct defects in genes or restore normal functioning of genes that cause neurodegeneration. A major goal is the delivery of neurotrophic factors such as glial cell-derived neurotrophic factor (GDNF) via a viral vector<sup>(18)</sup>. There have been modest reports of improvement in motor symptoms and improvement in dopamine function using AAV2-GDNF gene therapy, although challenges remain related to delivery methods, stability of gene expression, and long-term efficacy<sup>(19)</sup>. A major challenge is ensuring targeted delivery and maintaining stable therapeutic effects, and there are ongoing trials to evaluate various gene delivery techniques and vectors<sup>(17)</sup>. Table 2 represents the emerging therapies for parkinson's disease.

#### ii. Stem Cell Therapy

Stem cell therapy aims to transplant stem cells into the brain to replace damaged dopaminergic neurons. Embryo-derived stem cells and induced pluripotent stem cells (iPSCs) are the leading candidates being investigated. Clinical trials conducted by the California Institute for

Regenerative Medicine (CIRM) have shown that stem cells can survive in the brain and divide into dopamine-producing neurons. However, issues such as graft survival, integration with existing brain circuits, and immune

rejection remain significant challenges. Despite these problems, ongoing studies are working to improve the survival and integration of stem cells to provide a permanent solution for PD patients<sup>(21)</sup>.

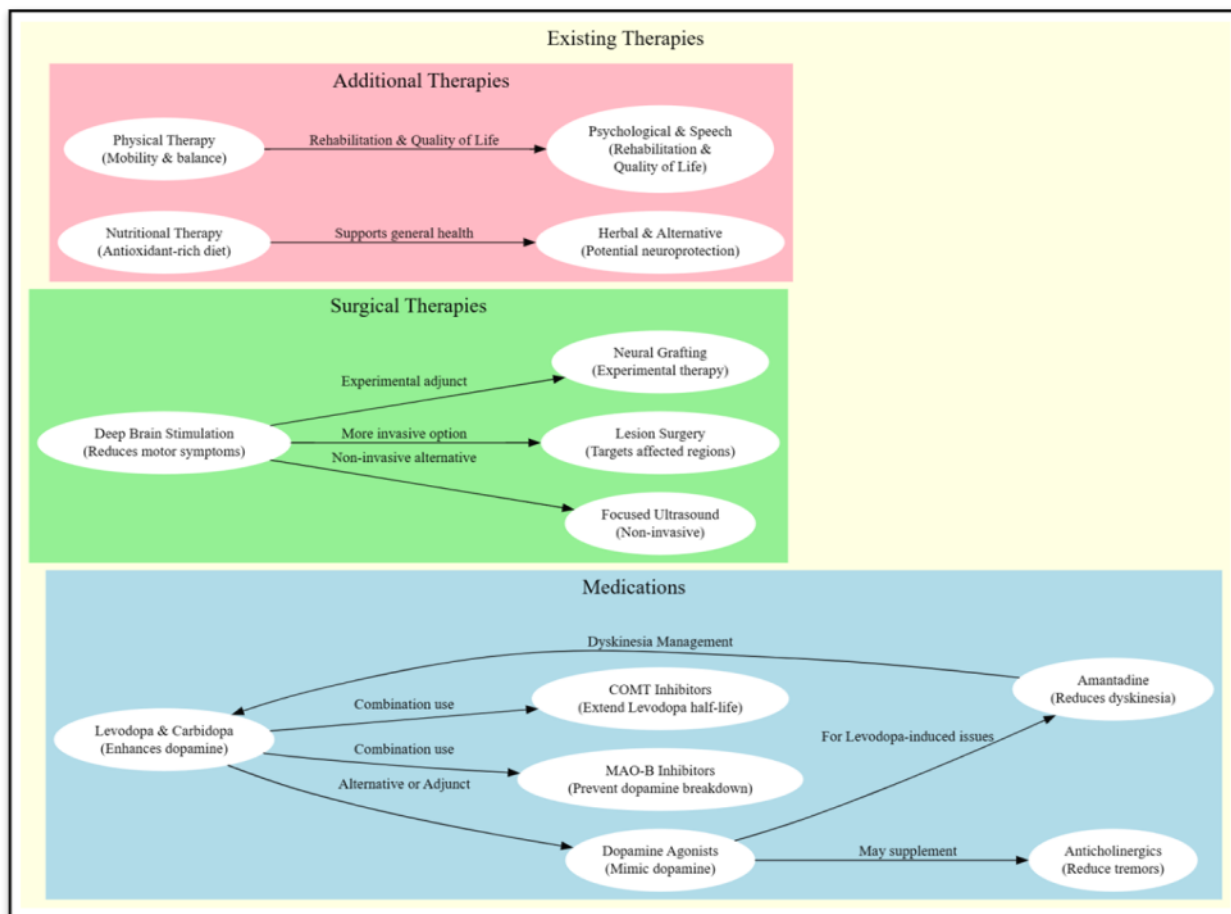


Fig. 4: Existing therapies for parkinson's disease

### iii. Immunotherapy

Immunotherapy aims to target abnormal protein aggregates associated with Parkinson's disease, especially alpha-synuclein, which plays a key role in the process of neurodegeneration<sup>(22)</sup>.

Passive immunization uses monoclonal antibodies such as BIIB054 (sinapanumab), which target alpha-synuclein aggregates. Phase II trials showed that BIIB054 is safe and well-tolerated, but motor benefits were limited, leading to a need to improve treatment strategies.

