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Review Article

Emerging Therapeutic Strategy for Parkinson's Diseases: From Gene Therapy to Personalised Medicine

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ABSTRACT

Parkinson's disease (PD) is the second most common neurodegenerative disorder and the fastest-growing neurological condition worldwide. It is primarily characterized by motor symptoms such as bradykinesia, rigidity, resting tremor, and postural instability, resulting from the progressive loss of dopaminergic neurons in the substantia nigra pars compacta. Non-motor symptoms—including sleep disturbances, constipation, urinary dysfunction, cognitive decline, and mood disorders—often develop years before motor onset, reflecting PD's multisystem involvement. The underlying pathophysiology involves complex interactions of genetic, environmental, and aging-related factors that contribute to mitochondrial dysfunction, oxidative stress, α-synuclein aggregation, impaired autophagy-lysosomal pathways, and neuro-inflammation. Mutations in genes such as SNCA, LRRK2, PRKN, PINK1, and GBA1 further highlight the role of genetic susceptibility. Environmental exposures, including pesticides and heavy metals, also increase risk, while factors like caffeine and smoking appear protective. Current diagnosis relies heavily on clinical features, supported by emerging biomarkers and neuroimaging techniques that detect early dopaminergic deficits. Although no disease-modifying therapies exist, advancements in understanding PD's molecular mechanisms are driving the development of novel therapeutic strategies, including gene therapy, neuroprotective agents, and personalized medicine approaches. Early identification through prodromal markers may be key to enabling effective intervention and slowing disease progression.

Introduction

Other than being the second most prevalent neurodegenerative disease after Alzheimer's disease, Parkinson's disease (PD) is currently the neurological condition with the fastest rate of growth. Bradykinesia, resting tremor, rigidity, and postural instability are common characteristics of Parkinson's disease (PD), while resting tremor may not be present in one-fifth of cases. Multiple motor and non-motor basal ganglia circuits as well as the progressive degradation of dopamine-producing neurones in the substantia nigra pars compacta are the hallmarks of Parkinson's disease [1].

Parkinson's disease (PD)) is characterized by bradykinesia, muscle rigidity, dysarthria, dysphagia, coordination problems or transient paralysis, and resting

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tremor. Additional symptoms include issues with the bladder and digestive system, irregular sleep patterns, and mental health-related symptoms. Parkinson's disease (PD) affects not only the death of dopaminergic (DA) neurons in the substantia nigra (SN) but also other brain pathways.

In the past, surgery was used to treat Parkinson's disease. The first pallidotomy was done on PD patients in history in 1952 by Narabayashi et al., who also reported the procedure's beneficial outcomes. L-dopa therapy was started in the early 1960s, although many PD patients did not respond well to low doses at first. Cotzias then started using high-dose therapy and the current L-dopa treatment protocol was created [2].

