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PARKINSON DISEASE: AN OVERVIEW

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ABSTRACT

Parkinson's disease (PD) is a chronic neurodegenerative disorder marked by the gradual loss of dopaminergic neurons in the substantia nigra, leading to both motor and non-motor dysfunctions. Current therapies are largely symptomatic, with L-DOPA remaining the primary treatment. However, prolonged use of L-DOPA often results in complications like levodopa-induced dyskinesia. To counter these effects, alternative approaches such as NMDA receptor antagonists and anticholinergic agents have been explored. NMDA receptor over activity can worsen motor symptoms, and agents like amantadine have shown success in decreasing dyskinesia severity, thereby improving the long-term viability of L-DOPA therapy. Amantadine remains the only FDA-approved drug specifically targeting levodopa-related dyskinesia. Future treatment directions are shifting towards modifying disease progression itself. Surgical options like deep brain stimulation (DBS) and lesion interventions are undergoing continuous advancement, with innovations focused on device miniaturization, enhanced battery life, and wireless compatibility, which may significantly enhance patient outcomes. In addition, research is focusing on α-synuclein (αS) pathology, a key factor in PD development. Therapies aimed at preventing αS aggregation and toxicity, such as NPT200-11 and NPT088, are showing promise in early studies. Although these approaches face challenges due to incomplete understanding of αS toxic forms, they offer a potential pathway toward disease-modifying treatments. Overall, new therapeutic strategies aim to move beyond symptom control toward altering the course of Parkinson's disease itself.

KEYWORDS: Parkinson 's disease, α-synuclein, Pathology, L-DOPA, Treatment.

INTRODUCTION

Parkinson's disease (PD), historically referred to as "paralysis agitans," was first described by James Parkinson in his 1817 essay On the Shaking Palsy. It is a common progressive neurodegenerative disorder defined by core motor symptoms including resting tremor, bradykinesia, muscle rigidity, and postural instability, along with a range of non-motor symptoms. Typically, PD develops between the ages of 55 and 65 and progresses gradually over time. While some cases exhibit familial patterns—falling under the genetic category—most cases are sporadic, accounting for approximately 90% of all PD diagnoses. Genetic PD often follows Mendelian inheritance, whereas sporadic forms result from complex interactions between genetic predispositions and environmental exposures. The exact mechanisms in sporadic cases remain incompletely understood (Tori, K.., 2020). The disease affects around 0.3% of the general population, with prevalence Increasing with age—impacting 1%–2% of individuals over 60, and rising to 3.5% in those aged 85 to 89. PD occurs more frequently in men than women, with a male-to-female ratio of 1.5:1. Some evidence suggests PD may be more common in White populations compared to those of Asian or African descent, though findings are inconsistent. In Canada, for instance, it was estimated that 85,200 individuals were living with PD in 2011, a number projected to double by 2031 (Philippe Rizek, P., 2016).

As an age-related disorder, PD has garnered increased scientific focus. Neurological conditions now represent the leading cause of disability worldwide, and PD is the most rapidly expanding among them. The Global Burden of Disease Study projects that global PD cases will rise from roughly 7 million in 2015 to nearly 13 million by 2040, highlighting the potentially overwhelming impact of PD as a public health challenge.

ENVIRONMENTAL RISK FACTORS

Research indicates a possible association between exposure to certain environmental agents—such as pesticides, industrial pollutants, and heavy metals (Ain, Q., 2009)—and an increased risk of developing Parkinson's disease (PD). Compounds like rotenone and paraquat, commonly used pesticides, function as mitochondrial toxins that may impair dopaminergic neurons in the nigrostriatal pathway. Similarly, heavy metals like manganese, lead, and copper have been implicated in elevating PD risk (Pandey, S., 2025, Johns Hopkins Medicine, 2025).

