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Inside Parkinson's: A journey through diagnosis, management, and research

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Abstract

Parkinson's disease (PD) is a multifaceted neurodegenerative illness that impairs a patient's quality of life by causing both motor and non-motor symptoms. This comprehensive review highlights the complex path of Parkinson's disease, covering topics from diagnosis and clinical manifestations to management and current research endeavors. To obtain an accurate and timely diagnosis, PD is diagnosed using a multimodal approach that combines clinical examination, neuroimaging, and occasionally biomarker investigation. Early identification is essential because it enables prompt intervention and individualized treatment plans that can reduce symptoms and enhance long-term results. An integrated approach including neurologists, physiotherapists, occupational therapists, and other medical specialists is needed to manage Parkinson's disease. The goal of current treatment choices is to alleviate symptoms, and the mainstay of pharmaceutical intervention is dopamine replacement therapy, such as levodopa. However, if the illness worsens, side effects including dyskinesias and motor fluctuations may appear, requiring doctors to modify treatment plans and take cutting-edge treatments like deep brain stimulation into account. Research is still being conducted to better understand the pathophysiology of Parkinson's disease, including alpha-synuclein aggregation, mitochondrial failure, and neuroinflammation. This goes beyond managing the disease's symptoms. New avenues for therapeutic intervention are being explored, encompassing gene treatments, regenerative medicine techniques, and medications that alter illness. To sum up, this article offers a thorough overview of Parkinson's disease, outlining the process from diagnosis to management to the forefront of current research endeavors.

1. Introduction

In 1817, James Parkinson became the pioneer in categorizing Parkinson's disorder as a neurological condition. Parkinson's disease affects the basal ganglia, a distinct region of the brain, causing a decline in its functionality. Consequently, the loss of abilities associated with these areas occurs. Research indicates that Parkinson's disease significantly alters the brain's chemistry. Typically, neurotransmitters regulate communication among brain cells (neurons). However, individuals with Parkinson's disease experience a deficiency in dopamine, a crucial neurotransmitter.

When your brain sends signals to activate your muscles, it relies on dopamine-dependent cells to refine those movements. Therefore, a shortage of dopamine leads to Parkinson's disease symptoms like tremors and sluggish movement. As the disease progresses, so do these symptoms in advanced stages, Parkinson's can also impact cognitive functions, often manifesting as depression and dementia symptoms. (Parkinson *et al.,* 1817)

2. Epidemiology of data

Following Alzheimer's disease in terms of neurodegenerative illness prevalence, Parkinson's disease ranks second. Worldwide, the total number of PD patients approaches four million, with idiopathic Parkinsonism affecting approximately 1% of individuals over 50 and 2-4% of those over 65, on average. (Rijk *et al.,* 2000; Nussbaum *et al.,* 2003). There is a rising trend in idiopathic Parkinsonism cases, alongside a decrease in the age of onset. Various ethnic groups experience the disease differently, influenced by geographical factors. For example, mainland China has reported the lowest incidence of PD among Chinese residents, with 15-20 patients per 100,000 people. Australia follows with the second-highest incidence, at 414 patients, while Argentina reports the highest incidence, with 650 patients per 100,000 people (Figure 1).

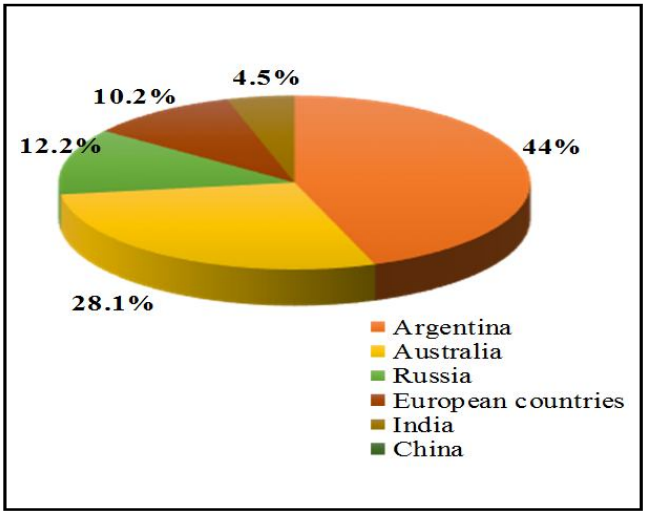

Figure 1: Epidemiology data.

