IJPPR
INTERNATIONAL JOURNAL OF PHARMACY & PHARMACEUTICAL RESEARCH
An official Publication of Human Journals
ISSN 2349-7203
HUMAN

Human Journals
**Review Article**
June 2023 Vol.:27, Issue:3


# Parkinson's Disease: A Systematic Review of Neurodegenerative Disease and Its Management

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ISSN 2349-7203
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**Submitted:** 22 May 2023
**Accepted:** 29 May 2023
**Published:** 30 June 2023

**Keywords:** Motor Dysfunction, Dopaminergic Neuron, synuclein, Supranuclear Atrophy, Neurodegeneration

**ABSTRACT**

Parkinson's disease (PD) is a neurodegenerative disorder that affects many people. While a variety of non-motor manifestations may occur, the typical clinical characteristics include a mobility disorder characterized by dyskinesia, resting tremor, and rigidity, with spasticity developing later. The cause of Parkinson's disease is unknown, but several genetic risk factors and several genes that cause rare familial forms of the disease have now been identified. Environmental factors such as tobacco smoke, coffee intake, and exposure to toxic substances have been proposed to alter the risk of Parkinson's disease development, while their function remains unknown. The movement problem is caused by the death of dopaminergic neurons in the substantia nigra pars compacta, with intracellular aggregation of -synuclein in the form of Lewy bodies and Lewy neurites being the pathogenic hallmark. Sleep difficulties are widespread in Parkinson's disease (PD), as reported by nearly two-thirds of PD patients. They are characterized clinically as disorders of the beginning and continuation of sleep, hypnagogic hallucinations, and severe daytime drowsiness SDD. DIMS is caused by degenerative changes in the CNS that affect sleep regulation centers, the persistence of daytime PD-related symptoms into the night, concurrent mental health disease, instability of circadian rhythms, and the effects of signal transduction pathways (and other) medication on circadian rhythm. This review gives detailed information about the manifestations and clinical approaches in treating PD and also focuses on the preferential signs and symptoms associated with the incurring stage of the disease.

## INTRODUCTION

Parkinson's disease (PD) is a prevalent neurodegenerative condition (a synucleinopathy) with a Western European prevalence of 4% of the community above the age of 80. With an older population, the management of Parkinson's disease is anticipated to become an increasingly essential and complex element of neurology and general medical treatment. The finding of many gene mutations that may shed insight into the processes of pathogenesis in sporadic cases of Parkinson's disease has increased our understanding of the disease's pathogenesis over the last decade.[1]

PD is pathologically defined by the loss of Nigro - striatal innervation, while neurodegeneration does not only affect nigral dopaminergic neurons but also cells in other areas of the neural network. Because of its broad pathology, Parkinson's disease is an extremely heterogeneous disorder, and no accurate diagnostic test is currently available. Today, diagnosis is dependent on clinical symptoms, with the existence of either of the following symptomatic features required for a diagnosis: resting tremor, bradykinesia, stiffness, and/or postural instability. Clinical criteria, on the other hand, can only lead to a diagnosis of probable Parkinson's disease (PD), whereas histological evaluation, with the detection of -synuclein-containing Lewy bodies (LBs) or Lewy neurites, is required for a conclusive diagnosis. Therapy is primarily symptomatic, with medications trying to either restore dopamine levels in the striatum or to act on striatal post-synaptic dopamine receptors. Nevertheless, because dopamine is not the sole neurotransmitter implicated in Parkinson's disease, a variety of different medications are being utilized to treat particular symptoms such as sadness or dementia. Yet, more research on innovative medicines to slow the rate of neurotoxicity or even to rebuild the dopaminergic cells is ongoing, including some in the early phases of clinical trials. As we learn more about the pathophysiology of Parkinson's disease and therapeutic targets, the possibilities for the advancement of disease-modifying medicines grow.