Interestingly, recent findings suggest that the risk of PD is not necessarily linked to living in rural areas but is instead associated with residing in regions where pulses are heavily cultivated. Pulses from the Fabaceae family naturally release rotenone, which may contribute to neurodegeneration. Environmental neurotoxins can enter the body through ingested food particles and influence oxidative stress within the brain, potentially triggering neurodegenerative changes. Certain dietary habits may elevate oxidative stress, promote inflammation, alter alpha-synuclein behavior, and harm dopaminergic neurons. The food we consume can impact brain health through the gut-brain axis.

One theory proposes that disruptions in the gut microbiota—also known as gut dysbiosis—may lead to low-grade inflammation, increased oxidative stress, cell damage, and compromised blood-brain barrier integrity. The gut microbiome may also affect short-chain fatty acid production, activate microglial cells, and influence alpha-synuclein aggregation. Additionally, it is believed that alpha-synuclein formed in the enteric nervous system can travel to the brain via the vagus nerve and affect the medulla oblongata, thus linking gut health directly to neurodegeneration in PD (Govind, M., 2023).

GENETIC DETERMINANTS OF RISK FOR SPORADIC PD AND THEIR IMPLICATED PATHWAYS

Protein Aggregation

The genes SNCA and tau produce proteins that are integral to the formation of Lewy bodies—abnormal protein clumps commonly found in PD brains. Because of this, Parkinson's disease is often likened to a prion-like disorder (Redenšek, S., 2017, Pandey, S., 2025).

SNCA

After identifying mutations in the SNCA gene as a cause of rare hereditary forms of PD, scientists discovered that its product, alpha-synuclein, is a major component of Lewy bodies. This discovery helped bridge the understanding between monogenic and sporadic PD. Notably, SNCA displays pleiotropy, meaning it influences disease risk in multiple ways. Rare mutations or gene duplications can result in early-onset PD with an autosomal dominant inheritance pattern. Meanwhile, common non-coding variants in the SNCA region are linked to increased risk for sporadic PD.

Initial clues came from the association of the REP1 polymorphism in SNCA's promoter region with PD. Subsequent genome-wide association studies (GWAS) confirmed risk variants extending from intron 4 to regions beyond the 3' untranslated region. SNCA remains one of the most studied genes in PD genetics, with multiple association signals found across diverse populations. Future high-depth sequencing efforts in genetically varied samples are needed to precisely identify all contributing variants (Billingsley, K.J., 2018).

Other Key Genes Involved in PD:

PARK2: Produces the protein parkin, essential for breaking down and recycling cellular proteins.

PARK7: Encodes DJ-1, a protein that defends cells against mitochondrial stress. Mutations are linked to early-onset PD.

PINK1: This gene codes for a kinase that protects mitochondria under stress. Mutations are also associated with early-onset PD.

LRRK2: Produces another protein kinase. Mutations in LRRK2 are a leading genetic cause of late-onset PD (Johns Hopkins Medicine, 2025).

PATHOLOGY

Parkinson's disease (PD) primarily affects dopamine-producing neurons located in the substantia nigra pars compacta. In cases of late-onset idiopathic PD and in dominantly inherited forms, neuronal degeneration is typically accompanied by the presence of Lewy bodies—abnormal protein deposits within neurons. Other brain regions, such as serotonergic neurons in the median raphe, noradrenergic neurons in the locus coeruleus, and cholinergic neurons in the nucleus basalis, are also involved to a lesser extent. As the disease progresses, Lewy bodies begin to appear in the limbic system and cortical association areas.

Clinically, PD manifests as a gradually worsening condition characterized by asymmetric limb stiffness, slow movement (bradykinesia), resting tremors, followed by postural instability and a range of non-motor symptoms, including depression, dementia, sleepiness during the day, and autonomic disturbances.

Interestingly, mutations in the glucocerebrosidase (GBA) gene represent the most prevalent genetic risk factor for PD. Up to 30% of individuals with "sporadic" PD may carry a single copy

of this mutation, depending on the studied population. When both copies of the GBA gene are mutated, it leads to Gaucher's disease—a lysosomal storage disorder. Another common genetic cause of dominantly inherited PD is the G2019S mutation in the LRRK2 gene (leucine-rich repeat kinase 2).