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In European countries, PD occurs at a rate of 100 to 200 instances per 100,000 people, on average. Russia sees a similar prevalence to the European average, with 180 cases per 100,000 people. In approximately 5-10% of cases, Parkinson's disease onset occurs before the age of 40, while juvenile Parkinsonism, affecting adolescents and teenagers, may start even earlier than the typical onset age of 57 years. Regardless of the cause or age of onset, PD significantly reduces life expectancy for patients. Compared to the general population, individuals with PD face a death rate approximately three times higher, factoring in age, gender, and ethnicity. Ten years after onset, 60% of patients either pass away or experience severe disability, increasing to 80% fifteen years later. Though individual experiences vary, the average lifespan from PD onset is approximately 9 years.

3. Symptoms

3.1 Motor-related symptoms

Parkinson's disease movement-related symptoms, or motor symptoms, include the following Table 1.

Table 1: Common motor-related symptoms in PD

Symptom	Description
Bradykinesia	The key symptom for diagnosing Parkinson's disease; is perceived as muscle weakness despite no actual loss of strength (Lang *et al*., 1998).
Resting muscle tremors	Prevalent in Parkinson's disease, affecting over 80% of patients during inactivity; distinguishes Parkinson's from essential tremor.
Firmness or rigidity	Characterized by cogwheel and lead-pipe rigidity; lead-pipe rigidity refers to constant stiffness; cogwheel rigidity combines stiffness with tremor (Diaz *et al*., 2009).
Unsteady walking or gait	Due to rigidity and slowness; progresses to drooping posture, shakier strides, and difficulty in turning (Gomez *et al*., 2007).

3.1.1 Additional motor symptoms can include

a. **A lesser amount of blinking than usual:** Another indication of poorer facial muscle control is this.

b. **Squished or little handwriting:** Micrographia is the name for the condition that develops from uncontrolled muscles.

c. **Gushing**: Another symptom is brought on by the absence of facial muscle control.

d. **A face expression that resembles a mask:** Hypomimia is a disorder in which there are little or no changes in facial expressions, dysphagia, or difficulty swallowing. This leads to a decrease in throat muscle control. This makes illnesses such as pneumonia or suffocation more likely.

e. **Extremely low-pitched speech (hypophonia):** This is due to diminished throat and chest muscle control.

4. Stages of Parkinson's disease

Parkinson's disease may have a minimal impact on individuals for many years, even decades. In 1967, Margaret Hoehn and Melvin Yahr introduced a staging system for Parkinson's disease. However, this staging approach is now less commonly utilized, as it is considered less effective compared to identifying individual variations in disease effects and tailoring treatments accordingly. Currently, the primary tool used by healthcare professionals to classify Parkinson's disease is the Movement Disorder Society's Unified Parkinson's Disease Rating Scale (MDS-UPDRS). This scale assesses four main aspects of a patient's experience with the disease

Stage 1: Non-motorized aspects of everyday interactions

This section covers non-motor (non-moving) symptoms such as dementia, depression, anxiety and other mental health problems. In addition, it asks about discomfort, incontinence and fatigue.

Stage 2: Motor elements of daily experience

This section covers the effects on motor tasks and skills, including speaking, eating, chewing, and swallowing, particularly if affected by tremors. It also addresses dressing and personal care in the bathroom.

Stage 3: A motor analysis

A medical expert uses this evaluation to assess the impact of Parkinson's disease on movement. Criteria include speech patterns, facial expressions, rigidity, walking pace and gait, balance, speed of movement, tremors, and more.

Stage 4: Motor issues

In this section, a healthcare specialist will assess how Parkinson's disease symptoms impact daily life, including their duration each day and their influence on leisure activities.

5. Molecular mechanism of Parkinson's disease

Parkinson's disease is a multifaceted condition influenced by both environmental and genetic factors. Key contributors to its development include the buildup of misfolded protein aggregates, impairment of protein elimination pathways, mitochondrial dysfunction, oxidative stress, excitotoxicity, neuroinflammation, and genetic alterations.

Exposure to certain environmental chemicals like fungicides, insecticides, and herbicides has been linked to the onset of Parkinson's disease (PD). People, especially farmers and those living in rural areas are at risk of developing PD when they come into contact with these toxins through direct touch or contaminated drinking water. In addition to chemicals, exposure to bacteria, viruses, and illegal drugs like synthetic heroin (MPTP) can also trigger PD (Solari *et al.,* 2013).