After Alzheimer's disease (AD), Parkinson's disease (PD) is the second-most common neurological illness (1), with an incidence of roughly 0.5-1% among those aged 65-69, rising to 1-3% among those aged 80 and older.[2-3]

With an aging population, the frequency and rate of Parkinson's disease are anticipated to rise by nearly 30% by 2030.[4] PD symptoms primarily involve somatomotor pathway defects (i.e., rigidity, bradykinesia, postural instability, gait dysfunction, and tremors)[4]. At its heart,

Parkinson's disease (PD) is characterized by progressive degradation of the nigrostriatal dopaminergic system, with significant loss of substantia nigra pars compacta (SNpc) neurons and dopamine depletion (DA).[6-7]Sleep and associated issues such as modest tremors, soft speech, structural difficulty, deficits in normal facial expressions, restricted limb mobility, attention loss, general exhaustion, and depression may appear early.[8]

## CLINICAL MANIFESTATIONS

Parkinson's disease manifests itself through both motor and non-Motor symptoms are the hallmarks of Parkinson's disease. Hoehn and Yahir's 1967 article looked at 183 Parkinson's patients and described these.

Stationary restlessness, bradykinesia, postural instability, and rigidity are examples. Tremor is a common symptom of Parkinson's disease, which is usually unilateral. Initially, the tremor is often noticed in one extremity (occasionally only one finger or the thumb). The tremor is slower (4-6 Hz) than a typical essential tremor (8-10 Hz) and is most noticeable when the limb is in a resting position (the phrase "resting tremor" is rather deceptive, as total relaxation typically eliminates the tremor). It gets suffocated by movement. Although less often, the skull, jaws, and tongues may be affected.[9]

Bradykinesia is characterized by slowed motion and the minimization of intricate motor activities. The amount of spontaneous movement is reduced. This is exemplified by Parkinson's disease's "masked facies" (also known as hypomimia). The blink rate slows and the eyes widen, giving the impression of staring. When the facial muscles move less, the face appears less emotional. As the problem worsens, the mouth frequently remains slightly open. Speech softens and becomes monotone, with words running together. Sialorrhea is caused by a reduction in spontaneous swallowing and an alteration in swallowing mechanics. Sialorrhea in Parkinson's disease is caused by an inability to handle saliva rather than an increase in saliva production.[10]Parkinson's disease is markedly variable in terms of onset age, clinical manifestations, rate of development, and therapy response. There have been several clinical subtypes proposed. Furthermore, the discovery of genetically specified forms of the disease, which can differ from one another. Several clinical factors, including sporadic forms, have challenged the unitarian perspective of Parkinson's disease and introduced a biological definition of sub-entities within the Parkinson's disease spectrum. Empirical analyses of specific clinical symptoms or the more empirical and assumption methodology of clustering by hierarchy and other forms of cognitive computing have been utilized in approaches to

subtyping Parkinson's disease.[11-12.]Age at onset (early vs late onset), prevailing motor phenotype (tremor-dominant vs non-tremor cases), motor comorbidity in response to levodopa treatment, nonmotor features (particularly neurogenic dysfunction, cognitive dysfunction, and REM sleep behavior disorder [RBD]), and rate of progression have all been used for subtyping with either approach.[13]

## EARLY PROGRESSIVE DIAGNOSIS

There is widespread agreement that the process and lead to clinically diagnosed Parkinson's disease begins considerably earlier than current diagnostic criteria can capture. To far, no indicators have been identified that would allow a high sensitivity and specificity identification of any of these hypothetical phases of pre-diagnostic Parkinson's disease. This is especially problematic when it comes to the prognosis of people who have one or more characteristics linked to a higher likelihood of developing clinically defined Parkinson's disease, such as a family history of the disorder or asymptomatic concept is adopted for disease-associated mutations, as well as non-motor features of prodromal Parkinson's disease like hyposmia or RBD.[14-15]

RBD is unique among clinical indications of Parkinson's disease risk in that more than 90% of people with isolated RBD acquire neurodegenerative parkinsonism—most often Parkinson's disease or Parkinson's disease dementia.[16]

