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# Nano-technology Used in the Diagnosis and Treatment of Parkinson Disease

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**ABSTRACT:** Parkinson's disease is a common movement disorder encountered in neurology, but diagnosing and managing it can be quite challenging. The diagnosis relies primarily on clinical evaluation, which can be difficult due to the wide range of motor and non-motor symptoms experienced by patients. Medical management of Parkinson's disease is complicated because there are limited drug options, with levodopa being the primary treatment. However, many patients develop levodopa-induced dyskinesia (LID) as a side effect. This condition typically arises after prolonged use of levodopa, but in some cases, it can occur after only a few days or months of treatment. For patients who cannot be effectively managed with medication alone, various surgical options, such as unilateral pallidotomy and deep brain stimulation, have shown promising results.

**Key Words:** CRISPR/Cas9, Dopaminergic pathways, Gallium nanoparticles, Neurodegenerative, Neuroglia, Parkinson's, Deep brain stimulation, Levodopa, Levodopa-Carbidopa intestinal gel, Non-motor symptoms, alpha synuclein. Blood brain Barrier, Solid Lipid nanoparticle,

**Key Message:**

This review examines the epidemiological features, pathophysiology, genetics, pathology, and clinicoradiological presentations of patients with Parkinson's disease (PD). Additionally, it explores the therapeutic options available for treating this progressive disorder. Parkinson's disease is a chronic neurodegenerative condition characterized by the early and significant loss of dopaminergic neurons in the substantia nigra pars compacta (SNpc) and the widespread presence of alpha-synuclein (aSyn), an intracellular protein.

**Abbreviation Used :**

Parkinson's disease (PD) is a progressive, multi-system neurodegenerative disorder that primarily affects individuals in their later years. It is the second most common neurodegenerative disease worldwide, with its incidence and prevalence increasing due to changing population demographics (Pringsheim et al., 2014). In industrialized countries, the prevalence of PD is generally estimated at about 0.3% of the overall population, rising to approximately 1% among people over 60 years of age (De Lau and Breteler, 2006). The prevalence of PD increases with advancing age for both men and women and continues to rise even at older ages (De Rijk et al., 1997). In Europe, the prevalence among individuals aged 85 to 89 has been reported at 3.5% (Clarke and Moore, 2007). The disease is characterized by distinct neuropathological changes in the brain. Notably, it involves the formation of abnormal proteinaceous spherical structures known as Lewy bodies, as well as spindle- or thread-like Lewy neurites that may branch out in the cell bodies of affected nerve cells. These changes begin at specific induction sites and progress in a predictable pattern throughout the nervous system (Braak et al., 2004).

## I. INTRODUCTION

Every year, a significant portion of the population is affected by various neurological diseases, such as Alzheimer's disease, Parkinson's disease (PD), glioblastoma, and different types of strokes. The number of cases is steadily increasing worldwide, which can be attributed to rapidly changing lifestyles, environmental factors, and genetic predispositions. Neurological disorders primarily involve issues related to the neurons and the nervous system, with Parkinson's disease being particularly prevalent. Parkinson's disease is a progressive neurodegenerative disorder characterized by tremors, bradykinesia (slowness of movement), rigidity, and postural instability, primarily affecting the motor system. This disease significantly impacts the quality of life. PD primarily results from the degeneration of dopamine-producing neurons in the substantia nigra, a crucial part of the brain responsible for

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movement control. As dopamine levels decline, communication between neurons is disrupted, leading to the hallmark motor symptoms of PD. In addition to these motor symptoms, there are non-motor symptoms that contribute to the disease burden. These include cognitive decline, mood disorders, and autonomic dysfunction. Consequently, there is a pressing need for accurate diagnosis and treatment of Parkinson's disease. Currently, medical practitioners focus on managing symptoms rather than finding a cure. Various treatment options are available for PD, including pharmacological and non-pharmacological therapies, surgical interventions, and emerging experimental approaches.

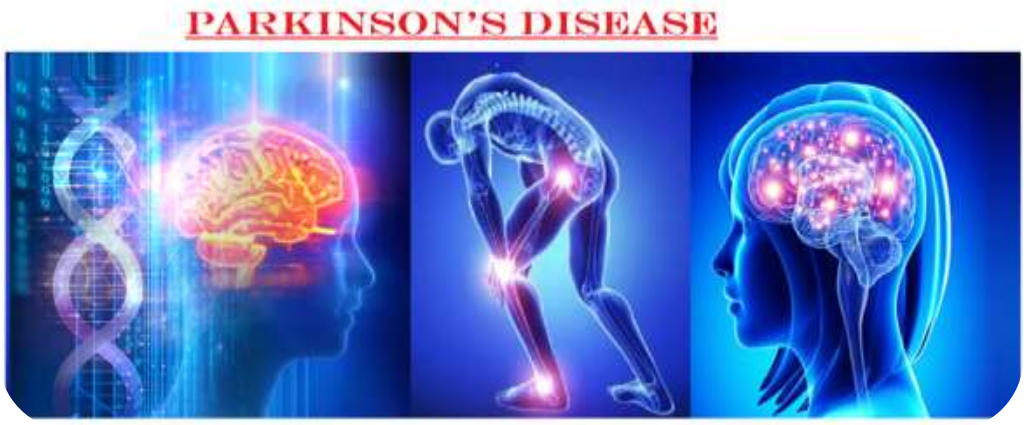


**Figure 1:** Shows the Intro Of PD

Levodopa is the most commonly used pharmacological treatment for Parkinson's disease (PD). It serves as a precursor to dopamine and is often combined with carbidopa to enhance its effectiveness and minimize side effects. In addition to levodopa, there are other pharmacological options such as dopamine agonists, monoamine oxidase B (MAO-B) inhibitors, and catechol-O-methyltransferase (COMT) inhibitors, all of which work to enhance or mimic dopamine activity in the brain. Surgical treatments include deep brain stimulation (DBS) and lesioning surgery. DBS is particularly beneficial for advanced PD patients who do not respond adequately to medication. However, despite these traditional treatments, patients may still experience fluctuating symptoms, medication side effects, and disease progression. This highlights the need for novel therapeutic strategies that address the limitations of conventional treatments. Several emerging techniques for treating PD include gene therapy, nanomedicine, stem cell therapy, and neuroprotective agents. While many of these techniques are still in the experimental phase and require clinical trials and further evaluation, nanotechnology-based nanomedicines are gaining significant attention among researchers for their potential in diagnosing and treating PD.

Nanomedicine, which applies nanotechnology and nanoparticles (NPs) in medicine, offers promising avenues for managing PD. By creating nanoparticles with controlled sizes, it becomes possible to deliver drugs more effectively and accurately target affected areas in the brain. NPs are materials whose sizes range from 1 to 100 nm. Due to their small size and high surface area-to-volume ratio, nanoparticles can easily traverse biological barriers, such as the blood-brain barrier.These blood-brain barriers (BBBs) traditionally limit the effectiveness of various treatments for neurological disorders. However, nanoparticles (NPs) can be easily modified on their surfaces with a range of organic compounds, ligands, and other agents to achieve target specificity, thereby enhancing their efficacy. Additionally, certain NPs can act as nanocarriers, transporting drugs intended for Parkinson's disease (PD) on their surfaces, which facilitates controlled and prolonged release of therapeutic agents. This targeted drug delivery should improve therapeutic bio availability and reduce side effects, potentially revolutionizing PD management. Recent theragnostic applications of Nano medicinal for PD include the development of various nanocarrier systems such as Liposomes, Nanogels, Dendrimers, and solid lipid nanoparticles (SLNs).

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All of these systems can encapsulate therapeutic agents for PD, shielding them from enzymatic degradation and ensuring their delivery to the target site. Furthermore, nanomedicine offers opportunities for neuroprotective strategies by utilizing antioxidant and anti-inflammatory NPs to protect and repair damaged neurons. Another promising approach for PD treatment is gene therapy (GT). GT utilizes NPs as carriers for delivering genes that could correct or alleviate the underlying causes of PD. Additionally, integrating CRISPR/Cas9 technology with nanotechnology can address the root causes of neurodegeneration in PD. These combined approaches significantly advance the search for more effective and targeted therapies. Research advancements in nanomedicine-based strategies hold the promise of improving symptom management and patient outcomes, potentially slowing the progression of PD. The future of PD treatment depends on successfully translating nanomedicine from laboratory research to clinical practice, paving the way for a new era in neurological care. In this review article, the authors emphasize the basics of Parkinson's disease, its pathophysiology, and currently available treatment methods. They highlight the drawbacks of existing medications for Parkinson's disease and focus on the role of nanotechnology, nanoparticles, and nanomedicine in its treatment. The authors also discuss emerging techniques such as gene therapy and CRISPR/Cas9 for potential PD treatment. Finally, they emphasize the possible integration of nanoparticles with other innovative technologies for the symptomatic management of PD, which will pave the way for advanced technology and a new era in PD neurological care.

**Sing And Symptoms Of Parkinson Disesase :**
**Main Symptoms -**
**Parkinson's disease is characterized by four primary symptoms:**
1. Tremors: Involuntary shaking in the hands, arms, legs, jaw, or head.
2. Muscle Stiffness:Muscles remain contracted for extended periods.
3. Slowness of Movement: Reduced speed in initiating and completing movements.
**4.** Impaired Balance and Coordination:This can lead to difficulty maintaining stability and may result in falls.

**Other Possible Symptoms :-**
- Depression
- Emotional changes
- Difficulty with swallowing, chewing, and speaking
- Urinary problems and constipation
- Skin issues

**Motor Symptoms:**
- Masked facial expressions (hypomimia)
- Decreased blinking
- Speech issues, such as a monotone voice or soft-spoken delivery
- Difficulty swallowing (dysphagia)
- Drooling
- Eye problems, including blurred vision,abnormal eye movements,
- Inability to open the eyes at will
- Small, cramped handwriting (micrographia)
- Involuntary muscle contractions causing repetitive or twisting movements (dystonia)
- Stooped posture
- Walking difficulties, such as shuffling, freezing, short quick steps, and a hunched posture

**Non-Movement Symptoms:**
- Anxiety, Apathy
- Bladder issues and incontinence
- Breathing and respiratory difficulties
- Cognitive changes
- Constipation and nausea
- Dementia
- Depression, Fatigue
- Hallucinations or delusions
- Loss of smell, Pain
- Skeletal and bone health concerns
- Skin changes, Sleep disorders
- Issues with speech and swallowing
- Vertigo, dizziness, and low blood pressure
- Vision changes

This information aims to provide a comprehensive understanding of the symptoms associated with Parkinson's disease.