6. Impact of oxidative stress and mitochondrial damage on Parkinson's disease

Oxidative stress and mitochondrial damage play a significant role in Parkinson's disease. In PD, mitochondria, often referred to as the "hot-spot" of degenerative processes, show abnormal activity in Complex-I. This disrupts the production of cellular ATP, leading to cell death (Karunanithi *et al.,* 2015). Moreover, certain brain chemicals

like dopamine (DA) and serotonin (5-HT) act as antioxidants. However, when dopamine and oxygen are broken down by monoamine oxidase-B (MAO-B), reactive oxygen species (ROS) are produced, contributing to oxidative stress (Lotharius *et al.,* 2002).

Table 2: Various molecular mechanisms involved in Parkinson's disease

Type	Description
Alpha-synuclein aggregation (SNCA)	Parkinson's disease features lewy bodies in dopamine neurons, containing misfolded SNCA and related proteins. Postmortem analysis often reveals various misfolded protein aggregates. SNCA mutations, like A53T, A30P, E46K, and H50Q, characterize familial PD with early onset. SNCA-induced membrane pore formation leads to neuroinflammation, excitotoxicity, and mitochondrial dysfunction, causing neuronal death (Kagedal *et al.,* 2014).
Tau	Neurodegenerative diseases like Alzheimer's, frontotemporal dementia with parkinsonism (FTDP), and progressive supranuclear palsy (PSP) exhibit neurofibrillary tangles (NFT) due to tau hyperphosphorylation (p-tau). Regions like the cortex and SNpc88 show tau accumulation, associated with FTDP-17. P-tau co-localizes with Lewy bodies (LB), accelerating dopamine (DA) neuron degeneration and death (Hepp *et al.,* 2016).
Gene mutations' impact on Parkinson's disease	Parkinson's disease involves genes like α-synuclein (SNCA), parkin (PARK2), DJ-1 (PARK7), and PINK1 (PARK6), with chromosome associations including 5, 6, 8, 9, and 17. Notably, parkin resides on chromosome 6, while chromosome 9 may impact L-DOPA resistance. Chromosome 17 (FTDP-17) links to late-onset PD, alongside genes like UCH-L1 and others on chromosomes X, 1, 2, and 4, influencing PD in select families (Westenberger *et al.,* 2012).
Protein breakdown mechanisms that are impaired in PD	
Ubiquitin-Proteasome system (UPS)	The Ubiquitin-Proteasome system (UPS) converts proteins efficiently, removing small intracellular and plasma-membrane polypeptides while eliminating misfolded proteins. UPS dysfunction accelerates neurodegeneration and is linked to Parkinson's disease pathology (Ciechanover *et al.,* 2015).
Chaperones for molecules (HSP or heat shock proteins)	Heat shock proteins (HSPs) aid in protein folding, refolding misfolded proteins, and degradation. In Parkinson's disease (PD), certain HSPs like 26, 40, 60, 70, 90, and 100 are vital but often downregulated, impacting neurodegeneration. HSPs interact with aggregated proteins, mitigating toxicity (Dokladny *et al.,* 2015).
Lysosomal autophagy pathway (ALP)	Large α-synuclein (SNCA) aggregates resist degradation by the ubiquitin-proteasome system (UPS) due to size, necessitating autophagy mechanisms like macro autophagy, micro autophagy, and chaperone-mediated autophagy (CMA) for lewy body (LB) clearance in Parkinson's disease (Dokladny *et al.,* 2015).