## DIAGNOSIS OF PARKINSON'S DISEASE

Parkinson's disease is often diagnosed based on clinical symptoms, history, and assessment, as well as the reactivity to dopamine drugs and the development of motor fluctuations over time. A resting tremor, a faint voice (hypophonia), veiled facies (originally recognized as a lowered blink rate), small writing (micrographia), stiffness (rigidity), and slowness of motions (bradykinesia) are indicative motor symptoms of the disorder shuffling steps and trouble with equilibrium. The UK PDS Brain Bank Criteria are the most widely adopted clinical requirements for the diagnosis of Parkinson's disease.[17]

**Table.1 Clinical indicators of atypical Parkinsonism**

| ***Multiple system atrophy*** | ***Progressive supranuclear*** | ***Palsy Corticobasal degenerations*** |
|---|---|---|
| • Poor response to levodopa<br>• Severe & early autonomic failure<br>• Orthostatic hypotension,<br>• Erectile dysfunction,<br>• Nocturnal stridor<br>• Early marked dysarthria<br>• Rapid disease progression<br>• Early postural instability<br>• Babinski sign or other pyramidal signs<br>• Cerebellar signs<br>• Jerky postural hand tremor<br>• Disproportionate antecollis | • Square wave jerks<br>• Levator inhibition<br>• Blepharospasm<br>• Pseudobulbar crying<br>• Early dysarthria and dysphagia<br>• Early postural instability and falls<br>• Early progressive gait freezing<br>• Early marked frontal dementia<br>• Akinetic rigid parkinsonism with poor levodopa response<br>• Slowing of vertical saccades<br>• Supranuclear downgaze palsy (often not present in the first year of onset) | • Levadopa-resistant unilateral akinetic parkinsonism<br>• Cortical sensory loss (ie, agraphesthesia, astereognosia with intact primary sensory modalities)<br>• Limb apraxia, alien limb phenomenon<br>• Focal arm myoclonus or dystonia<br>• Early cognitive impairment with frontal signs and language problems (ie, progressive, non-fluent aphasia)<br>• Early postural instability and falls |

**Table 2. Major Symptoms observed during Initial PD**

| | |
|---|---|
| ***Nonmotor symptoms*** | ❖ Neuropsychiatric features<br>❖ Apathy.<br>❖ Anxiety, and panic attacks.<br>❖ Mood disorders, especially depression.<br>❖ Hallucinations, illusions, delusions.<br>❖ Cognitive deterioration, ranging from mild impairment to dementia. |
| ***Dysautonomia*** | ❖ Orthostatic hypotension.<br>❖ Constipation.<br>❖ Urinary dysfunction (urgency, retention).<br>❖ Sexual dysfunction.<br>❖ Excessive sweating.<br>❖ Seborrhoea.<br>❖ Sialorrhea (i.e., drooling, also attributable to decreased swallowing movements) |
| ***Sleep disorders*** | ❖ Insomnia.<br>❖ Rapid eye movement (REM) behavior disorder.<br>❖ Restless legs syndrome.<br>❖ Periodic limb movements in sleep.<br>❖ Excessive daytime sleepiness. |
| ***Sensory impairment*** | ❖ Hyposmia (i.e., loss of sense of smell).<br>❖ Decreased visual contrast and color discrimination.<br>❖ Decreased visual motion perception.<br>❖ Abnormal sensations, such as paresthesias (i.e., tingling).<br>❖ Pain.<br>❖ Fatigue |
| ***Orofacial manifestations*** | ❖ Dental Caries and Periodontal Disease.<br>❖ Sialorrhea and Drooling.<br>❖ Xerostomia.<br>❖ Burning Mouth Syndrome.<br>❖ Mastication Disorders.<br>❖ Bruxism.<br>❖ Subjective Taste Impairment.<br>❖ “Masklike” facial appearance with infrequent blinking and lack of expression is caused by bradykinesia. |