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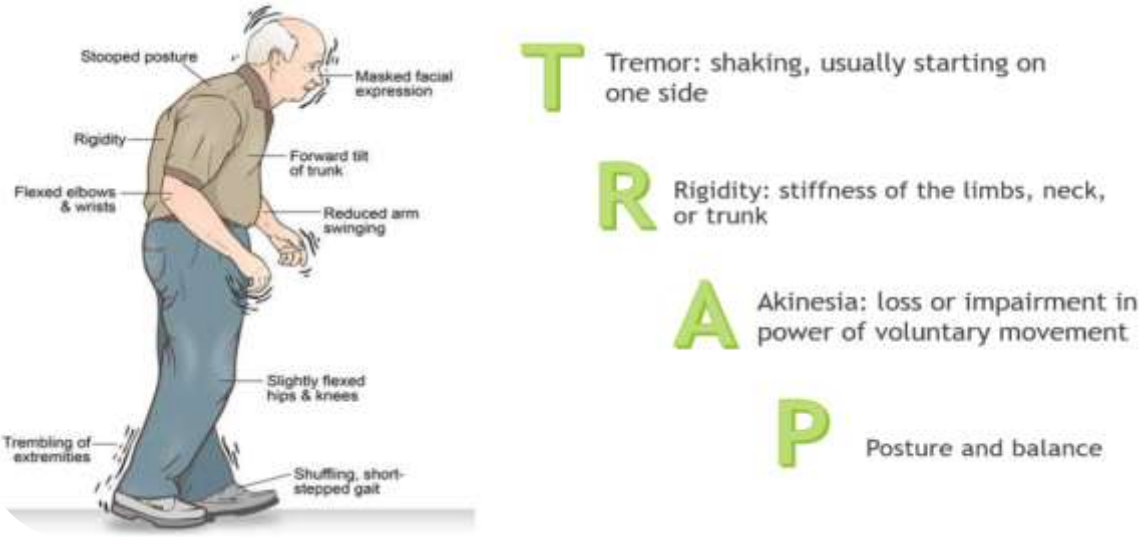


**Figure 2 :**Shows the Sing & Symptoms of PD's

**What Are the Causes of Parkinson's Disease :**

1. Genetic factors
2. Environmental factors
3. Excersice
4. Caffeine consumption
5. Environmental-Genetic factors

**1. Genetic factors :**

Traditionally, Parkinson's disease has been considered a non-genetic disorder. However, around 15% of individuals with PD have a first-degree relative who has the disease.[8] At least 5–15% of cases are known to occur because of a mutation in one of several specific genes, transmitted in either an autosomal-dominant or autosomal-recessive pattern.[9]Mutations in specific genes have been conclusively shown to cause PD. A large number of these genes are linked to translation.[10][11] Genes which have been implicated in autosomal-dominant PD include PARK1 and PARK4, PARK5, PARK8, PARK11 and GIGYF2 and PARK13 which code for alpha-synuclein (SNCA), UCHL1, leucine-rich repeat kinase 2 (LRRK2 or dardarin) (LRRK2 and Htra2 respectively[9][12] Genes such as PARK2, PARK6, PARK7 and PARK9 which code for parkin (PRKN), PTEN-induced putative kinase 1 (PINK1), DJ-1 and ATP13A2 respectively have been implicated in the development of Autosomal-recessive PD[9][13][14] Furthermore, mutations in genes including those that code for SNCA, LRRK2and glucocerebrosidase (GBA) have been found to be risk factors for sporadic PD[15] In most cases, people with these mutations will develop PD.

**2. Environmental Factors :**

Exposure to pesticides, metals, solvents, and other toxicants has been studied as a factor in the development of Parkinson's disease.[7] No definitive causal relationship has yet been established. Recent studies also reveal that individuals that sustain mild head injuries (concussions) also have an increased risk of acquiring the disease.[42][43] As discussed below, exercise and caffeine consumption are known to help decrease the risks of acquisition.

**3. Excersice :**

While many environmental factors may exacerbate Parkinson's disease, exercise is considered to be one of the main protective factors for neurodegenerative disorders, including Parkinson's disease. The types of exercise interventions that have been studied can be categorized as either aerobic or goal-based.[47] Aerobic exercise includes physical activity that increases the heart rate. Aerobic exercise is beneficial to the overall brain through mechanisms that promote neuroplasticity, or the rewiring of the brain circuitry.[47] Goal-based exercises are often developed with the guidance of a physical therapist to use movement to improve motor task performance and enhance motor learning.[47] While exercise has consistently been shown to be beneficial, the optimal interventional benefit is still being researched.[48]

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**4. Caffeine consumption :**

Smokers and nonsmokers with different rates of caffeine consumption were monitored for their susceptibility to PD. The results indicate that higher coffee/caffeine intake is associated with a significantly lower incidence of PD and that this effect appeared to be independent of smoking.[49]

**5. Dietary Factors :**

Emerging research suggests that diet may influence the risk of developing Parkinson's. A 2023 study found that adherence to a Western dietary pattern—characterized by high consumption of red and processed meats, fried foods, high-fat dairy products, and refined grains—is associated with an increased risk of Parkinson's.[50] Individuals with the highest adherence to this dietary pattern had significantly higher odds—approximately seven times—of developing the disease. Conversely, diets rich in fruits, vegetables, whole grains, and lean proteins have been associated with a reduced risk of Parkinson's, potentially offering protective benefits. Further research is needed to establish causality and better understand the mechanisms underlying these associations.

**6. Environmental-Genetic factors :**

- **Polymorphism of CYP2D6 gene and pesticide exposure -**

The CYP2D6 gene is primarily expressed in the liver and is responsible for the enzyme cytochrome P450 2D6. A study showed that those who had a mutation of this gene and were exposed to pesticides were twice as likely to develop Parkinson's Disease; those that had the mutation and were not exposed to pesticides were not found to be at an increased risk of developing PD; the pesticides only had a "modest effect" for those without the mutation of the gene.[31][51]

**Pathophysiology of Parkinson's Disease -**

**1.1 Mechanism of Neurodegeneration -**

Parkinson's disease (PD) is caused by the progressive degeneration of dopaminergic nerve cells in the substantia nigra, a part of the brain essential for controlling movement. As these neurons die, dopamine levels decline rapidly, disrupting the balance between motor and non-motor functions. Additionally, the presence of Lewy bodies, which are abnormal aggregates of the protein alpha-synuclein, contributes to neuronal dysfunction and the clinical symptoms of the disease. A critical aspect of understanding PD lies in elucidating the neurodegenerative process. Although the exact cause of neuronal death in PD is unclear, it is believed to result from a complex interplay of genetic, environmental, and mitochondrial factors. Several key pathways contribute to neurodegeneration in PD, including oxidative stress (OS), mitochondrial failure, and neuroinflammation. Oxidative stress is a common phenomenon in the brains of individuals with PD, resulting from an imbalance between the production of harmful chemicals known as reactive oxygen species (ROS) and the brain's ability to neutralize them. Increased oxidative stress damages cellular components—such as lipids, proteins, and DNA—leading to neuronal dysfunction and death. This issue is exacerbated by mitochondrial dysfunction, which impairs energy production and increases ROS generation. Neuroinflammation is characterized by the activation of microglia and the release of pro-inflammatory Cytokines. These cytokines play a crucial role in the neurodegenerative process, contributing to neuronal injury and cell death.

**1.2 Role of alpha-synuclein -**

A small soluble protein (alpha-nuclein) is present in the brain in large amounts, mainly at the presynaptic terminals, and is expected to plays an important role in synaptic function and neurotransmitter release (37). Various pieces of literature have found that alpha-synuclein undergoes pathological aggregation in PD, forming insoluble fibrils. These insoluble fibrils accumulate as Lewy bodies and Lewy neurites within the nerve cells. The aggregation of such fibrils disrupts cellular function and contributes to neuronal death through several phenomena (38, 39).Moreover, these proteins may misfold, further impair proteasomal and autophagic pathways. As a result, there will be an accumulation of damaged proteins and organelles. The synaptic function of the alpha-synuclein could also be disrupted by interfering with vesicle trafficking and the release of the neurotransmitter. Besides this, alpha-synuclein aggregates can spread from cell to cell, which may propagate pathology throughout the brain in a prion-like fashion. The presence of these aggregates is a hallmark of PD and is closely associated with the progression and symptomatology of the disease (38).

**1.3 Dopaminergic pathways -**

The dopaminergic pathways, particularly the nigrostriatal pathway, play a crucial role in the motor symptoms of Parkinson's disease (PD). These pathways consist of dopaminergic neurons

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that project from the substantia nigra pars compacta to the striatum, a brain region involved in coordinating movement. When these neurons are lost, dopamine levels in the striatum significantly decrease. This reduction disrupts the balance of excitatory and inhibitory signals needed for smooth and controlled movements. Dopamine is essential for modulating the activity of the basal ganglia, a group of nuclei integral to motor control. A depletion of dopamine in PD leads to overactivity of the indirect pathway and underactivity of the direct pathway within the basal ganglia circuitry. This imbalance results in increased inhibitory output to the thalamus and motor cortex, causing characteristic motor symptoms of PD such as bradykinesia (slowness of movement), rigidity, and tremors. The degeneration of dopaminergic neurons not only affects motor symptoms but also has consequences for non-motor functions. Dopaminergic pathways are involved in regulating mood, cognition, and autonomic functions. This explains the wide range of non-motor symptoms observed in PD patients, which may include autonomic dysfunction, depression, anxiety, and cognitive impairment. In conclusion, the pathophysiology of PD involves the complex interplay of neurodegeneration, the pathological role of alpha-synuclein, and the disruption of dopaminergic pathways. Understanding these processes is essential for developing effective therapeutic strategies aimed at slowing or halting the progression of PD and improving the quality of life for patients. Figure 1 illustrates the pathophysiology of Parkinson's disease.

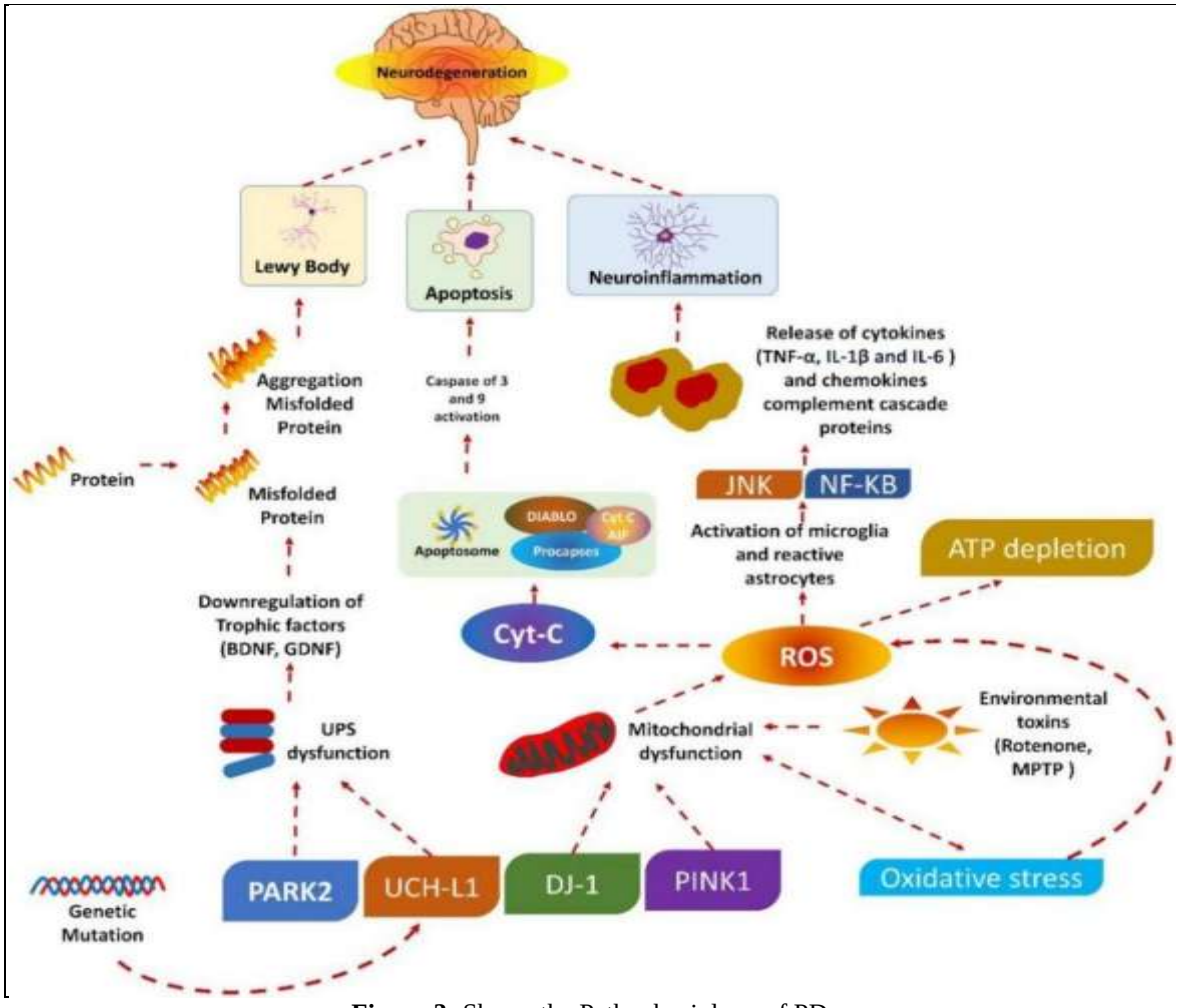


**Figure 3 :**Shows the Pathophysiology of PD

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| Gene | Mechanism of action | Dominant/recessive | References |
|---|---|---|---|
| *SNCA* | Engaged in protein degradation, membrane contacts, dopamine regulation, synaptic vesicle supply, autophagy, and mitochondrial dysfunction | Autosomal dominant PD | (192) |
| *PARK7* | Mutations in the DJ-1 gene cause gene expression loss. The animal models showed that the DJ-1 gene may be a neuroprotective redox sensor | Autosomal recessive familial PD | (193) |
| *PINK1* | Controls mitophagy, which eliminates damaged mitochondria. When mitochondria lose electrical charge, PINK1 activates and phosphorylates ubiquitin at serine 65. A thorough analysis of the mechanisms reveals Parkin's high-affinity binding, which phosphorylates *hPINK1* at Ser65 in the N-terminal ubiquitin-like region. This activates E3 ligase, ubiquitylating the outer mitochondrial membrane substrate. Neuronal damage sources are unknown | Early onset recessive familial PD | (194) |
| *LRRK2* | PD mutations modify the kinase and GTPase activities. It enhances the process of adding phosphate groups to substrates and to itself through self-phosphorylation. The connection between neuronal injury is uncertain | Late-onset autosomal dominant familial PD | (195) |
| *PRKN* | Encodes RBR E3 ubiquitin-protein ligases. When this activity is lost due to mutation, it leads to the build-up of protein, mitophagy, and dysfunction in the mitochondria. The *PRKN* gene is named based on the consistent and predictable phenotypic outcomes it produces | Autosomal recessive juvenile PD (AR-JP) | (196) |

**Table 1**: A summarized presentation of various genes involved in PD& their respective mechanisms of actionis given in.