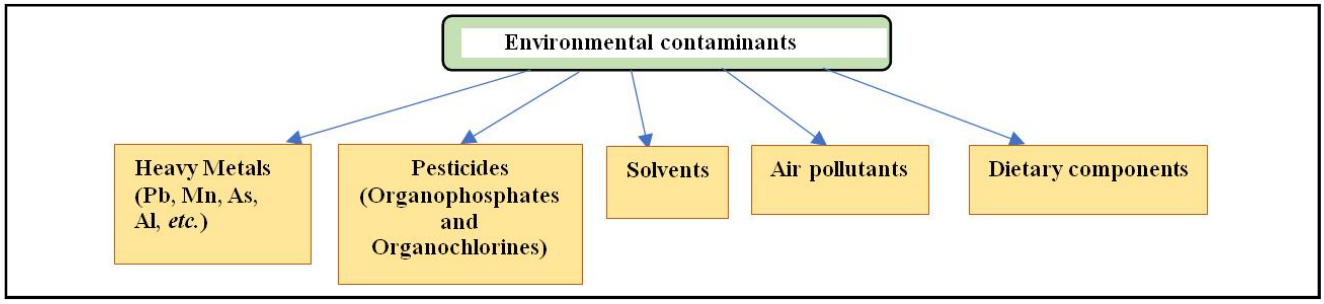

Figure 3: Various environmental neurotoxins causing PD

7. Diagnosis

Parkinson's disease diagnosis relies solely on clinical criteria due to the absence of a definitive test. Historically, confirmation of lewy bodies at autopsy served as the gold standard (GS). In practice, diagnosis hinges on key motor signs, associated symptoms, and response to levodopa (LD). While PD's typical presentation aids diagnosis, distinguishing it from other parkinsonisms can be challenging, especially in the early stages when symptoms overlap with other conditions (Tolosa *et al.,* 2006).

7.1 Early PD treatment

Recent recommendations advocate initiating PD treatment promptly upon diagnosis. Studies, notably with rasagiline (R), support early therapy initiation, suggesting disease modification by the MAOB inhibitor (Olanow *et al.,* 2009). Retrospective analyses on entacapone (E) and rotigotine (R) trials echo this benefit. However, the PROUD study on pramipexole (PPX) found no difference in motor function or dopamine transporter imaging between immediate and delayed therapy initiation.These findings bolster the case for early treatment,

aligning with quality-of-life studies showing better outcomes with immediate therapy initiation. Early PD diagnosis, crucial for maximizing medication's disease-modifying or neuroprotective effects, relies on motor symptoms as the primary clinical criteria. Non-motor symptoms, which often appear later, also support early diagnosis. The levodopa test, improving motor skills by at least 30% with a 200 mg dose, aids in early diagnosis until more advanced methods emerge, ensuring clinical indicators and the levodopa test remain central to PD diagnosis (Grosset *et al.,* 2007).

7.2 Differential diagnosis

Parkinson's disease comes in four main types: primary (idiopathic), secondary (acquired), neurodegenerative, and multisystem degeneration (parkinsonism plus syndromes). PD stands out from other forms of Parkinson's by its specific symptoms like tremors, early gait issues such as freezing, and response to levodopa medication. While changes in dopamine receptors are thought to contribute to poor response in some patients, this is not the only explanation. For instance, in progressive supranuclear palsy (PSP), dopamine receptors seem intact, suggesting other factors are at play (Piccini *et al*., 2006). Orofacial dyskinesias, often seen in multiple system atrophy (MSA), can develop with levodopa use, but initial responses are generally positive. Although, levodopa typically improves PD symptoms, it does not always distinguish PD from other types of Parkinsons. Neuroimaging techniques like positron emission tomography (PET) and MRI scans can aid in diagnosis, but further refinement is needed for better accuracy. While brain ultrasound shows promise, it is not yet widely used for diagnosis due to some limitations (Stockner *et al.,* 2007).

8. Development in therapeutics

8.1 Stem cell therapy

Stem cell therapy holds promise for Parkinson's disease (PD), a complex neurodegenerative condition influenced by aging, genetics, and environmental factors (Pang *et al.,* 2019). PD is characterized by the presence of lewy bodies, progressive loss of A9-type midbrain dopaminergic (mDA) neurons in the substantia nigra pars compacta (SNpc), and subsequent damage to the nigrostriatal dopamine pathway, leading to core motor symptoms (Kalia *et al*., 2016).

Cell therapies, particularly utilizing dopamine-producing cells like ventral mesencephalic neurons from xenogeneic or aborted human fetal tissues, have shown significant and long-term improvements in PD pathology (Jiang *et al.,* 2021). However, ethical and practical concerns regarding tissue availability have limited their widespread use, prompting exploration into alternative cell sources. Human pluripotent stem cells (hPSCs), including induced pluripotent stem cells (iPSCs), offer a promising solution, allowing the production of patient-specific cells without ethical concerns (Shi *et al.,* 2017).