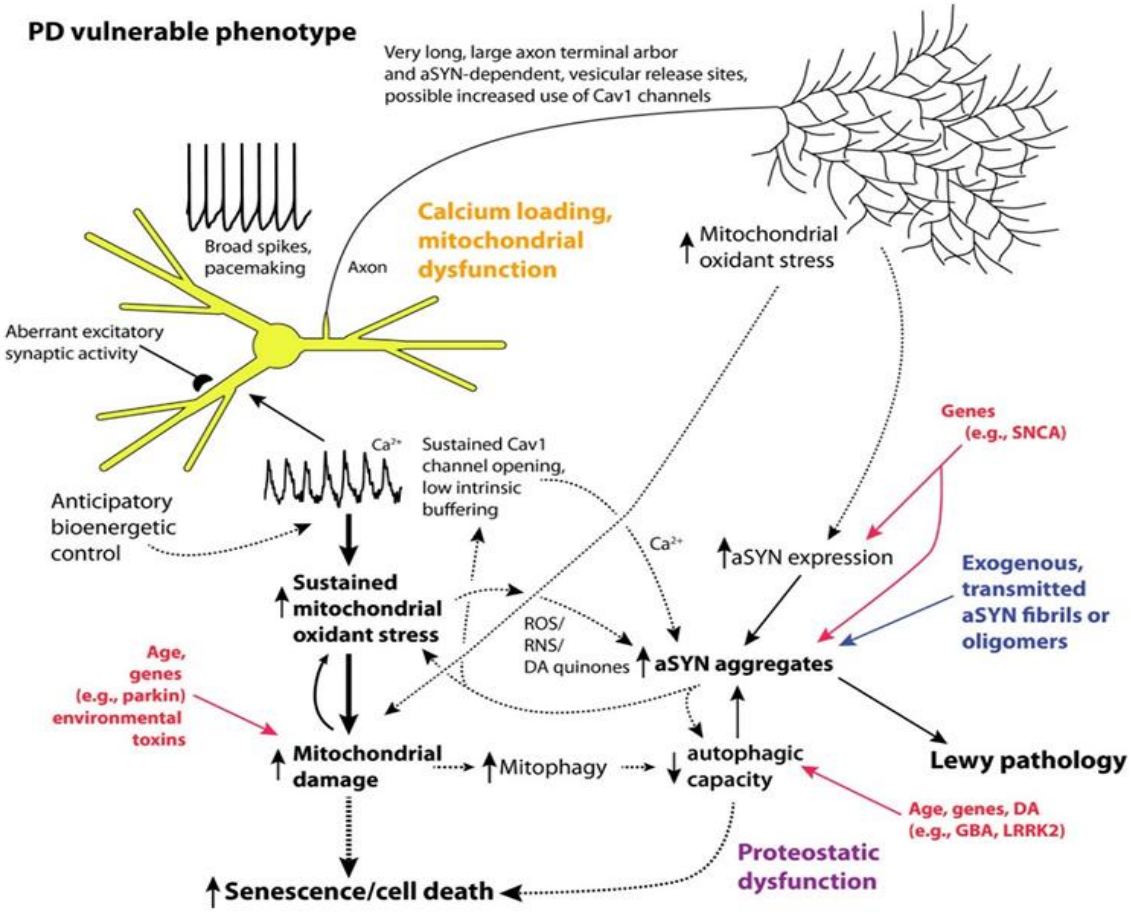

Figure 1: Overview of Parkinsons Disease [2].

Dopamine and Parkinson's disease

The exact reason for the increased susceptibility of dopaminergic neurons in the SNpc to damage in Parkinson's disease is still unclear and continues to be a significant area of investigation. The degeneration of dopaminergic (DA) neurons in the SNpc leads to bradykinesia and rigidity, which are the two main motor symptoms associated with PD. Various proposed phenotypic characteristics may play a role in the vulnerability of these neurons dopaminergic neurons in the SNpc are the focus of this review. To clarify the reason for the destruction of dopaminergic neurons in the substantia nigra pars compacta (SNpc) during Parkinson's disease, there are two main theories. One theory is rooted in the discovery

The substantia nigra pars compacta (SNpc) in patients with Parkinson's disease (PD) often contains Lewy pathology, characterized by protein aggregates predominantly made up of fibrillary forms of alpha-synuclein (aSYN). In contrast, many peripheral and central neurons show Lewy pathology without any signs of impending death, indicating that the reverse may not hold true.