**Diagnosis Stratergy For Parkinson's Disesase :-**

Diagnosis of Parkinson disease requires obtaining history regarding prodromal symptoms, family history, and current concerns. Examination must show the core features of bradykinesia and rigidity and/or tremor, but other examination features such as the presence of orthostatic hypotension can also be helpful. Once history and physical examination features of parkinsonism are confirmed, the clinician excludes features potentially indicative of atypical parkinsonism ("red-flag symptoms") and assesses the patient response to levodopa (or potentially other dopaminergic medications) to confirm Parkinson disease.

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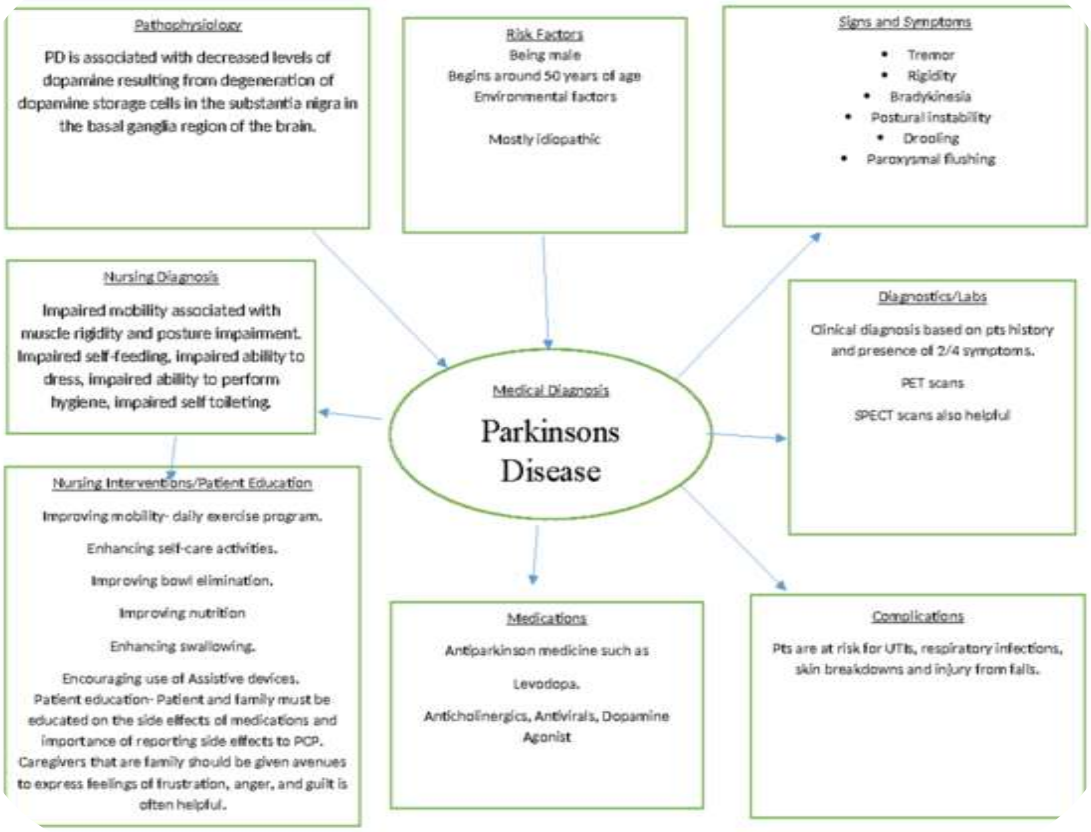


**Figure 1:** Shows the Diagnosis Stratergis for Parkonson Disease

**Current treatment approaches for the Parkinson Diseases -**

Traditional approaches, such as pharmacological, non-pharmacological, andsurgical, and some emerging treatment techniques, GT, stem cell therapy, neuroprotective agents, and nanomedicine, exist for treating PD (44). Figure1,2 shows the broader categories of treatment options for PD, while , show various existing treatment strategies for PD.

**Figure 1**.Treatment options for PD adapted from Church (190).

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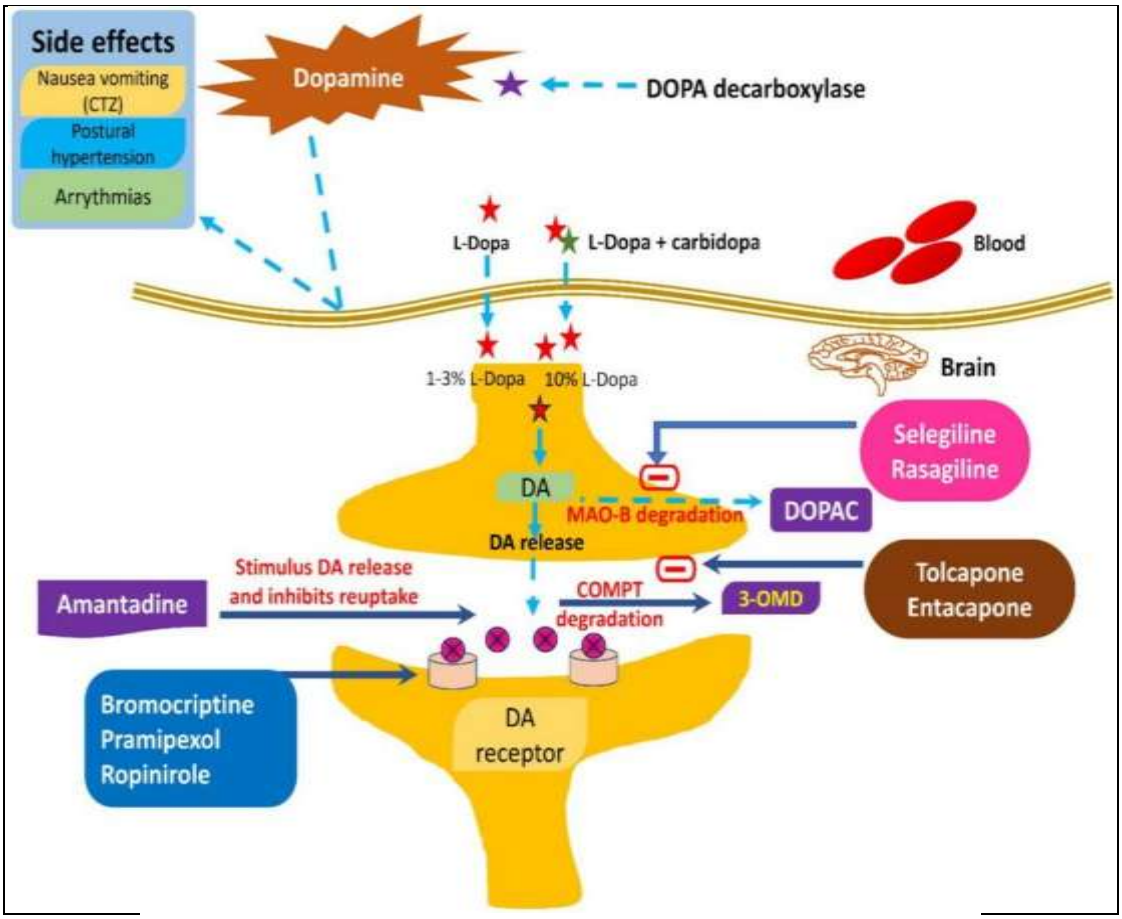


**Figure 2:** Current therapeutic management of PD along with their side effects.

**Pharmacological treatments of Parkinson Disease -**

Pharmacological treatments for Parkinson's Disease (PD) include levodopa, carbidopa, dopamine agonists, MAO-B inhibitors, COMT inhibitors, anticholinergics, and amantadine. Levodopa is a highly effective and widely used medication for PD. It acts as a precursor to dopamine, allowing it to cross the blood-brain barrier (BBB), where it is converted into dopamine within the brain. Carbidopa is often administered alongside levodopa to prevent its early conversion to dopamine outside the central nervous system. This combination helps reduce side effects such as nausea and increases the amount of levodopa that reaches the brain. Commonly used dopamine agonists include pramipexole, ropinirole, and rotigotine. These medications mimic dopamine's effects by directly activating dopamine receptors in the brain. They can be used alone or in combination with levodopa to help reduce fluctuations in motor control. Selegiline and rasagiline are both MAO-B inhibitors. MAO-B is an enzyme that degrades dopamine in the brain, so inhibiting it can lead to increased dopamine levels and improved motor symptoms. Entacapone and tolcapone are COMT inhibitors that block the enzyme catechol-O-methyltransferase, which breaks down levodopa. These inhibitors are used with levodopa to extend its effects and diminish "off" periods where symptoms may exacerbate. Benztropine and trihexyphenidyl are anticholinergics that help manage tremors and rigidity by reducing acetylcholine activity, a neurotransmitter that can become overactive in PD due to dopamine loss. Amantadine, although primarily an antiviral drug, also alleviates certain PD symptoms, particularly dyskinesia (involuntary movements) associated with long-term levodopa use. Current evidence suggests that dopamine prodrugs and levodopa do not effectively alleviate the degeneration of dopamine neurons. Furthermore, these medical treatments often result in side effects such as arrhythmia, gastrointestinal discomfort, and extreme emotional changes. To date, no drugs have been proven to delay or stop

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the progression of PD, despite neuroprotective testing. Additionally, there are no effective biomarkers for PD, and the presence of secondary effects like hallucinations and delusions exacerbates the challenge of diagnosis and treatment. The resistance of the BBB also complicates treatment options. Overall, various pharmacological treatment for PD are illustrated in Table 2

**TABLE**

**Pharmacologic options for treating the motor symptoms of Parkinson's disease**

| | Class | Agent | Usage | Adverse effects[17] |
|---|---|---|---|---|
| First line | Dopamine precursor | Carbidopa/levodopa | Monotherapy to treat bradykinesia, postural instability, and rigidity | Orthostatic hypotension, dizziness, headache, depression, dyskinesia |
| Second line | Dopamine agonist | Pramipexole, ropinirole | Monotherapy or adjunct to levodopa to treat bradykinesia, postural instability, and rigidity | Orthostatic hypotension, drowsiness, dizziness, insomnia, abnormal dreams, nausea, constipation |
| | | Bromocriptine | Due to adverse effects and monitoring (baseline and annual ESR, renal function, and chest x-ray[16]) required, this drug is indicated only if the patient has failed all other pharmacologic therapy | *Contraindications*: uncontrolled HTN, syncopal migraines<br>*Adverse effects*: dizziness, nausea, hypoglycemia, pulmonary fibrosis, somnolence, hallucinations, rhinitis |
| | Monoamine oxidase B inhibitors | Selegiline | Off-label use as monotherapy. Adjunctive therapy in patients with decreasing response to carbidopa/levodopa | Headache, dizziness, insomnia, nausea, hypotension |
| | | Rasagiline | Monotherapy or adjunct to carbidopa/levodopa to treat bradykinesia, postural instability, and rigidity | Orthostatic hypotension, headache, dizziness, rash, nausea |
| | | Safinamide | Approved March 2017 as adjunctive therapy to reduce off time | Orthostatic hypotension, hypertension, falls, increased ALT and AST, nausea |
| Third line | Antiviral | Amantadine | Monotherapy or adjunctive therapy to treat dyskinesia. Should not be drug of first choice, according to NICE recommendations[16] | Orthostatic hypotension, syncope, peripheral edema. Avoid use 2 weeks before and 2 weeks after live influenza vaccine |

ALT, alanine aminotransferase; AST, aspartate aminotransferase; ESR, erythrocyte sedimentation rate; HTN, hypertension; NICE, The National Institute for Health and Care Excellence.