## METAL RELATIONSHIP IN PARKINSON'S DISEASE

Some metals having neurotoxic properties have been linked to secondary Parkinsonism. Manganese was considered to be one of the main elements linked to Parkinsonism.[18] In truth,

mercury, copper, and other metals can be liberated from metal body implants such as implants in the mouth, phagocyted by blood macrophages, and carried into the brain. Furthermore, mercury vapor does not require transit through macrophages because it can quickly cross the blood-brain barrier (BBB).[19-20] Metal debris accumulates in the brain after apoptosis and can be picked up by brain macrophages such as neuronal glial cells and neuro-melanocytes. In this regard, it is worth noting that neuro-melanocytes in the substantia nigra are one of the cell types implicated in dopamine synthesis.[21-22] Metals' role in Parkinson's disease pathogenesis remains a major topic in neurotoxicology and medicinal chemistry. Metallic toxicants or the depletion of critical metals for human health play this role[23-27]. Iron deficiency, for example, may develop PD with restless legs syndrome when it occurs as an abnormality of either the peripheral or central nervous systems, as it contributes to a drop-in brain dopamine and 5-HT. Iron accumulation within the basal ganglia and midbrain deep grey matter nuclei was also linked to PD development.[28]

Cigarette smoking enhances the resorption of radon daughters, Pb210 and Bi210, which are causal causes of Parkinson's disease[29]. Actually, there is some evidence of a link between persistent lead exposure and Parkinson's disease [30], which is frequently related to chemical toxicants or occupational medicine [31].

Neuro-melanocytes are cerebral macrophages that can accumulate harmful metal oxides. As a result, metal debris ingestion may damage the survival of neuro-melanocytes and, consequently, dopamine synthesis.[32]

**Toxicity with a synergistic effect**

Metals can make other metals and insecticides more hazardous. When combination exposures of iron-copper, lead-copper, and lead-iron were compared to the effects of single metals, synergistic effects between metals and PD were seen [32-34]. When mercury is coupled with other metals such as lead, aluminium, manganese, cadmium, and zinc, it demonstrates synergistic effects, worsening mercury toxicity even at low and benign amounts [35-36]. Chemicals and metals were discovered to have synergistic effects when combined in animal and cell experiments [37-39]. When a mercury solution that kills 1 in 100 rats (LD1Hg) is coupled with a lead solution that also kills 1 in 100 rats (LD1Pb), all of the rats die (LD100Hg+Pb)[40]. Another animal experiment involving When modest amounts of mercury, lead, and manganese were mixed in rats, synergistic effects were observed [41].

In an in vitro investigation, mercury coupled with safe amounts of aluminum hydroxide or the antibiotic neomycin dramatically enhanced neuronal death [42-43]. Zinc significantly enhanced mercury toxicity by increasing cytotoxicity and inhibiting tubulin [44-46]. Interestingly, a PD-associated protein known as DJ-1 protects cells from toxic stressors and can bind both mercury and lead[47]. DJ-1 protein genetic variations have no protective effects against mercury exposure and thus increase the risk of Parkinson's disease [48-49].

**Metal Exposure's Effect on Dopaminergic Neurons**

Parkinson's disease is distinguished by a large and specific loss of neurons that produce dopamine in the substantia nigra of the brain that begins prior to the onset of symptoms. Oxidative damage contributes to the degradation of dopaminergic neurons [50]. Prior to this, glutathione depletion in the substantia nigra occurs, which is the earliest biochemical consequence identified [51]. This loss is thought to play a critical role in Parkinson's disease, with a 40–90% drop in glutathione found in the substantia nigra as the disease progresses [52-54]. Glutathione deficiency is associated with disease severity and dopaminergic neuron degeneration [55]. Elevated lipid peroxidation and reduced mitochondrial efficiency are also detected in PD patients' substantia nigra and other parts of the PD brain, indicating oxidative stress.

Dopaminergic neurons in the Substantia nigra have lengthy axons with microtubules made up of tubulin molecules [56]. Very low concentrations of inorganic mercury block tubulin production but not other ATP- or GTP-binding proteins [57-58]. Tubulin has at least 14 groups made up of sulfhydryl (SH-), and mercury has a strong affinity for sulfhydryl. As a result, it is hypothesised that mercury could have a role in tubulin functional loss and the creation of neurofibrillary tangles. The effect of wild-type -synuclein on the dividing of microtubules and tubulin dimers, on the other hand, demonstrated that Parkinson's disease-linked mutants lack this capability [59]. Other metals, such as aluminium, iron, lead, and zinc, are unable to prevent tubulin binding to GTP [60-61]. Aluminum, iron, and zinc levels in the substantia nigra of Parkinson's disease patients were higher than in controls. Iron build up in the substantia nigra of Parkinson's disease patients was double that of controls [62-66].