CLINICAL DIAGNOSIS OF PD

Parkinson's disease is a neurodegenerative disorder that falls under the clinical spectrum of Parkinsonism. It is defined by the progressive loss of dopamine neurons in the substantia nigra pars compacta and the development of Lewy bodies within brain cells. Diagnosis is largely based on a patient's clinical history and symptomatology. Key early signs include disturbed sleep, loss of the sense of smell, and constipation.

Other notable clinical indicators include micrographia (smaller handwriting), diminished facial expressiveness, and decreased arm swing on one side of the body. A reduced ability to detect odors is often one of the earliest symptoms. As PD advances, additional signs such as soft speech (hypophonia), excessive drooling due to impaired swallowing, and postural instability may emerge. Non-motor symptoms, especially depression, which affects around 40% of patients, often become more problematic over time. In some adults, asymmetrical tremors may be mistaken for PD, but they may actually have dystonia with no dopaminergic deficiency, as confirmed by imaging. Although PD is mainly diagnosed clinically, neuroimaging like MRI or CT is generally unnecessary unless other conditions, such as vascular parkinsonism or normal pressure hydrocephalus, are suspected.

SPECT imaging using a dopamine transporter (DAT) tracer can help distinguish PD from other disorders such as essential tremor, dystonic tremor, psychogenic parkinsonism, or drug-induced parkinsonism (DIP), all of which typically show normal DAT scans. In PD, dopamine uptake in the basal ganglia is decreased.

TREATMENT APPROACH

DOPAMINERGIC THERAPY

According to the American Academy of Neurology (AAN), drug treatment should begin once a Parkinson's disease (PD) patient starts experiencing functional limitations. Several medications

are available to manage motor symptoms, including levodopa/carbidopa, dopamine agonists (ergot and non-ergot forms), monoamine oxidase-B (MAO-B) inhibitors, injectable apomorphine, catechol-O-methyltransferase (COMT) inhibitors, N-methyl-D-aspartate (NMDA) receptor antagonists, and anticholinergic agents. In more advanced stages, medications can be administered through alternative delivery systems like intestinal infusions, skin patches, or subcutaneous injections. When patients experience persistent motor fluctuations or involuntary movements (dyskinesias), they may be candidates for deep brain stimulation (DBS).

Dopaminergic treatments are particularly effective for symptoms such as bradykinesia (slowness of movement) and muscle rigidity. However, MAO-B inhibitors provide only moderate benefit. Both dopamine agonists and levodopa can help slow disease progression and reduce disability. While tremors often show inconsistent improvement with dopamine therapy, they tend to respond better to anticholinergic drugs like trihexyphenidyl (Öksüz, N., 2022).

MAO-B, COMT INHIBITORS, AND NMDA ANTAGONISTS

MAO-B inhibitors (such as rasagiline and selegiline) and COMT inhibitors (like entacapone) help extend the effects of dopamine by slowing its breakdown. MAO-B inhibitors act by preventing dopamine degradation in the synaptic cleft, while COMT inhibitors stop the premature conversion of levodopa before it reaches the brain, thereby enhancing its availability. Patients with mild symptoms are often started on MAO-B inhibitors due to their relatively gentle side-effect profile and lower dosing frequency, delaying the need for stronger dopaminergic drugs. These inhibitors can also be added later to help manage specific symptoms like tremors and dyskinesias. Unlike levodopa, MAO-B doses generally do not need to be adjusted over time.