**Table 2 :** Common pharmacological drugs for treating symptoms of PD

Table.3 shows the classification of Dopamine Agonists, which are classified into two main classes: ergot-derived and non-ergot-derived. Among the ergot-derived dopamine agonists, bromocriptine, marketed as Parlodel, is administered orally. Cabergoline and lisuride are oral drugs in this category, though their market names are not specified. Pergolide, known as Permax, is another ergot-derived agent available in oral form (55, 56).

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| Drug Classification | Drug Name |
|---|---|
| **Dopamine-Replacement** | Sinemet (Levodopa and carbidopa) |
| | Entacapone (Comtan) |
| | Stalevo |
| **Dopamine Agonist** | Mirapex and Requip |
| | Apokyn |
| **Other Medications** | Amantadine |
| | Selegiline (L-deprenyl) |
| | Artane and Cogentin |

**Table 3 :** Classification of Dopamine Agonist

The pharmacological management of PD aims to enhance motor function by increasing dopamine levels. Additionally, there are limited treatments for non-motor symptoms, which can be significantly debilitating. Few treatments can impede or alter the progression of the disease. Levodopa and dopamine agonists are commonly utilized drugs for PD, although they may induce adverse consequences. Each patient's treatment plan is personalized based on their symptoms, side effects, and requirements (43).

**Non-pharmacological treatments of Parkinson Disease -**

The non-pharmacological treatments for Parkinson's diseases (PDs) encompass various approaches, including physical therapy, occupational therapy, speech therapy, nutritional therapy, and exercise. Physical therapy aims to enhance mobility, balance, and strength through exercises, gait training, and the use of assistive devices. Occupational therapy assists patients in maintaining their independence by improving their ability to perform daily activities and recommending adaptive strategies and equipment. Speech therapy addresses challenges related to communication and swallowing. It offers exercises to improve articulation, volume, and speech clarity, as well as techniques for managing dysphagia (difficulty swallowing). Nutritional therapy focuses on providing proper nutrition to help manage symptoms and promote overall health. Consulting with a trained dietitian can be beneficial for optimizing food choices, ensuring adequate nutrient intake, and managing gastrointestinal symptoms. Exercise plays a crucial role in improving motor symptoms, balance, and overall well-being. This may involve regular physical activities such as aerobic exercises, strength training, and flexibility exercises. Kalbe et al. recently emphasized the importance of non-pharmacological interventions in managing Parkinson's disease. These therapies are considered supportive or "add-on" strategies designed primarily to alleviate motor symptoms. Physiotherapy, speech-language therapy, and occupational therapy have emerged as essential components of comprehensive PD management. Furthermore, non-pharmacological interventions such as cognitive training, cognitive-behavioral therapy, and art or light therapy, once thought to be unconventional, are now being integrated into therapeutic guidelines. Several advancements have been made in this field, including (i) the expansion of intervention types, (ii) the standardization of intervention protocols, (iii) the development of digital intervention forms, (iv) scientific evaluations of intervention feasibility and effects, (v) a better understanding of the mechanisms behind therapy-induced plasticity, (vi) the integration of non-pharmacological interventions into patient care concepts, and (vii) a shift from solely symptomatic treatments to preventive approaches. Figure 6 summarizes the various non-pharmacological treatments for Parkinson's diseases.

**Surgical treatment of Parkinson Disease -**

Parkinson's disease (PD) can also be treated with surgical therapies, primarily deep brain stimulation (DBS) and lesioning surgery. DBS is a surgical procedure where electrodes are implanted into the subthalamic nucleus or the globus pallidus internus in the brain. These electrodes are connected to a pulse generator that is placed in the thoracic cavity. The pulse generator sends electrical impulses to the brain to help regulate abnormal brain activity. In lesioning surgery techniques, such

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as pallidotomy and thalamotomy, a small lesion is created in targeted areas of the brain to disrupt abnormal brain activity. DBS is generally preferred over lesioning surgery among the available surgical options. Sharma et al. reviewed both DBS and lesioning techniques for PD, discussing the indications, selection processes, and management strategies involved. The authors recommended that a multidisciplinary team make decisions regarding surgical treatment for PD, considering the patient's clinical characteristics, treatment effectiveness, ease of use, associated risks, and overall quality of life. While DBS remains the most favored surgical technique, there is increasing interest in new approaches, such as MR-guided focused ultrasound. Recently, Foltynie et al. presented the latest evidence supporting optimal PD treatment. These investigators outlined an expert approach to various aspects of treatment choice with a still-developing evidence base. They suggested treatment strategies for different stages of PD. For example, the initial treatment should involve a comprehensive discussion about the diagnosis, available treatment options, and how to maintain the patient's independence and quality of life based on their specific symptoms. Some patients may not experience sufficient relief from symptoms with initial treatments. If specific symptoms persist, it may be necessary to explore other treatment options. Continuous dopaminergic therapy or electrical stimulation aims to navigate the narrow therapeutic window between providing symptom relief and managing peak-dose dyskinesia, which can occur during the advanced stages of PD. Non-motor symptoms, such as mood disturbances, sleep issues, and pain, can significantly impact quality of life and may be more challenging to manage than motor symptoms. These non-motor symptoms are often linked to low dopamine levels and require careful management.

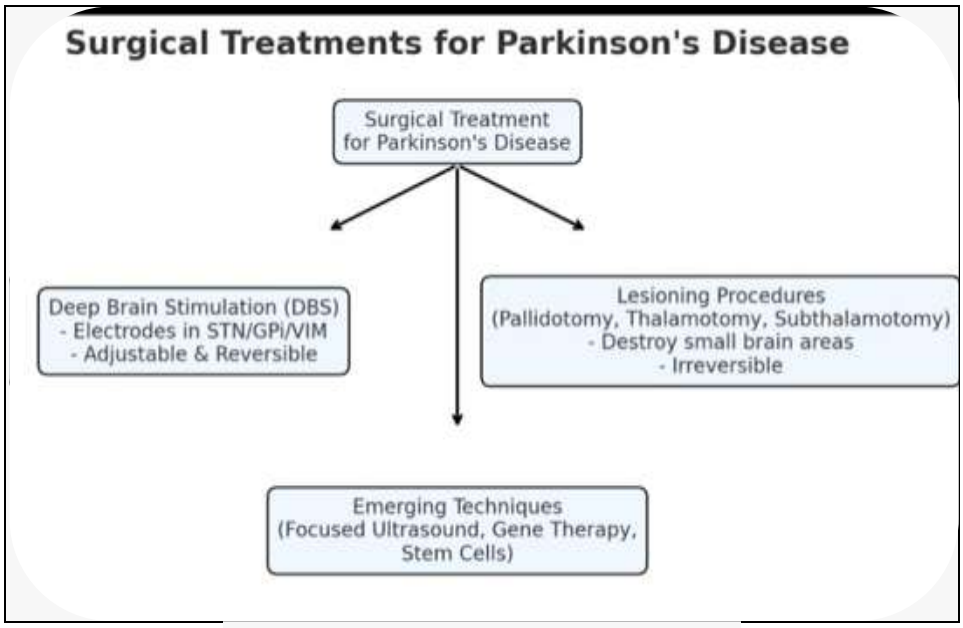


**Figure 4:** Shows the Surgical Treatment For PD

**Emerging and experimental approaches for the treatment of PDs -**

Emerging and experimental approaches for treating Parkinson's disease (PD) include gene therapy (GT), stem cell therapy, neuroprotective agents, and nanomedicine. Research has demonstrated that in GT, genetic material is introduced into the brain to correct or modify the underlying genetic causes of PD. Several early-stage clinical trials are exploring the use of viral vectors to deliver genes that may either enhance dopamine production or protect nerve cells. Stem cell therapy is a relatively new area of research, focusing on the potential to replace lost dopaminergic neurons in the brain. However, these approaches remain in experimental stages. Similarly, neuroprotective agents are still in their infancy, with ongoing investigations aimed at formulating drugs that can help protect neurons from degeneration. These neuroprotective agents include antioxidants, anti-inflammatory drugs, and agents that target mitochondrial function.

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Nanomedicine, another innovative technique, is still in its early stages but shows great promise for treating PD. By leveraging nanotechnology, it may enhance drug delivery and targeting, potentially increasing the efficacy of current treatment methods while reducing side effects. Various nanocarriers, such as liposomes and nanoparticles, have been studied for their ability to cross the blood-brain barrier (BBB) and deliver therapeutic agents directly to affected brain regions. Conversely, research by Yuan et al. has investigated the neurotoxic effects of silica nanoparticles (SiO2 NPs), particularly in relation to promoting PD-like pathology in both in vitro and in vivo studies. This suggests a potential connection between exposure to SiO2 NPs and the initiation and progression of PD. While these emerging approaches offer hope, it is important to recognize their limitations. Acknowledging these challenges is essential for understanding the current landscape of PD treatment. Some of the complications associated with existing treatment methods are summarized belowin Table 3.

| Therapy/drug | Drug name | Brand name | Biological limitations | Complications | References |
|---|---|---|---|---|---|
| Dopamine (DA) | Carbidopa/levodopa | Sinemet IR, Sinemet CR, Rytary, Duopa Inbrija | Characterized by hydrophilicity, Inability to traverse the BBB, limited plasma half-life, and low bioavailability | Nausea, dyskinesia, drowsiness | (197, 198) |
| Dopamine agonist | Apomorphine<br>Pramipexole<br>Ropinirole<br>Rotigotine | Apokyn, Kynmobi<br>Mirapex, Mirapex ER<br>Requip, Requip XL<br>Neupro | Poor pharmacokinetic profile and inadequate BAV | Sedation, visual hallucinations, euphoria, psychosis, delirium | (76, 77, 199) |
| Amantadine | | Gocovri | Primarily really cleared. Close monitor kidney impairment and avoid it in severe cases | Decreased concentration, fatigue, euphoria, psychosis | (75) |
| COMT inhibitors (entacapone) | Opicapone<br>Entacapone<br>Carbidopa, levodopa, and entacapone<br>Tolcapone | Ongentys<br>Comtan<br>Stalevo<br>Tasmar | Poor pharmacokinetic profile, inability to cross the BBB, and poor BAV | Psychosis, abnormal disturbances, agitation | (78, 199) |
| L-dopa | | Sinemet® Madopar | Short half-life, insufficient pharmacokinetic profile, and BAV (less than 1% can penetrate the brain milieu) | Depression, visual hallucinations, hypomania, abnormal sleep and dreams, psychosis, cognitive impairment | (79, 80) |
| MAO-B inhibitors (selegiline) | Selegiline<br>Rasagiline<br>Safinamide | Elderpryl, Zelapar<br>Azilect<br>Xadago | Poor pharmacokinetic profile, inability to cross the BBB, and poor BAV | Psychosis, abnormal sleep, agitation | (81, 82) |
| Anticholinergics | Trihexyphenidyl | Cogentin | No direct action on the dopaminergic system; their effects are limited to acetylcholine (muscarinic) receptors | Constipation, urinary retention, hallucinations, drowsiness, tachycardia, confusion, blurred vision, dementia, cognitive deficits, and related symptoms | (200–203) |
| | Benzhexol (trihexyphenidyl) benztropine mesylate | Cogentin | Limited efficacy over time | Agitation, insomnia, delirium, anxiety, psychosis, visual hallucinations | (83) |
| Adenosine A2A receptor antagonist | | Nourianz<br>Istradefylline | Eliminated only through hepatic metabolism. Monitor closely in situations of hepatic impairment and avoid severe instances | Insomnia, nausea, dizziness, constipation, hallucination, and dyskinesia | (204) |

**Table 3**. Biological limitations and complications associated with the current treatment approaches for PD.

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**Nanoparticles for the Treatment of Parkinson Disease :**

NPs offer a promising approach to treating PD due to their small size. Besides this, the NPs could be easily engineered for specific targeting and the potential to improve drug bioavailability and efficacy (84). The NPs could be of various shapes, sizes, and origins, i.e., metallic or organic, solid or liquid, and carbon-based. The widely used NPs for treating PDs are lipid-based NPs, polymeric NPs, metal NPs, and carbon-based NPs, described below in detail. NMs hold substantial promise for progressing diagnostics in PD through three vital strategies (85, 86). Firstly, NMs offer the potential for governing crucial biomarkers such as α-synuclein, a protein associated with PD pathology (87). By preparing nanoscale tools and sensors, the detection and quantification of α-synuclein levels can be improved, assisting early diagnosis and disease monitoring. Secondly, NMs enable the monitoring of active dopamine neurons, providing beneficial insights into the status of dopaminergic neurotransmission, which is central to PD. NMs are efficient carriers for delivering therapeutic agents to specific target regions in the brain. The current NMs demonstrate effectiveness by addressing dopamine deficiency, caspase-3 activation, α-synuclein accumulation, OS, mitochondrial dysfunction, inflammation, and growth factor supplementation (88). The findings indicate a broad spectrum of potential approaches for Parkinson's disease therapy (89). Generally, NPs can be classified as inorganic, organic, or carbon-based NPs (Figure 7).