Recent advancements in direct differentiation methods have led to functional mDA populations from both human embryonic stem cells (hESCs) and iPSCs, showing promising preclinical results in PD animal models. This progress suggests that hESCs and iPSCs could become common cell sources for mDA neurogenesis in PD transplantation therapies, leveraging our improved understanding of the molecular basis of mDA neurogenesis (Kim *et al.,* 2020).

8.2 Repetitive transcranial magnetic stimulation (rTMS)

Repetitive transcranial magnetic stimulation (rTMS) involves delivering numerous TMS pulses quickly in succession, altering brain activity for extended periods (Chou *et al*., 2015). Excitability changes may persist for hours, influenced by pulse delivery frequency; >5 Hz pulses (high-frequency rTMS) are excitatory; while 1 Hz pulses (low-frequency rTMS) are inhibitory. Health Canada has approved these procedures as a treatment for non-responsive major depressive disorder (MDD) (Downar *et al*., 2016). While clinical approval for motor and cognitive symptom relief in conditions like stroke, spinal cord injury, and Parkinson's disease is pending, the scientific literature supports their efficacy (Goodwill *et al.,* 2017).

8.3 MRI-guided focused ultrasound therapy (MRgFUS)

MRI-guided focused ultrasound therapy (MRgFUS) utilizes ultrasonic waves to heat a specific brain target, known as sonication, with MRI guiding the procedure and ultrasound (US) radiation acting as the surgical tool to create the lesion. Rapid tissue heating to 57°C per second induces denatured protein production, causing normal and diseased tissues to die, leading to thalamotomy. The extent of the lesion is determined by the equivalent thermal dose, which depends on the duration and area of tissue exposure to heat. MRgFUS surgery, conducted in an MRI suite, allows precise target definition, treatment planning, and intervention guidance using MRI with high accuracy. Real-time MR thermometry monitors lesion effects at clinically low temperatures, believed to be reversible, while definitive irreversible thermal ablation is considered if no side effects occur (Sapareto *et al.,* 1984).

8.4 Calcium targeting therapies

Calcium targeting therapies involve medications like diltiazem, verapamil, and nifedipine, known as calcium channel blockers (CCBs), commonly used to treat hypertension. These drugs inhibit voltage-gated Ca^{2+} currents in cardiac myocytes and arterial smooth muscles, exerting vasorelaxant and cardio-depressant effects. Isradipine and other CCBs also reduce excitotoxicity, preventing dopamine loss (Kuhnert *et al.,* 2012). Nimodipine, a dihydropyridine (DHP) CCB, has neuroprotective effects by reducing vasospasms after subarachnoid haemorrhage (Vijiaratnam *et al.,* 2021).

Voltage-gated Ca^{2+} channels, particularly L-type calcium channels (LTCCs), play a crucial role in stress-induced Ca^{2+} oscillations, contributing to the death of substantia nigra dopaminergic (SN DA) neurons (Gudala *et al.,* 2015). Epidemiological studies suggest that brain-permeable DHP LTCC inhibitors, used as antihypertensives, decrease the incidence of Parkinson's disease (PD). Preclinical studies on DHPs in PD models demonstrate potential protective benefits. However, inconsistent results in toxin-based animal models of PD pose challenges in drawing clear conclusions (Winklhofer *et al.,* 2010). Variability in experimental designs, including measurement methods, animal models, treatment regimens, and PD models, contributes to the mixed findings. Despite this, evidence suggests that DHPs significantly reduce the mortality of substantia nigra dopaminergic (SNDA) cells induced by mitochondrial-targeting toxins in various studies. The preventive benefit of DHPs in PD may necessitate early initiation of therapy after symptom onset, considering multiple contributing factors (Zamponi *et al.,* 2015).

8.5 Dopaminergic drugs

8.5.1 Levodopa (L-DOPA)

Levodopa is commonly prescribed to Parkinson's disease patients to increase dopamine (DA) levels. As DA cannot cross the blood-brain barrier, L-DOPA serves as a precursor. While L-DOPA effectively improves baseline symptoms like "rest tremors", it cannot restore or replace damaged DA neurons or halt PD progression. However, its use may lead to side effects such as rapid falling asleep, drowsiness, low blood pressure, restlessness, nausea, and vomiting. Carbidopa is often co-administered with L-DOPA to prolong its therapeutic effect, as L-DOPA is rapidly converted to DA, reducing its effectiveness upon reaching the target area (Cenci *et al.,* 2014).