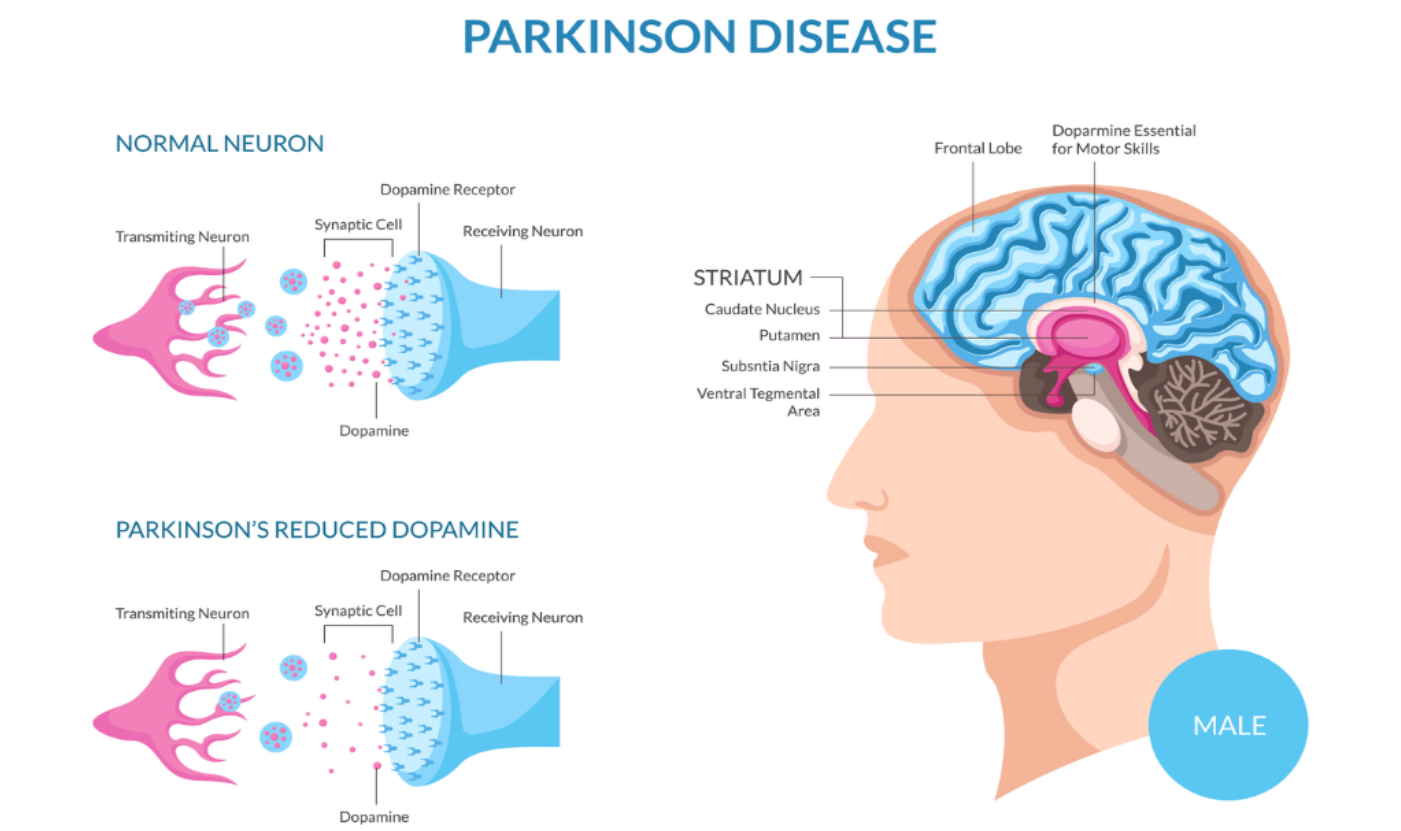

Figure 2: Role of dopamine in Parkinsons Disease [3].

The second hypothesis, which is not mutually exclusive, suggests that dysfunction of mitochondria is responsible for the loss of dopaminergic neurons in the SNpc in Parkinson's disease (PD). Loss-of-function mutations in the genes Parkin (PARK 2), PINK1 (PARK 6), and DJ-1 (PARK 7) lead to recessive, early-onset forms of PD. Furthermore, the proteins encoded by these genes have direct impacts on mitochondrial function, influencing various processes such as oxidative phosphorylation, quality control, and defence against oxidants. Mitochondria have been implicated in the pathogenesis observed in the brains of PD patients [3].

Etiology

Parkinson's disease (PD) is influenced by multiple factors, including both genetic predispositions and environmental influences. The primary risk factor for PD is age, with the average age of onset at 60 years. The incidence of the disease increases with age, reaching 93.1 cases per 100,000 person-years in individuals aged 70 to 79 years.

- Cigarette smoking:
- Genetic Factors
- Caffeine
- Pesticides, herbicides, and heavy metals
- Role of Aging
- Gender
- Race
- Infection. [4,5,6]

Signs and symptoms

Parkinson's disease (PD) is a neurodegenerative disorder primarily identified by the key motor symptoms of slowness of movement, resting tremors, stiffness, and instability when standing, along with various non-motor symptoms like loss of smell, constipation, depression, and REM sleep behaviour disorder (RBD). PD ranks as the second most prevalent neurodegenerative disease following Alzheimer's disease and is the most common movement disorder, impacting 1% of individuals over 60 years old. Factors that increase risk include exposure to pesticides and traumatic brain injuries, while factors that appear to offer protection encompass tobacco use and regular physical activity. When considered separately, aging, genetics, and environmental influences account for only a small portion of PD cases. Hence, the causes of most PD instances are likely to be multifactorial, involving complex interactions between aging, genetic predisposition, and environmental elements.