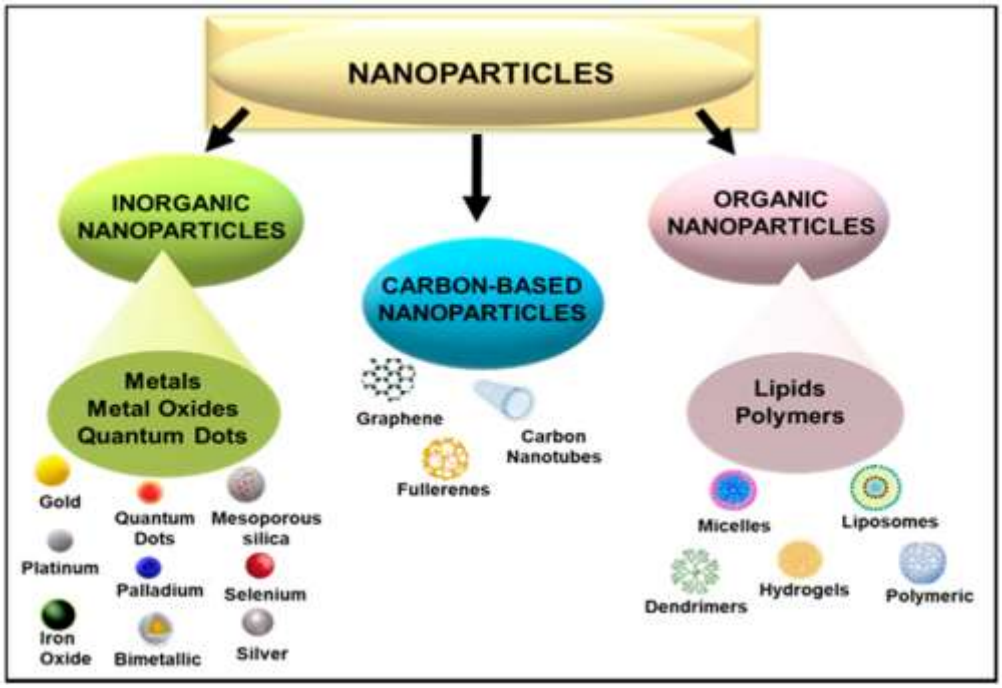


**Figure 5 :**Major Classes of Nanoparticle used as Nanomedicine

**1. Lipid-based Nanoparticles :**

**Lipid-based nanoparticles** are very small spherical particles composed of lipids. They are a novel pharmaceutical drug delivery system (part of nanoparticle drug delivery), and a novel pharmaceutical formulation.[1][2] There are many subclasses of lipid-based nanoparticles such as: lipid nanoparticles (LNPs), solid lipid nanoparticles (SLNs), and nanostructured lipid carriers (NLCs).A lipid nanoparticle is typically spherical with an average diameter between 10 and 1000 nanometers. LNPs are made up of phospholipids, cholesterols, ionizable lipids, and polyethylene glycol-derived lipids (PEGylated lipids).[1] Each of these components play a key role in LNPs used for mRNA vaccines that target SARS-CoV-2 (the virus that causes COVID-19). The ionizable cationic lipids bind to mRNA, PEGylated lipids stabilize LNPs, and phospholipids and cholesterol give LNPs their structure.[6] Because of rapid clearance by the immune system of the positively charged lipid, neutral ionizable amino lipids were developed. A novel squaramide lipid (a partially aromatic four-

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membered ring that can participate in pi–pi interactions) has been used as part of the delivery system use.

Lipid-based NPs mainly comprise liposomes and SLNs, which are commonly investigated for treating PD. Such NPs encapsulate hydrophilic and hydrophobic drugs, protect them from degradation, and enhance their delivery across the BBB (90). Liposomes are spherical vesicles made up of lipid bilayers and are particularly advantageous due to their biocompatible nature and ability to fuse with cell membranes (Figure 8). The fusion of the liposomes with the cell membrane facilitates the release of the drug directly into the target cells. SLNs are made up of solid lipids, which offer a stable alternative to liposomes and can be applied for the effective delivery of lipophilic drugs effectively (91).

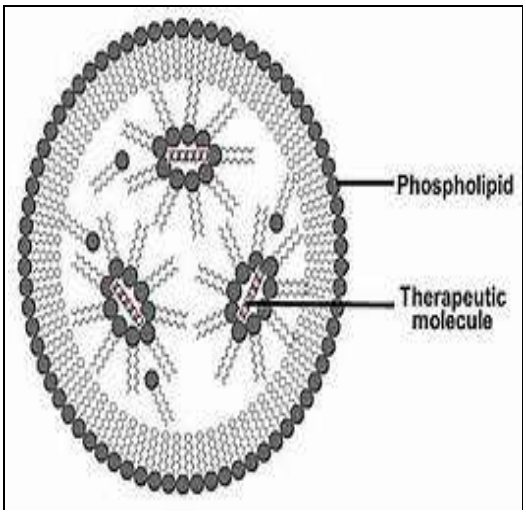


**Figure 6 :**A schematic diagram of LNP exhibiting the outer Phospholipid layer and the encapsulated therapeutics produced from Jagran et al. (145) with permission

**2. Metallic Nanoparticles :**

Metallic nanoparticles (NPs), such as silver (Ag), gold (Au), zinc (Zn), platinum (Pt), and iron (Fe), play a crucial role in treating Parkinson's disease (PD) due to their small size and unique optical and electronic properties. These features allow NPs to be exploited for both therapeutic and diagnostic purposes in PD. Among the various metallic NPs used in treatment, gold nanoparticles (AuNPs) and silver nanoparticles (AgNPs) are particularly noteworthy. For example, AuNPs can be functionalized with drugs or targeting molecules, making them effective for targeted drug delivery or as contrast agents for imaging. In addition, these metallic NPs can modulate the activity of enzymes involved in oxidative stress (OS), which is a key pathological feature of PD, providing neuroprotective effects. Noble NPs like gold and silver have gained substantial attention due to their high stability, easy synthesis methods, and convenient surface functionalization. Both AuNPs and AgNPs have shown promise in inhibiting the aggregation of extracellular and intracellular protein aggregates in neurodegenerative disorders. They can act as stabilizers by selectively attaching to specific areas of protein molecules, thereby preventing protein misfolding, which leads to abnormal structures and harmful clusters. Moreover, these noble NPs can function as "seeds" for protein aggregation. By mimicking the protein's original form, they attract misfolded proteins and assist in their attachment to the NP surface. This isolation process reduces the proteins' potential to combine and form larger aggregates. Both AuNPs and AgNPs also exhibit exceptional catalytic capabilities.

They can facilitate the breakdown of misfolded proteins through catalytic mechanisms, such as the generation of reactive oxygen species (ROS) or activating cellular enzymes responsible for protein degradation. Additionally, both types of NPs can eliminate ROS, which significantly contribute to neuronal damage through neuroinflammation. By reducing ROS levels, these NPs may alleviate brain inflammation caused by oxidative stress. Literature indicates that noble NPs may also impede the synthesis and release of pro-inflammatory cytokines like interleukin-1β (IL-1β), tumor necrosis factor-alpha (TNF-α), and IL-6, all of which play a significant role in neuroinflammation. Thus, NPs have the potential to decrease the inflammatory cascade in the brain by inhibiting these cytokines. Furthermore, AuNPs and AgNPs are involved in regulating the nuclear factor kappa B (NF-κB) pathway, a crucial transcription factor that activates many pro-inflammatory genes. By disrupting the NF-κB signaling pathway, these NPs inhibit the production of inflammatory mediators. Additionally, these composites can carry plasmid DNA (pDNA) and selectively target specific cell types. Au NPs have been shown to enter cells via endocytosis, helping to protect PC12 cells and dopaminergic neurons from death. In in vivo PD models, Au NPs effectively penetrate the blood-brain barrier (BBB) and accumulate in the brains of mice. Overall, AuNP composites exhibit favorable therapeutic effects in both in vitro and in vivo models of PD. Notably, treatment with AuNPs at a concentration

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of 20 nm and a dosage of 2.5 mg/L successfully reversed the symptoms of induced PD without causing any harmful effects.

**3. Polymeric Nanoparticles :**

Polymeric nanoparticles (NPs) are organic compounds made from biocompatible and biodegradable polymers such as polylactic acid (PLA) and polyglycolic acid (PGA). These polymeric NPs play a significant role in treating Parkinson's disease (PD). One major advantage of using these NPs for PD treatment is their ability to release drugs in a controlled and sustained manner. This feature reduces the frequency of dosing, making it easier for patients to adhere to their treatment plans. Polymeric NPs dissolve within the body, allowing the encapsulated drug to be released over a predetermined period. Additionally, these NPs can be functionalized with targeting ligands to enhance their specificity for dopaminergic neurons. Various studies have explored the administration of exogenous dopamine (DA) and L-dopa into the central nervous system (CNS) to supplement reduced levels of endogenous DA and counteract the loss of dopaminergic neurons. Advanced polymeric nanoparticle formulations hold potential for improving PD symptoms by delivering DA directly to the brain. Arisoy et al. developed a nanoparticle system using PLGA and WGA to deliver L-dopa through the nasal route, allowing the drug to reach the brain directly and bypass the blood-brain barrier (BBB). This method demonstrated better drug delivery to the brain with fewer side effects compared to traditional oral or nasal methods, as evidenced by tests on mice with PD. The NP system maintained a high drug retention rate of 73% and released L-dopa over 9 hours, indicating its effectiveness and safety in the nasal cavity. However, this delivery method may pose challenges for patients with nasal conditions such as sinusitis or rhinitis, which could affect its efficacy.