8.5.2 MAO-B inhibitors

Decreased dopamine levels in Parkinson's disease may result from elevated levels of the catalytic enzyme monoamine oxidase-B (MAO-B) in the diseased brain. Thus, inhibiting MAO-B is a beneficial strategy to maintain DA levels in PD. Well-tolerated MAO-B inhibitors such as selegiline (L-deprenyl) and rasagiline can extend the benefits of L-DOPA treatment for a year or more when used in combination. These inhibitors hold promise for restoring cell function or reducing the loss of DA neurons in PD (Riederer *et al.,* 2004), despite the presence of potential side effects.

8.5.3 COMT inhibitors

Monoamine oxidase (MAO) can convert dopamine (DA) to dihydroxyphenylacetate, which is then metabolised to homovanillic acid by the enzyme catechol-o-methyltransferase (COMT). Inhibiting COMT indirectly prevents DA degradation, offering another therapeutic strategy for improving Parkinson's disease. Entacapone and tolcapone are common COMT inhibitors that extend the effects of L-DOPA by halting DA degradation. Moreover, these medications have fewer side effects and may potentially reduce L-DOPA sensitivity in PD patients (Korczyn *et al.,* 2004).

8.5.4 Dopamine agonists

Dopamine agonists are effective in early-stage Parkinson's disease (PD), as they elevate dopamine (DA) levels in the brain. They can also complement L-DOPA therapy in advanced PD stages by enhancing its uptake. Pramipexole and ropinirole are commonly prescribed dopamine agonists for PD treatment, although they may be less effective than L-DOPA in reducing bradykinesia. However, these drugs can also cause several side effects similar to those of L-DOPA (Brooks *et al.,* 2000).

9. Discussion

Disease-modifying treatments, precision medicine strategies targeted to the unique profiles of patients, and personalized medicine are the main areas of focus for Parkinson's disease research in the future. To maximize therapy effectiveness and reduce adverse effects, personalized medicine seeks to uncover genetic markers, biomarkers, and particular disease subtypes. The aim of disease-modifying medicines is to reduce or stop the course of the illness by targeting underlying pathogenic processes such as neuroinflammation and alpha-synuclein aggregation. Regulatory barriers, financial constraints, and the requirement for thorough clinical trials to confirm treatment efficacy are some of the obstacles that must be overcome to translate research findings into clinical practice. This discussion provides a thorough summary of all the important elements of Parkinson's disease, from diagnostic and management techniques to new treatments and emerging therapies and future directions, emphasizing the multidimensional approach required for effectively managing this complex neurological condition.

10. Conclusion

The complicated neurodegenerative ailment known as Parkinson's disease, which was first identified by James Parkinson in 1817, is defined by the decline of the basal ganglia and a severe lack of the essential neurotransmitter dopamine. The epidemiological data indicate a growing number of Parkinson's patients worldwide, with varying incidence rates among different ethnic groups and geographical locations. Motor-related symptoms such as bradykinesia, muscle tremors, stiffness, and gait disturbances are hallmark features of the disease. In addition, the disease is often accompanied by non-motor symptoms such as depression, loss of smell, sleep disturbances and cognitive impairment. Parkinson's disease develops in several stages, which affects the quality of life and life expectancy of patients. The accumulation of misfolded proteins like alpha-synuclein, genetic changes, alterations in protein degradation pathways including the ubiquitin-proteasome system and mitochondrial damage resulting in oxidative stress are some of the basic causes driving Parkinson's disease. Diagnosis is primarily clinical, with no definitive test available, and differential diagnosis can be challenging, particularly in the early stages. Recent advancements in therapeutics offer hope for Parkinson's patients. Stem cell therapy, repetitive transcranial magnetic stimulation (rTMS), MRI-guided focused ultrasound therapy (MRgFUS), calcium-based therapies, dopaminergic medications such as levodopa, MAO-B inhibitors, COMT inhibitors, and dopamine agonists are available. To enhance the lives of persons who have Parkinson's disease and eventually find a solution for this crippling ailment, it is critical to keep studying and developing new therapies.

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Conflict of interest

The authors declare no conflicts of interest relevant to this article.

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