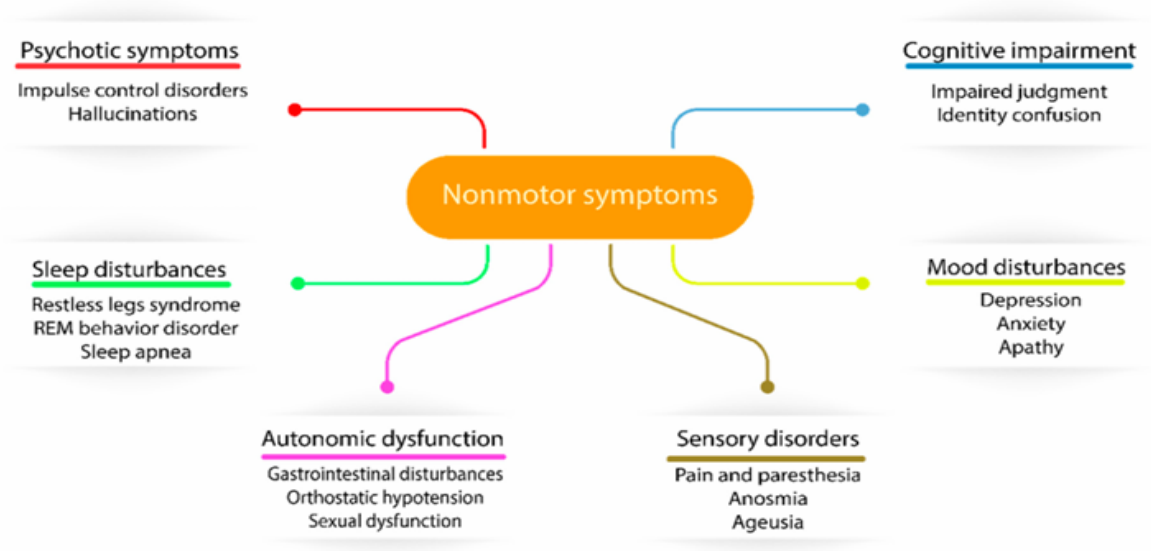

Figure 3: Non motor symptoms of Parkinsons Disease [7].

A resting tremor occurs when a limb is relaxed, either against gravity or when resting on a surface, usually oscillating at a frequency of 4–6 Hz. In contrast, essential tremor typically presents at a frequency of 8–10 Hz. Resting tremor is characteristically lessened or suppressed by movement and is often the first motor symptom observed in these individuals.

The primary feature of bradykinesia involves a reduction in the speed, amplitude, or smoothness of movements performed continuously, which becomes more noticeable over time. This slowing can also affect the voice and facial expressions (hypomimia). However, for a diagnosis to be made, limb bradykinesia must be evident. [7]

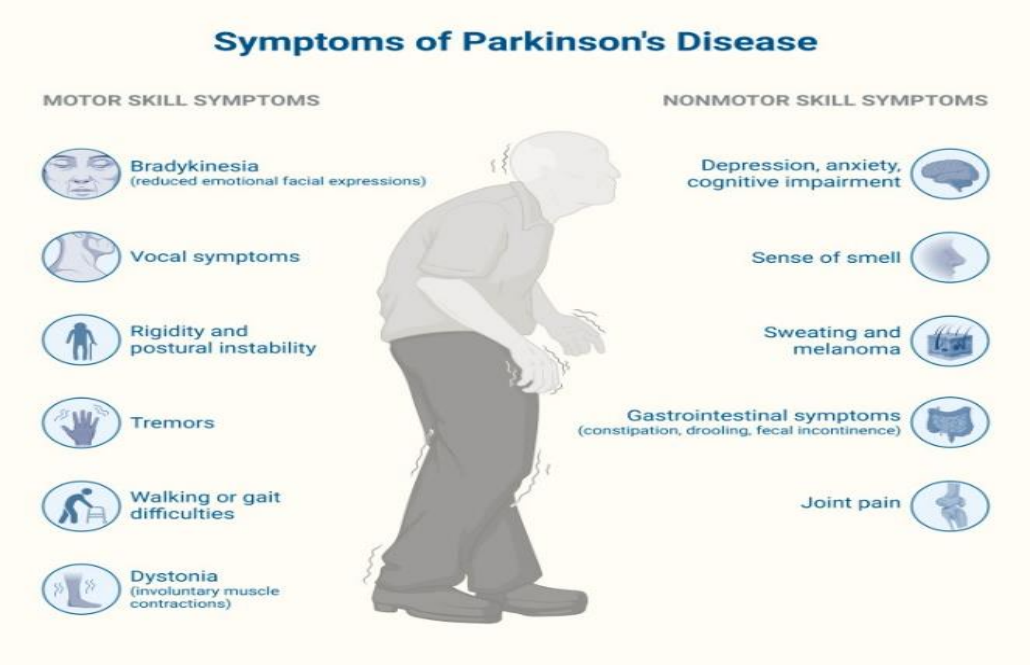

Figure 4: Common symptoms of Parkinsons Disease [7].