Ragusa et al. successfully synthesized chitosan NPs containing DA and investigated the neuroprotective properties of the system in vitro using human neuroblastoma SH-SY5Y cells. They examined the varied effects of DA, uncoated chitosan NPs, and chitosan-DA NPs on reactive oxygen species (ROS) generation. Monge-Fuentes et al. developed a new NP system loaded with DA (7 µg DA per mg of NPs) composed of albumin and PLGA, with diameters ranging from 353 to 497 nm, a polydispersity index (PDI) of 0.4 to 0.6, and a zeta potential of -27 to -37 mV. This system improved motor skills in PD mice by effectively delivering dopamine and crossing the BBB. Vong et al. created a nano-polymeric drug system (NanoDOPA) to enhance the brain delivery and therapeutic efficacy of L-dopa in a mouse model of PD. The drug was gradually released through chymotrypsin degradation, significantly improving the in vivo pharmacokinetic profile of L-dopa compared to free L-dopa. The administration of NanoDOPA in the MPTP-induced PD mouse model resulted in substantial improvements in motor symptoms and a reduction in dyskinesia commonly associated with L-dopa treatment

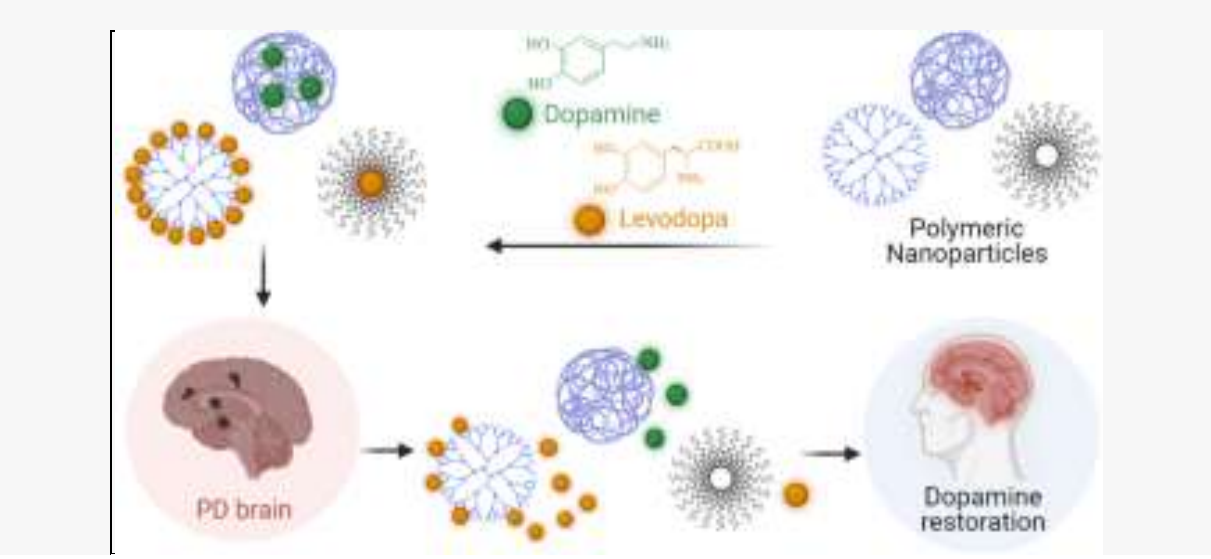


**Figure 7 :**The utilization of Polymeric Nanoparticulate systems to replace DA/L-dopa in PD

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1. **Carbon-based Nanoparticles :**

Besides polymeric and metallic NPs, certain carbon-based NPs are widely used to treat PD. These carbon-based NPs include carbon nanotubes (CNTs), fullerenes, and graphene. The CNTs could be either single-walled (SWCNTs) or multi-walled (MWCNTs) (114). All these carbon-based NPs have high surface area, high mechanical strength, and the ability to penetrate cell membranes, which hold a promising potential for treating PD. Moreover, the CNTs could be further surface functionalized with various molecules to increase their solubility and biocompatibility. Surface-functionalized and biocompatible CNTs could be used to target the delivery of therapeutic agents (115). Both graphene and its derivatives have excellent conductivity and flexibility, which could be used to deliver drugs. Besides this, graphene and its derivatives act as scaffolds for neuronal growth, potentially facilitating the repair of damaged neural tissues (116).

One study used molecular dynamics simulation tools to investigate the impact of 4 forms of last-generation graphene-based nanostructures on preventing α-synuclein amyloid fibrillation. This study found that nitrogen-doped graphene (N-graphene) is the best in preventing the formation of harmful protein aggregates linked to PD, making it a promising option for treatment. This was so because N-graphene is the most effective at disrupting the structure of α-synuclein amyloids, showing strong interactions and causing significant instability compared to other monolayers (117, 118).

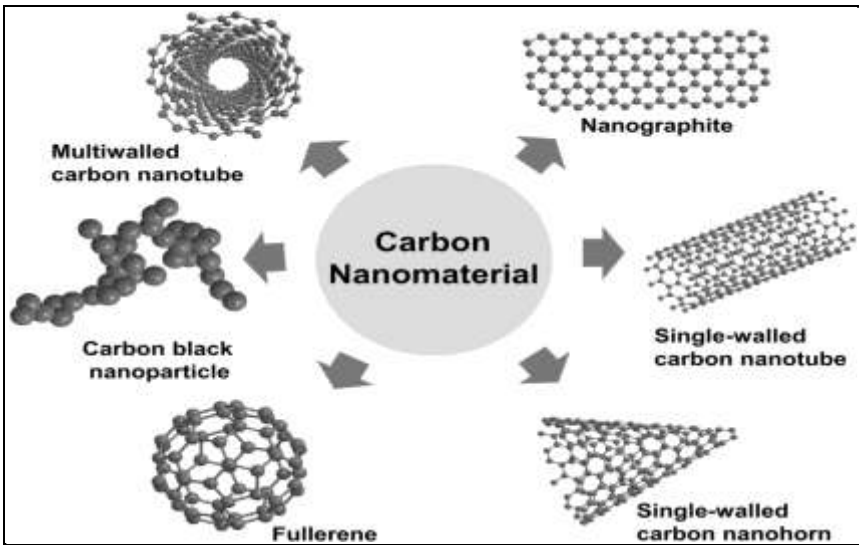


**Figure 8 :**Carbon Based Nanoparticle used in PD

**4. Metal-Organic Frameworks :**

The investigators have found that enzyme-integrated metal-organic frameworks (MOFs) had antioxidant activity and chiral-dependent BBB trans endocytosis. These frameworks may treat PD as anti-neuroinflammatory drugs (119). By adding extremely small platinum nanozymes (Ptzymes) to L-chiral and D-chiral imidazolate zeolite frameworks, chiral nanozymes are generated. In male PD mouse models, Ptzyme@D-ZIF accumulated more brain tissue than Ptzyme@L-ZIF. This was due to longer plasma presence and more BBB crossing routes, including clathrin- and caveolae-mediated endocytosis. These variables explain Ptzyme@D-ZIF's increased therapeutic efficacy in reducing behavioural and pathological changes. Bioinformatics and biochemical studies show that Ptzyme@D-ZIF prevents neuroinflammation-induced apoptosis and ferroptosis (120) in damaged neurons. In enzyme-integrated chiral ZIF platforms, live organisms, metabolism, and therapeutic effects vary, suggesting the potential for PD medicines (121).

**Mechanisms Of Action of NPs :**

The therapeutic effect of the NPs could be exerted on the PD through various processes. One basic feature is enhancing the drug delivery across the BBB, which ensures that a higher concentration of the therapeutic agent reaches the brain (122). This particular feature has an important role in PD as several drugs have limited ability to cross the BBB on their own (123). Besides this, NPs could also provide a controlled and sustained release of

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drugs, which maintains the therapeutic levels over extended periods and reduces side effects involved with peak-dose fluctuations. In addition to this, NPs can be designed to target specific cellular pathways associated with PD pathology. It has been found that customized NPs could deliver antioxidants or anti-inflammatory agents to lower the OS and neuroinflammation, which are the major contributors to neuronal degeneration. Besides this, NPs could also be used to deliver neurotrophic factors or GT agents. The Neurotrophic factors or GT agents promote neuronal survival and repair, which offers potential disease-modifying effects (124).

| Nanoparticles | ROA | Outcome of study | References |
|---|---|---|---|
| L-dopa/dopamine (DPA) | Intracranial | Implantation of DOPA-loaded NPs in the frontal lobe of mice, surgically resulting in constant dispersion till 30 days with low systemic scape | (208) |
| | NA | In the brains of rats, nano silica-DOPA reservoirs surgically implanted showed circling behaviour by apomorphine | (209) |
| | Intraperitoneal injection (IPI) | Successful delivery of dopamine-loaded CNP through BBB; concentration peak around 80 min | (210) |
| | NA | The study performed *in vitro* exchange of NPs conjugated with galactose and DOPA by an artificial membrane through GLUT-1 receptors | (211) |
| | Subcutaneous injection | NPs combined with L-dopa and benseraziде showed dyskinesias | (13) |
| | Intranasal | NPs + L-dopa in a gel resulted in brain recovery | (212) |
| | NA | Zinc and aluminum-based NPs combined with L-dopa showed the potential for releasing the drug without any toxic effects in a sustained manner | (213, 214) |
| | Intranasal | Release of combined nano-dopa particles exhibited improved results; motor coordination increased twofold after 28 days compared to conventional treatment | (215) |
| | | Association of L-dopa and CNTs showed a sustained release pattern *in vitro*, with less toxicity to PC12 cells | (216) |
| | Intranasal | Delivered dopamine NPs to brain; elevated dopamine volume was found in the striatum after repeated administration, with no evident tissue damage | (217) |
| | IV infusion | Dopamine PLGA-NPs in rats exhibited successful cross of BBB, resulting in increased and impulsive locomotor functions and significantly lower rotational scores | (206) |
| Ropinirole (RPN) | Transdermal | Transdermal nanocarrier + RPN generated twice boosted bioavailability in comparison to free drug transdermal approaches | (218) |
| | NA | RPNs associated with NPs had better bioavailability and controlled release patterns *in vitro*. Close to 98% penetration to *ex-vivo* sheep mucosa | (219) |
| | Intranasal | Delivery of RPN NPs had a constant release pattern, resulting in reduced tremors in rats compared to RPN alone | (220, 221) |
| | NA | RPN chitosan NPs released to rats had better bioavailability than free drug solution | (222) |
| | NA | Delivery of chitosan-coated RPN nanoemulsion; enhanced muscular coordination and swimming in mice | (223) |
| Bromocriptine (BrP) | Intraperitoneal | In rats, BrP SLNs have a faster onset and longer half-life than free BrP, stabilizing plasmatic levels | (224) |
| | Intraperitoneal | Encapsulated BrP is used in rats, resulting in attenuating motor deficits | (225) |
| | Intraperitoneal | BrP chitosan NPs were observed to improve absorption and brain targeting, depicting a better future as a nano-drug | (226) |
| Apomorphine | | Apomorphine-loaded nanobubbles have the potential to penetrate artificially, proven in successful release patterns | (227) |
| | Oral | In the brains of rats apomorphine, SLNs were delivered, and an observed high increase in bioavailability resulted in an improved diseased state | (228) |
| Urocortin | Intranasal | Urocortin with odorranalectin-NPs prolonged nasal residence time, increasing intranasal absorption. Rotational movement induced by apomorphine reduction | (229) |
| Rasagiline | Intranasal | Rasagiline chitosan NPs used intranasally in mice were observed to have better bioavailability than single-drug or intravenous NPs | (230) |
| Selegiline | | Selegiline HCl-loaded-chitosan NPs prepared and tested *in vitro*, presenting a controlled-release profile up to 1 day and 4 h | (231) |

**Table 5**. AImplication of Nanomedicines on PD.

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**Targeting and Delivery Strategies of NPs for PD :**

For the successful treatment of PD by NPs, there are two important features: firstly, effective targeting and delivery. From the various pieces of literature, it has been observed that numerous investigations have developed strategies to enhance the specificity and efficiency of NPs delivery to the brain and the affected neurons (22, 125).

**1. Surface Functionalization -**

Nanoparticles (NPs) have been shown to enhance drug delivery across the blood-brain barrier (BBB) and improve diagnostic accuracy. Functionalization of these nanoparticles with specific molecules allows for targeted delivery. Numerous studies have demonstrated that NPs can be functionalized with targeting ligands such as antibodies, peptides, or small molecules. These surface-functionalized NPs bind specifically to the receptors or proteins expressed on the surface of dopaminergic neurons. Such targeted strategies ensure that therapeutic agents are delivered directly to damaged cells, thereby reducing unwanted side effects and improving therapeutic outcomes. Additionally, functionalized NPs can serve as contrast agents in imaging techniques, selectively accumulating in affected brain areas to enhance disease detection and monitoring. For instance, one study involved the functionalization of selenium nanoparticles (SeNPs) with polyvinylpyrrolidone (PVP) and polysorbate 20, which showed potential for enhancing the delivery of dopamine and L-dopa across the BBB, demonstrating efficient internalization and improved pharmacokinetic profiles. Furthermore, another study utilized functionalized gold nanoparticles (AuNPs) to target α-synuclein, which improved diagnostic accuracy by enhancing signal detection in biological samples, enabling earlier and more precise diagnoses. In research conducted by Huang et al., exenatide-modified deferoxamine nanoparticles were developed to specifically target lesion areas in the brain. This approach combined iron chelation and inflammatory suppression to address neurological deficits in mice with Parkinson's disease.