This was validated in additional research. Thus, large quantities of trivalent iron were discovered in Lewy bodies and dopaminergic neurons in the substantia nigra of Parkinson's disease patients. In adult rats, unilateral injection of Fe (III) chloride into the substantia nigra

resulted in a 95% drop in striatal dopamine and impairment of dopamine-related behavioural responses, showing that iron may trigger the loss of dopaminergic neurons in Parkinson's disease [67]. The uptake of 11C-nomifensine, a potential ligand for the evaluation of monoamine re-uptake sites at presynaptic dopaminergic terminals, was reduced within the striatum following subcutaneous injections of manganese oxide, indicating that manganese exposure may also result in dopaminergic neuron loss[68-69].Metals with a high affinity for sulfhydryl groups, such as Hg, Cd, Cu, and Zn, reduced the number of D2 dopamine receptor sites. Low amounts of Hg (1 mM) were able to totally destroy D2 dopamine receptors, whereas 3 mM copper or cadmium only induced a 40-60% drop in dopamine receptors[70]. Mercury affects brain regions that are unable to metabolize mercury[71-73]. Inorganic mercury, even at low levels, induces neurotoxicity within moments of exposure. Inorganic mercury at very low levels destroys intracellular microtubules and causes axon degeneration. This catastrophic neurodegeneration cascade is unique to mercury and has not been observed in other metals such as aluminum, cadmium, lead, or manganese [74]. Mercury depletes glutathione and affects mitochondrial activity [75-78].

**Table.3 There are parallels between the effects of mercury (Hg) exposure/ingestion and the repercussions of Parkinson's disease**

| Mercury Exposure/Ingestion | Parkinson's Disease |
|---|---|
| ***Loss of dopamine receptors*** | *Significant dopaminergic neuron loss happens prior to the beginning of Parkinson's disease symptoms.* |
| ***Tubulin degeneration*** | *Tubulin degeneration, high tubulin concentration in dopaminergic neurons* |
| ***Axon degeneration*** | *Degeneration of axons* |
| ***Glutathione depletion*** | *The earliest biochemical process in the substantia nigra appears to be a core event.* |
| ***Glutamate increased*** | *Dopaminergic neurons are lost as glutamate levels rise.* |
| ***Amyloid-ß increased*** | *Increased amyloid-ß increases aggregation of -synuclein* |
| ***Tau phosphorylation*** | *Tau phosphorylation is a critical defect that causes -synuclein aggregation.* |
| ***Mitochondrial dysfunction*** | *Mitochondrial dysfunction appears to play a major role* |
| ***Glutathione susceptibility*** | *Increased risk of PD, earlier onset of PD* |
| ***APOEe4 susceptibility*** | *Increased risk of Parkinson's disease (PD), Parkinson's disease with dementia (PDD), earlier beginning of PD, and earlier onset of psychosis in PD* |

**Management and Treatment of PD**

**Levodopa-Carbidopa**:. Dopamine cannot pass the blood-brain barrier by itself. The amino acid levodopa is metabolized to create dopamine, which accommodates the dopamine shortage present in Parkinson's disease. Small dosages of mixed carbidopa-levodopa are administered twice or three times daily with meals in the form of a 25/100 mg half tablet. Nausea, dizziness, and somnolence are frequent side effects.

**Dopamine Agonists:** These medicines directly activate dopamine receptors. Bromocriptine is an ergot derivative, whereas ropinirole and pramipexole are non-ergot derivatives. Pramipexole is dosed at 0.125 mg three times per day, whilst ropinirole is dosed at 0.25 mg three times each day.

**Catechol-O-methyltransferase (COMT) inhibitors:** Entacapone inhibits peripheral COMT, an enzyme involved in the breakdown of dopamine. It aids in the reduction of levodopa breakdown, increasing the drug's accessibility to the brain. Entacapone is dosed at 200mg with each levodopa dose, and up to eight doses can be given per day, whereas tolcapone is dosed at 100 mg three times per day.