Rigidity, characterized by increased and sustained resistance to passive movement, particularly in the joints, is another key symptom. This differs from spasticity, which is dependent on the speed of movement. Postural instability usually emerges in the later stages of the condition and is linked to the overall severity of the disease. It is described as a propensity to lose balance and fall.

Urinary dysfunction or incontinence can occur at any stage of PD, although early signs may raise concerns for

multiple system atrophy (MSA). NMS associated with sleep disturbances includes excessive daytime drowsiness, fragmented sleep, insomnia, REM sleep behavior disorder, restless legs, central sleep apnea, and nocturnal akinesia.[7]

Cardinal Motor Symptoms in PD

Bradykinesia, rest tremor, rigidity, and the loss of postural reflexes are the most frequently recognized motor symptoms of Parkinson's Disease (PD); however, other clinical features may also manifest as the disease advances, including bulbar dysfunction, neuro-ophthalmological issues, and respiratory problems. A key indicator that can aid in distinguishing PD from other parkinsonian disorders—thereby facilitating disease identification—is that the majority of motor symptoms respond positively to dopaminergic treatment.[8]

Pathophysiology

The basal ganglia is a complex assembly of subcortical nuclei situated deep within the brain and is essential for regulating many functions, including movement, cognition, and emotional responses. It is made up of several nuclei, including the caudate nucleus, putamen, globus pallidus, subthalamic nucleus, and substantia nigra, each serving distinct roles. The pathways within the basal ganglia are complex, involving multiple circuits that affect the activity of both cortical and subcortical structures.

The dopaminergic pathways, particularly the nigrostriatal pathway, play a crucial role in the motor symptoms associated with Parkinson's disease (PD). These pathways are composed of dopaminergic neurons that extend from the substantia nigra pars compacta to the striatum, an area of the brain linked to movement coordination. When these neurons degenerate, there is a marked decrease in dopamine levels in the striatum.

Consequently, this leads to an imbalance between the excitatory and inhibitory signals required for smooth and coordinated movements. Dopamine is essential for regulating the activity within the basal ganglia, a cluster of nuclei important for motor control. The reduction of dopamine in PD results in increased activity of the indirect pathway and decreased activity of the direct pathway within the basal ganglia circuitry.

This disruption heightens the inhibitory output to the thalamus and motor cortex, leading to the hallmark motor symptoms of PD, such as bradykinesia, rigidity, and tremors. The loss of dopaminergic neurons impacts not only motor functions but also non-motor functions, as these pathways also influence mood, cognition, and autonomic functions.[9]