**2. Nanogels -**

Nanogels have also gained significant attraction in nanomedicine as nanocarriers. These three-dimensional, hydrophilic polymer networks could swell up in aqueous environments. As a drug delivery system, nano gels have several advantageous features for the PD, like high drug loading capacity, biocompatible nature, and safeguarding the encapsulated drugs from degradation (137, 138). Currently, investigators are emphasizing the development of smart nanogels that respond to environmental stimuli, like temperature, pH, or magnetic fields, to acquire controlled and site-specific release of drugs. Investigators have developed temperature-responsive nano gels that could release the drugs loaded on them at elevated temperatures found in inflamed or diseased tissues. This ensures that the drug is delivered precisely where it is needed in the brain. Moreover, nanogels could also be functionalized with targeting ligands to increase their specificity for dopaminergic neurons. Several reports report the formulation of multifunctional nano gels that combine drug delivery with imaging capabilities, which helps in enabling real-time monitoring of PD treatment efficacy (139).

**3. Dendrimers -**

Dendrimers are organic molecules characterized by their highly branched, tree-like polymeric structure, including well-defined architectures and many functional groups on their surfaces (140). The distinctive design of dendrimers allows for exact regulation of size, shape, and surface functioning. These characteristics render them an attractive contender for drug delivery applications. Dendrimers may be designed for the targeted delivery of drugs, genes, or other therapeutic agents to the brain to treat PD (141). Recent investigations indicate the development of dendrimers with targeting moieties capable of selectively traversing the BBB and binding to dopaminergic neurons. Furthermore, dendrimers can be engineered to release encapsulated pharmaceuticals reacting to particular stimuli, similar to liposomes. The regulated release of the medicine from the dendrimer guarantees that the drug is delivered exclusively to the target location, minimizing systemic adverse effects. Currently, investigators are examining the capability of dendrimers to concurrently deliver various therapeutic drugs, perhaps providing a comprehensive strategy for PD treatment (142, 143).

**4. Solid lipid Nanoparticles -**

SLNs are submicron-sized particles of solid lipids that could encapsulate lipophilic and hydrophilic drugs (Figure 10). Such SLNs offer numerous advantages, like controlled drug release, biocompatibility, and protecting the encapsulated drugs from degradation (97, 144). Investigators have reported improving the stability of SLNs,

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drug loading capacity, and targeting capabilities. SLNs could be functionalized by targeting ligands to improve their specificity for dopaminergic neurons in treating PD. Moreover, SLNs could also be tailored like dendrimers and liposomes to ensure the crossing through the BBB, which remains a major challenge for neurologists who treat PD (97). The engineered SLNs ensure that the loaded therapeutic agents reach the specific sites of the brain for the treatment of PD. Nowadays, several investigators are exploring the role of SLNs in delivering neuroprotective agents, antioxidants, and anti-inflammatory drugs. Such types of SLNs offer the potential to modify the progression of PD and improve patient outcomes. Besides, this investigation is also going on the co-delivery of multiple drugs using SLNs, which will provide a synergistic approach for the treatment of PD

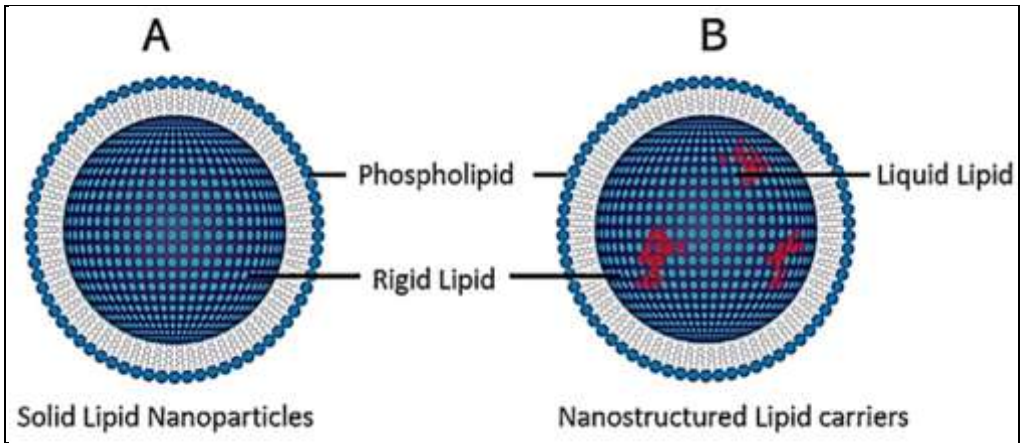


**Figure 10 :** General structure of **(A)** SLNPs and **(B)** nanostructured lipid carriers (NLCs), reproduced from Jagaran et al. (145) with permission.

**5. Controlled Release -**

Specifically, engineered NPs could help to achieve the controlled drug release from NPs under specific stimuli, like variation in the pH, temperature, or the presence of specific enzymes, which could trigger. The engineered NPs may ensure the drug is released at the desired site and time, demonstrating enhanced therapeutic efficacy and reduced side effects. In one of the studies, the investigator developed various organic NPs for the encapsulation and sustained release of puerarin to improve brain delivery for treating PD. The engineered NPs extend their in vivo half-life and improve their bioavailability and accumulation in the brain to treat the symptoms of PD. Compared to the puerarin alone, puerarin-NPs showed significantly improved cellular internalization, permeation, and neuroprotective effects (131).

**6. Liposomes -**

Liposomes are spherical vesicles comprising phospholipid bilayers that can encapsulate hydrophilic and hydrophobic drugs (Figure 9). Liposomes offer significant advantages as drug delivery systems for PD, particularly due to their ability to encapsulate various types of drugs and their potential for targeted delivery to specific cells or tissues, such as dopaminergic neurons (132, 133). The surface modification of the liposome with ligands (antibodies or peptides) ensures targeted delivery to dopaminergic neurons, which could improve their targeting capabilities and efficacy and reduce side effects. In addition to this, PEGylation (attachment of polyethylene glycol chains) has been employed for longer circulation time and reduced immunogenicity. The liposomes could be engineered for the PD drug's effective, controlled, and sustained release. Various external factors could trigger the release of drugs from these engineered liposomes, for instance, variation in the pH or enzymatic activity (134–136).

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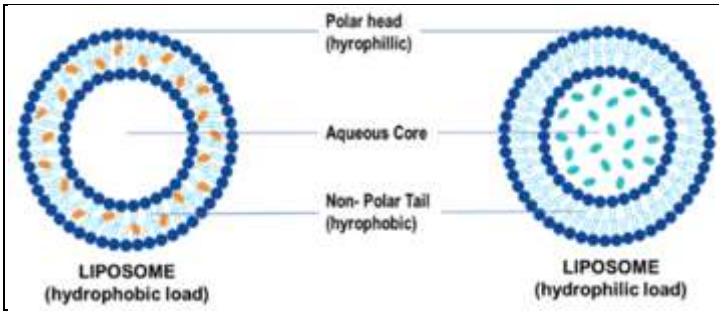


**Figure 9:**Schematic diagram of liposome and encapsulation of hydrophilic and hydrophobic molecules, reproduced from Jagaran et al. (145) with permission.

**Gene Therapy and Nanomedicine :**

Gene therapy (GT) aims to introduce, remove, or modify the genetic material within a patient's cells, offering a promising strategy for disease modification. The integration of GT with nanomedicine could enhance the precision and effectiveness of gene delivery to target cells. Numerous studies are investigating the application of GT for the treatment of Parkinson's disease (PD), focusing on gene delivery systems, CRISPR/Cas9 technology, and nanoparticles (NPs), as well as discussing clinical applications and challenges. For effective GT, robust drug delivery systems are crucial for transporting therapeutic genes to specific cells and tissues. NP-based innovative methods may provide several advantages over traditional viral vectors, including lower immunogenicity, higher loading capacity, and the potential for targeted delivery and controlled release. Lipid-based NPs (LBNPs), such as liposomes and lipid nanoparticles (LNPs), are widely used for gene delivery. These LBNPs can encapsulate genes, protecting them from enzymatic degradation and facilitating their entry into cells. Furthermore, LBNPs can be surface-modified with specific ligands that target dopaminergic neuron receptors, enhancing the precision of gene delivery in PD. Research has also indicated that polymeric NPs could serve as effective gene delivery systems. These polymeric NPs can encapsulate plasmid DNA, siRNA, or mRNA, protecting them from degradation and allowing for sustained release.

The specificity of polymeric NPs for neuronal cells can be enhanced through functionalization with targeting moieties. Several NPs are designed to mimic the structure and function of viral vectors, known as viral mimetic NPs. These NPs have low immunogenicity and can effectively deliver genetic material to the brain by leveraging natural cellular uptake processes, potentially allowing for targeted delivery to specific neuronal populations and improving therapeutic outcomes for PD. The combination of GT and nanomedicine shows great promise for treating PD. Preclinical studies have demonstrated the feasibility and efficacy of utilizing NPs for gene delivery in PD models. GT can deliver neuroprotective genes to enhance neuronal survival and function. For example, genes encoding neurotrophic factors like GDNF (glial cell line-derived neurotrophic factor) may support dopaminergic neurons and slow disease progression. NPs provide a targeted and efficient delivery system for these therapeutic genes, ensuring they reach the affected neurons in the brain. Additionally, combining CRISPR/Cas9 technology with NPs holds the potential for correcting genetic mutations associated with PD. Some researchers are using CRISPR/Cas9 to target and edit mutations in the LRRK2 gene, which is implicated in familial forms of PD. NPs facilitate precise delivery of CRISPR/Cas9 components to neurons, enabling accurate gene editing and potential disease modification. Despite the advancements in combining GT and nanomedicine for PD treatment, several challenges remain in clinical applications. This combination must ensure efficient and targeted delivery of genetic material to the brain while overcoming the blood-brain barrier (BBB). Furthermore, achieving long-term expression of therapeutic genes in the brain presents a significant challenge. A thorough evaluation of safety and immunogenicity for all NP-based gene delivery systems during clinical trials is essential. Researchers are focused on optimizing NP design, improving targeting strategies, and developing new materials to enhance delivery efficiency and safety. Integrating advanced imaging techniques and biomarkers may also aid in monitoring therapeutic outcomes and guide the development of personalized GT strategies for PD.

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**Nanomedicine for Neuroprotection :**

Nanomedicine offers promising strategies for neuroprotection in PD treatment by utilizing NPs to deliver neuroprotective agents across the BBB. These NPs can enhance drug bioavailability, target specific brain regions, and minimize side effects, making them a cutting-edge approach to managing neurodegenerative diseases. Recent advancements in nanomedicine offer promising strategies for neuroprotection, which aims to preserve and restore neuronal function. The various nanomedicines demonstrating neuroprotective effects are antioxidant NPs, anti-inflammatory NPs, and neurotrophic factor delivery for neuroprotection in PD. All these types of neuroprotective NPs are described briefly below.

**1. Antioxidant Nanoparticles -**

The onset of oxidative stress (OS) is marked by an imbalance between the production of reactive oxygen species (ROS) and the brain's antioxidant defenses, which plays a crucial role in the development of Parkinson's disease (PD). Excessive ROS can damage cellular components, ultimately leading to neuronal death. Antioxidant nanoparticles (NPs) are engineered particles designed to effectively scavenge ROS within biological systems. These nanoparticles enhance the delivery of antioxidants to specific target sites, thereby improving their therapeutic potential. Integrating antioxidants into NPs boosts their bioavailability and allows for targeted delivery, which helps reduce side effects while increasing efficacy. Researchers are actively developing various antioxidant NPs, such as nanoceria, polymeric antioxidant NPs, and selenium NPs (Se-NPs), to combat oxidative stress and protect neurons. These antioxidant NPs have become a promising therapeutic strategy for treating PD due to their ability to address oxidative stress and neuroinflammation, both of which are key pathological features of the disease. Furthermore, these nanoparticles can enhance drug delivery across the blood-brain barrier, improve pharmacokinetic profiles, and provide neuroprotective effects.