To address cognitive issues or hallucinations that may arise in advanced stages, cholinesterase inhibitors like rivastigmine can be beneficial. Meanwhile, NMDA receptor antagonists such as amantadine and memantine serve as adjunctive therapies. These drugs block both NMDA and acetylcholine receptors, thereby supporting dopamine release and mitigating overactive glutamate signaling in the brain, which is associated with dyskinesias. For example, amantadine has been shown to reduce dyskinesia severity by about 60% when combined with levodopa in late-stage PD. The extended-release form of amantadine is currently the only FDA-approved drug specifically for managing levodopa-induced dyskinesias, helping to extend “on” time and

reduce motor complications. However, no current therapies significantly improve symptoms common in advanced stages such as postural instability, difficulty swallowing or speaking, dyskinesias, and constipation. NMDA antagonists may also offer neuroprotective benefits by preventing excitotoxicity and promoting nerve regeneration and growth.

ANTICHOLINERGICS IN EARLY PARKINSON'S DISEASE

Anticholinergic medications were among the first used to treat PD. These drugs work by blocking acetylcholine receptors, aiming to restore the dopamine-acetylcholine balance disrupted by the disease. Although they have mostly been replaced by levodopa and newer dopaminergic drugs, anticholinergics still have a place in treatment, especially for tremor-dominant PD in the early stages. Common agents in this group include benztropine, trihexyphenidyl, diphenhydramine, orphenadrine, biperiden, ethopropazine, and procyclidine. These medications are typically used as monotherapy in early PD or alongside other medications like levodopa. Due to their low concentrations in the bloodstream, limited pharmacokinetic data is available on these agents (Tori K. Lee, T. K., 2020, Ali, M., 2022).

FUTURE ASPECTS

Current Parkinson's disease treatments primarily focus on easing motor symptoms and do not stop the disease from progressing. Addressing this gap by developing disease-modifying therapies remains a key unmet need. Researchers are exploring new molecular targets for this purpose.

On the surgical front, high-frequency DBS and lesion-based procedures are being refined. Upcoming improvements in DBS include better electrode design, smaller and cranial-implanted pulse generators, longer-lasting and rechargeable batteries, and wireless connectivity — all aimed at increasing efficiency and patient comfort.

Efforts to target alpha-synuclein (α-synuclein or αS) include strategies to prevent its aggregation, lower its production, enhance its breakdown, and block its uptake by brain cells. However, one challenge is that the most harmful form of α-synuclein has yet to be clearly identified, limiting the success of these therapies. Despite this, investigational compounds like NPT200-11 and

NPT088 are undergoing clinical trials. In preclinical studies, NPT200-11 has shown promise in reducing α-synuclein buildup and associated neuroinflammation in brain tissue.

CONCLUSION

Parkinson's disease (PD) continues to be a significant treatment challenge due to its progressive and multifaceted nature. While levodopa (L-DOPA) remains a cornerstone in managing early symptoms, its extended use is often linked to complications like motor fluctuations and dyskinesias. The inclusion of NMDA receptor antagonists, such as amantadine, has proven helpful in minimizing these motor issues and boosting the effectiveness of dopaminergic treatments. Although anticholinergic medications are now less commonly used, they still play a role in treating patients with tremor-dominant PD. Drugs like benztropine and trihexyphenidyl remain relevant, especially when tailored to individual patient needs, despite the limited data on their absorption and distribution in the body.

Promising developments in deep brain stimulation (DBS) have significantly improved outcomes for patients unresponsive to medication. New advancements — including miniaturized devices, enhanced electrodes, rechargeable batteries, and wireless systems — are expected to further enhance treatment in the coming years. Simultaneously, research is intensifying on disease-modifying strategies, particularly targeting α-synuclein, a key protein implicated in PD. Although the exact toxic forms of α-synuclein are still under investigation, early experimental drugs like NPT200-11 and NPT088 have shown encouraging results in reducing its harmful effects and related inflammation in animal models. These innovations offer the potential to slow or stop the disease's progression, rather than simply easing its symptoms.

In conclusion, while current therapies have greatly enhanced the quality of life for PD patients, the future lies in discovering treatments that can alter the disease course itself. A combination of novel drugs, surgical innovations, and deeper biological insights will be essential in moving toward this goal. Continued research efforts, personalized care, and teamwork across medical disciplines are critical for shaping the next generation of Parkinson's treatment and offering renewed hope for patients.

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