Active immunization, such as AFFITOPE PD01A, aims to stimulate the immune system to produce antibodies against alpha-synuclein. Initial clinical trials have shown good safety profiles and reductions in alpha-synuclein levels, but more research is needed to evaluate their long-term effects on disease progression<sup>(23, 24)</sup>.

### iv. CRISPR/Cas9-based gene editing

CRISPR/Cas9 technology provides a precise way to edit the genes responsible for Parkinson's disease. For example, mutations in the LRRK2 gene have been linked to an increased risk of PD, and CRISPR/Cas9 has been used to correct these mutations in stem cells generated from patients. Research by Li et al. (2018) showed that editing the LRRK2 gene can reduce alpha-synuclein

levels, suggesting potential therapeutic applications for gene-based PD treatments. This technology opens the door to personalized medicine, offering the possibility of correcting gene-level mutations<sup>(24)</sup>. The challenge is to deliver CRISPR tools to the brain safely and effectively and to ensure precise editing without any off-target effects.

### v. RNA-based therapies

RNA-based therapies, such as antisense oligonucleotides (ASOs) and RNA interference (RNAi), offer a new approach to reduce the production of harmful proteins involved in Parkinson's disease. For example, ASOs targeting the LRRK2 gene have been developed to reduce the overactivity of this gene, which contributes to neurodegeneration. Initial trials with ASOs have shown safety and potential disease-modifying effects. RNAi therapies targeting alpha-synuclein expression have also shown positive results in animal models, offering hope for reducing toxic protein accumulation in the brain. These treatments hold the promise of providing disease-modifying treatments that may slow or stop the progression of PD.

### vi. Neuroprotective therapy

Neuroprotective therapies aim to protect neurons from damage and degeneration, in order to slow the progression of Parkinson's disease.

Nilotinib, a leukemia drug, has shown to promote autophagy, the process of clearing toxic protein aggregates such as alpha-synuclein. Clinical trials indicated modest motor improvements and increased dopamine metabolite levels in the cerebrospinal fluid, which suggest neuroprotective effects. Another potential compound, Urolithin A, has demonstrated improvement in mitochondrial functionality and reduction of neurodegeneration in animal models in preclinical studies<sup>(25)</sup>. These treatments act to preserve dopaminergic neurons and support their survival, providing the potential to alter the course of the disease.

#### vii. Gut microbiome modification

Emerging evidence indicates that imbalance (dysbiosis) in the gut microbiome plays a key role in the progression of Parkinson's disease, and there is a strong link between inflammation in the gut and neuroinflammation<sup>(29)</sup>. Treatment methods targeting the gut microbiome, such as fecal microbiota transplantation (FMT), have indicated improvements in motor symptoms in PD patients with gut dysbiosis. A case study by Huang et al. (2018) showed significant improvement in a PD patient's motor symptoms after FMT, supporting the theory of the gut-brain axis. Probiotics, such as *Lactobacillus* and *Bifidobacterium* strains, are being tested for modulating gut-brain interactions and reducing systemic inflammation, and clinical studies are ongoing to evaluate their long-term benefits in PD management<sup>(30)</sup>.

#### viii. Wearable technology and AI

Wearable technology and artificial intelligence (AI) are revolutionizing the management of Parkinson's disease, enabling real-time monitoring of motor symptoms and treatment optimization. Devices such as kinetigraphs continuously track tremor, bradykinesia, and dyskinesia, giving clinicians objective data to optimize treatment plans. Additionally, AI-based drug discovery has the potential to accelerate the identification of neuroprotective compounds, help identify new therapeutic targets by analyzing large data sets. These technologies improve clinical decision making and offer great potential for personalized approaches to PD care.

#### ix. Emerging drugs

Several emerging drugs are showing promise in the treatment of Parkinson's disease. Ambroxol, used to treat respiratory conditions, has increased glucocerebrosidase (GCase) activity in patients with GBA1 mutations, which are associated with increased risk of PD. Phase II trials have reported a reduction in alpha-synuclein levels in the cerebrospinal fluid, giving it potential as a disease-modifying therapy<sup>(28)</sup>. Another emerging drug, istradefylline, is an A2A receptor antagonist that has shown improvement in motor symptoms in PD patients. It has been approved for use in Japan and is under review in other regions, highlighting its therapeutic potential for managing symptoms in PD.

## CONCLUSION

Parkinson's disease (PD) is a complex neurodegenerative disorder that remains a major challenge today due to its complex pathophysiology and lack of definitive treatment. Although treatment methods such as dopamine replacement therapy and deep brain stimulation are effective in managing symptoms, they are unable to halt disease progression. Emerging treatments such as gene therapy, stem cell transplantation and immunotherapy are opening promising avenues to modify the disease. CRISPR/Cas9 technology, RNA-based therapy and wearable devices are paving new avenues for personalized and precision medicine, while the gut-brain axis is an exciting area to understand the pathogenesis of Parkinson's disease.

Although progress has been made in these areas, challenges remain in translating preclinical findings into clinical success, ensuring long-term safety, and overcoming ethical and access-related barriers. Large and diverse clinical trials, as well as multidisciplinary collaborations, are needed to effectively address these issues. Integrating emerging technologies with traditional medical strategies has the potential to revolutionize Parkinson's disease management, improving patients' quality of life and long-term outcomes. Through continued innovation and research efforts, we are moving toward a future where Parkinson's disease can be effectively controlled or even cured.

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