**2. Selenium Nanoparticles-**

Se-NPs have been used as an antioxidant for various therapeutic purposes. Literature has proven that both types of Se-NP functionalized and non-functionalized, can protect mitochondria by increasing the levels of ROS-scavenging enzymes in the brain. It has been reported that Se-NPs can also promote the synthesis of dopamine. Se-NPs can lower cellular toxicities by inhibiting the aggregation of tau, α-synuclein, and/or Aβ. The ability of the BBB to absorb Se-NPs, which maintain a healthy microenvironment, is essential for the homeostasis of the brain. Recently, Umapathy et al. (167)

**3. Polymeric antioxidant Nanoparticles -**

The investigation revealed that polymeric nanoparticles (NPs) could be loaded with various antioxidant compounds, including curcumin, resveratrol, and N-acetylcysteine. These nanoparticles provide a sustained release of antioxidants, ensuring prolonged protection against oxidative stress (OS). To enhance their neuroprotective effects, the nanoparticles can undergo surface functionalization with targeting ligands, thereby improving their specificity for dopaminergic neurons. El Nebrisi emphasized the underlying processes of curcumin's neuroprotective properties as a potential treatment for patients with Parkinson's disease (PD). Curcumin, derived from turmeric, is a polyphenolic compound known for its potent anti-inflammatory, mitochondrial protective, antioxidant, free radical scavenging, and iron-chelating effects. It serves as a promising therapeutic and nutraceutical agent for treating PD. The immune system's "cholinergic anti-inflammatory pathway" is primarily regulated by stimulating nicotinic receptors, particularly the selective α7 nicotinic acetylcholine receptors (α7-nAChR). Recently, α7-nAChR has been proposed as a potential therapeutic strategy for PD

**4. Cerium oxide NPs (Nanoceria) -**

Cerium oxide nanoparticles (nanoceria) exhibit intrinsic antioxidant properties due to their ability to switch between Ce3+ and Ce4+ oxidation states, mimicking the activity of natural antioxidant enzymes. Recent studies have shown that nanoceria can scavenge reactive oxygen species (ROS), reduce oxidative stress (OS), and protect dopaminergic neurons in models of Parkinson's disease (PD). The functionalization of nanoceria with targeting ligands improves their delivery to the brain and enhances their neuroprotective effects. Dillion et al. reported that Parkinson's disease is closely linked to oxidative stress, and cerium oxide nanoparticles can act as free radical scavengers. The researchers hypothesized that cerium oxide nanoparticles may serve as a promising disease-modifying therapy for the treatment of Parkinson's disease. They were the first to demonstrate that cerium oxide nanoparticles preserve striatal dopamine levels and protect dopaminergic neurons

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in the substantia nigra in an MPTP mouse model of Parkinson's disease. Ultimately, the researchers concluded that cerium oxide nanoparticles could be a potential novel nanopharmaceutical for the treatment of neurodegenerative disorders.

**6. Anti-inflammatory Nanoparticles -**

Neuroinflammation is marked by the activation of microglia and the release of pro-inflammatory cytokines, both of which contribute to the progression of Parkinson's disease (PD). Anti-inflammatory nanoparticles (NPs) can be designed to deliver anti-inflammatory agents directly to the affected areas, reducing systemic side effects and improving therapeutic effectiveness. These anti-inflammatory NPs are being developed to modulate the inflammatory response and protect neurons from damage caused by inflammation (168).

**I. Dexamethasone-loaded NPs -**

Dexamethasone is a powerful anti-inflammatory steroid that plays a significant role in modulating neuroinflammation, which is a crucial factor in the progression of Parkinson's Disease (PD). Researchers have found that encapsulating dexamethasone—a strong anti-inflammatory corticosteroid—in nanoparticles (NPs) can improve its delivery to the brain while minimizing systemic side effects. Recent studies have shown that dexamethasone-loaded NPs can effectively cross the blood-brain barrier (BBB) and may further reduce neuroinflammation, thereby protecting dopaminergic neurons in models of PD. These nanoparticles can also be engineered for controlled release, providing sustained anti-inflammatory effects. The encapsulation of dexamethasone in PLGA NPs facilitates targeted delivery and controlled release, which helps reduce systemic side effects and enhance the drug's efficacy

**II. Nanoparticles targeting inflammatory pathways -**

Nanoparticles (NPs) targeting inflammatory pathways represent a promising strategy for managing Parkinson's disease (PD) by addressing neuroinflammation and oxidative stress, which are critical in the disease's progression. These NPs are designed to cross the blood-brain barrier (BBB) and specifically target inflammatory pathways, helping to mitigate the effects of neuroinflammation and promote neuronal health. Additionally, NPs can be customized to focus on specific inflammatory pathways involved in PD. One study reported that NPs were loaded with inhibitors of nuclear factor kappa B (NF-κB), a key regulator of inflammation. These inhibitors can suppress microglial activation and reduce the production of pro-inflammatory cytokines, highlighting the importance of NF-κB in regulating inflammation.

**Neurotrophic factor Delivery :**

Neurotrophic factors are essential proteins that support the growth, survival, and differentiation of neurons. They play a vital role in the development and maintenance of the nervous system by preventing cell death (apoptosis) and promoting neuronal regeneration. Key neurotrophic factors include brain-derived neurotrophic factor (BDNF), nerve growth factor (NGF), and neurotrophin-3. These proteins are involved in various cellular processes that ensure the proper functioning of neurons. Research indicates that delivering neurotrophic factors to the brain is a promising strategy for neuroprotection and neurorestoration in conditions such as Parkinson's disease (PD). Additionally, nanoparticles (NPs) serve as an effective delivery system for these neurotrophic factors, enhancing their stability and bioavailability.

**1. Glial cell line-derived neurotrophic factor-loaded NPs -**

GDNF-loaded nanoparticles (NPs) have been investigated as a potential treatment for Parkinson's disease (PD) due to the neuroprotective effects of GDNF on dopaminergic neurons. GDNF not only supports these neurons but also plays a significant role in neural development and repair. However, delivering it across the blood-brain barrier (BBB) remains a challenge. NPs could help overcome these obstacles by enhancing the delivery and stability of GDNF in the brain. By encapsulating GDNF, NPs protect it from degradation by enzymatic activity and facilitate its transport to the brain. Recent studies have demonstrated that GDNF-loaded NPs can significantly improve the survival of dopaminergic neurons and enhance motor functions while minimizing neurodegeneration in PD models. Nevertheless, several major drawbacks hinder the clinical application of these NPs. They have a limited ability to cross the BBB, and the clinical efficacy of GDNF in treating PD has been inconsistent. Clinical trials indicate that GDNF does not significantly improve motor symptoms in PD patients and is associated with a higher incidence of serious adverse events. Additionally, prolonged exposure to GDNF can lead to the

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dephosphorylation of key signaling pathways, which may reduce its neuroprotective effects. This underscores the need for optimized delivery methods.

**2. Brain-derived neurotrophic factor-loaded NPs -**

BDNF (Brain-Derived Neurotrophic Factor) is a vital protein that belongs to the neurotrophin family. It plays a significant role in neuronal growth, synaptic plasticity, and overall brain health. BDNF regulates the growth of axons and dendrites, enhances synaptic plasticity, and is essential for long-term potentiation, all of which are crucial for learning and memory. Additionally, BDNF's influence extends to various psychiatric and neurological disorders, making it a focal point for therapeutic research and potential interventions. BDNF also promotes the survival and maturation of dopaminergic neurons, which are particularly important in the pathology of Parkinson's Disease (PD). Nanoparticles (NPs) have the ability to cross the blood-brain barrier (BBB) and deliver BDNF to the brain, thereby increasing its bioavailability. This targeted delivery allows for a sustained release of BDNF, focusing on dopaminergic neurons. The administration of BDNF through NPs may potentially slow disease progression and improve motor function. Preclinical studies have shown promising results in animal models, where NP-mediated delivery of BDNF has led to neuroprotective effects. Boyton et al. demonstrated that encapsulating BDNF within NPs can provide a controlled and sustained release, which may enhance therapeutic efficacy and reduce the frequency of administration. Furthermore, modifying the surface of NPs with targeting ligands can improve the specificity and effectiveness of BDNF delivery, promoting the survival and function of neurons. Table 6 summarizes all the nanoparticles utilized for neuroprotection in the treatment of Parkinson's Disease.

| Nanoparticles | Types of neuroprotectant | MOA | Role | References |
|---|---|---|---|---|
| MgO-based polydopamine (anti-SNCA plasmid, puerarin) | Antioxidant | Antioxidation, anti-inflammation, inhibition of α-synuclein accumulation | Targets deep tissues, activates under NIR light, penetrates BBB | (232) |
| Cerium oxide NPs (nanoceria) | Antioxidant | Mimic natural antioxidant enzymes by switching oxidation states ($Ce^{3+}$/$Ce^{4+}$), functionalized for targeted brain delivery | Scavenge ROS, lower OS, and safeguard dopaminergic neurons | (156, 157) |
| Polymeric antioxidant NPs | Antioxidant | Provide sustained release of antioxidants like curcumin, resveratrol, and N-acetylcysteine | Target dopaminergic neurons, reduce inflammation, and protect against OS | (159–161) |
| Mannitol-modified PLGA (dihydroquercetin, Pt nanozymes) | Antioxidant | Antioxidative activities, anti-inflammatory effects | Mitigates oxidative damage, promotes microglia polarization | (176) |
| Selenium NPs (Se-NPs) | Antioxidant | Increase ROS-scavenging enzymes, promote dopamine synthesis, inhibit aggregation of tau and α-synuclein | Protect mitochondria, enhance brain homeostasis, and reduce neurodegeneration | (127) |
| Dexamethasone-loaded NPs | Anti-inflammatory | Cross BBB for controlled release of dexamethasone, reducing systemic side effects | Modulate neuroinflammation and safeguard dopaminergic neurons | (169, 173) |
| Fe-Cur NCPs (curcumin) | Anti-inflammatory | Scavenging radicals, suppressing neuroinflammation | Alleviates OS, mitochondrial dysfunction, inflammatory conditions | (233) |
| NPs targeting inflammatory pathways | | Block peripheral inflammatory cell infiltration, target NF-κB pathways, and promote Nrf2-GPX4 pathway activation | Address neuroinflammation and OS and enhance neuronal health | (172) |
| GDNF-loaded NPs | Neurotrophic | Encapsulate GDNF to protect it from enzymatic degradation and enhance brain delivery | Improve dopaminergic neuron survival and motor function, reduce neurodegeneration | (177, 178) |
| pGDNF DNA NPs | Neurotrophic | Induces transgene expression, protects dopamine neurons | Non-invasive GT enhances neuroprotection | (234) |
| BDNF-loaded NPs | Neurotrophic | Encapsulate BDNF for controlled release and enhance delivery to dopaminergic neurons | Promote neuronal growth, synaptic plasticity, and brain health; slow PD progression | (180, 182) |
| GMO NPs | Curcumin, piperine | Augmented inhibition of α-synuclein oligomers and fibrils | Enhances bioavailability, penetrates BBB, anti-parkinsonism effect | (235) |

**Table 6**. Summary of all the Nanoparticles used for Neuroprotection in Parkinson's disease treatment.

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## II. CONCLUSION

Exploring Nanomedicine as a treatment for Parkinson's disease offers a promising and transformative approach. Nanoparticles have several advantages over traditional therapies, including improved drug delivery, targeted therapeutic interventions, and the ability to cross biological barriers such as the blood-brain barrier (BBB). Various types of nanoparticles—such as lipid-based, polymeric, and metallic nanoparticles—have shown potential in effectively delivering therapeutic agents to the affected regions of the brain. Moreover, integrating gene therapy and CRISPR/Cas9 technology with nanomedicine opens up new possibilities for tackling the underlying causes of neurodegeneration in Parkinson's disease. This combination could enable precise and efficient delivery of genetic material to specific neurons, potentially correcting genetic mutations and promoting neuroprotection. Despite these advancements, several challenges remain to be addressed. These include optimizing nanoparticle design, ensuring the long-term expression of therapeutic genes, and thoroughly evaluating safety and immunogenicity

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