**Monoamine Oxidase (MAO) Inhibitors:** Drugs such as selegiline and rasagiline inhibit dopamine metabolism by inhibiting the enzyme monoamine oxidase. Selegiline's daily dose is 5 mg, which is commonly taken in the morning to avoid sleeplessness. Rasagiline can be started at 0.5 mg once day and subsequently raised to 1 mg once daily.

**Amantadine:** It works by inhibiting the N-methyl-D-aspartate and acetylcholine receptors. It is available as 100 mg immediate-release pills or capsules that are used twice or three times daily.

**Anticholinergic drugs:** Acetylcholine receptors are blocked by benztropine and trihexyphenidyl. They may be beneficial in the treatment of tremors and stiffness. Trihexyphenidyl is often used in doses of 0.5 to 1 mg two times day, progressively increasing to 2 mg three times daily. The recommended benztropine dosage is 0.5 to 2 mg twice day[79].

**Surgery:** Deep brain stimulation is rarely used to treat Parkinson's disease. This entails transmitting electrical impulses to certain areas of the brain (typically the SN or the globus pallidus, which engages with the SN) using a neurostimulator device, as well as a brain

implant called as a 'brain pacemaker. 'DBS is typically used to target the area of the subthalamic nucleus (STN). Along with the operation, activation of the dorsolateral STN boundary can boost its efficiency[79].

**Gene Therapy:** The scientific development of PD gene treatments has made significant progress in the last decade. The widespread loss of dopaminergic neurons is followed by a drop in the levels of amino acid aromatics decarboxylase (AADC), the enzyme that converts L-dopa to dopamine. Following promising preclinical results, adeno-associated viral vectors containing human AADC genes were recently delivered to putamina neurons and the subthalamic nucleus of Parkinson's disease patients. This instrument can control sufficient amounts of dopamine production by taking proper dosages of levodopa. Another gene therapy target in Parkinson's disease is glutamic acid decarboxylase (GAD), which promotes GABA synthesis in the subthalamic nucleus of GABA-ergic neurons.[80]

## CONCLUSION/DISCUSSION

Parkinson's disease is a long-lasting, progressively neurological illness that causes both motor and non-motor symptoms. The majority of the reason is still unknown. Despite there is no cure, there are several treatment options available, including medication and surgery. Although Parkinson's disease is not lethal on its own, the consequences can be severe. Non-motor symptoms appear in Parkinson's disease long before motor symptoms, and the existence of non-motor symptoms early allows for early identification and treatment of PD, leading to improved patient quality of life and substantial cost savings in treatment. Parkinson's disease is a diverse illness with both fast and slowly advancing types. Treatment includes both pharmacologic (usually levodopa formulations taken with or without additional drugs) and nonpharmacologic (such as exercise and biological, occupational, and cognitive therapies). Deep brain stimulation and therapy with levodopa-carbidopa enteral administration can benefit people with drug-resistant tremors, symptoms that increase after the medicine wears off, and dyskinesias. Multiple epidemiological investigations have found substantial links between Parkinson's disease and metal exposure, with numerous putative mechanisms of action revealed. While numerous metals may contribute to the pathophysiology of Parkinson's disease, mercury appears to be the most hazardous element. Mercury is cytotoxic in all chemical forms and appears to play a role in the progression of Parkinson's disease. There are several parallels between the effects of mercury exposure/ingestion and the symptoms/consequences of Parkinson's disease. Specific neuronal

alterations and neurodegenerative consequences associated with Parkinson's disease are only seen in the presence of mercury at the lowest doses. Because of their high tubulin concentration and enhanced glutamate toxicity, nigral dopaminergic neurons are particularly vulnerable to mercury.

**ACKNOWLEDGEMENT:** I would like to express my gratitude to my co-authors and the Department of Pharmacy (I.P.S.R, Unnao), who guided me throughout this project. I would also like to thank my friends and family who supported me and offered deep insight into the study.

**CONFLICTS OF INTEREST**: No conflicts of interest were raised by any of the authors in reference to the publication/investigation.

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