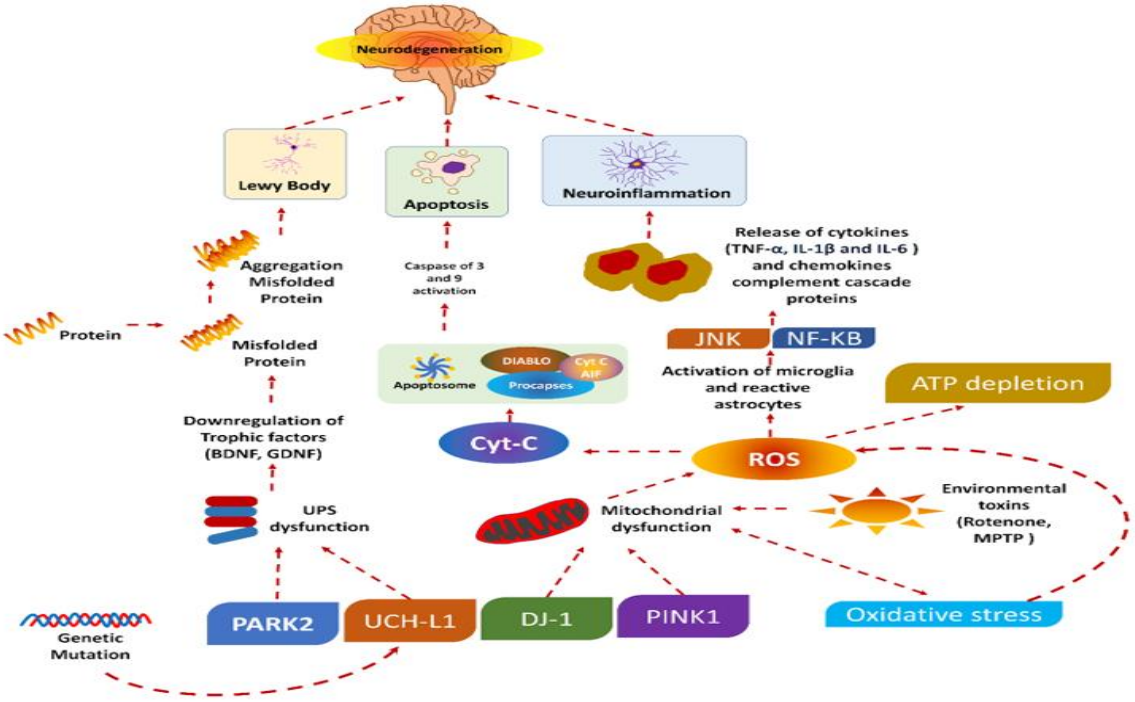

Figure 5: Pathophysiology of Parkinsons Disease [8,9].

The basal ganglia consist of two separate pathways

The direct and indirect circuits that play a role in controlling movement. These circuits begin in the striatum, made up of the putamen and caudate nucleus, and aim for different nuclei within the basal ganglia. [9]

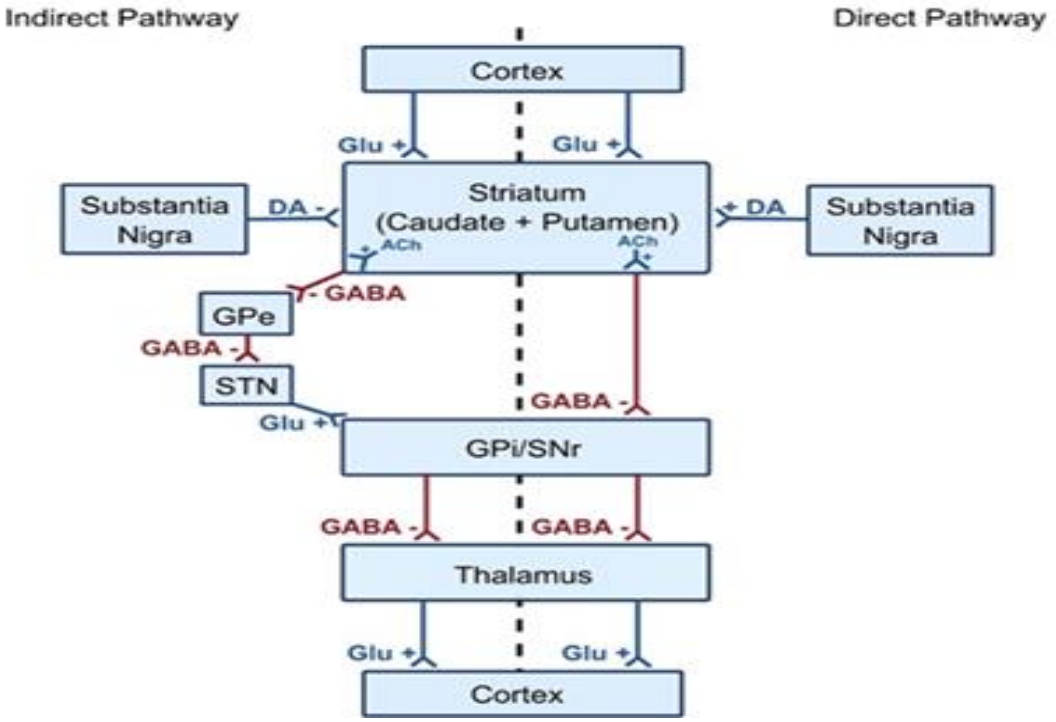

Figure 6: Pathways of basal ganglia [9].

Role of alpha-synuclein

A small soluble protein known as alpha-synuclein is found abundantly in the brain, particularly at presynaptic terminals, and is believed to have a significant role in synaptic function and neurotransmitter release. Numerous studies have shown that alpha-synuclein can undergo pathological aggregation in Parkinson's disease (PD), leading to the formation of insoluble fibrils. These fibrils accumulate as Lewy bodies and Lewy neurites within nerve cells. The aggregation of these fibrils disrupts cellular function and contributes to neuronal death through various mechanisms. The synaptic functions of alpha-synuclein could also be compromised by interfering with vesicle trafficking and neurotransmitter release. [9]

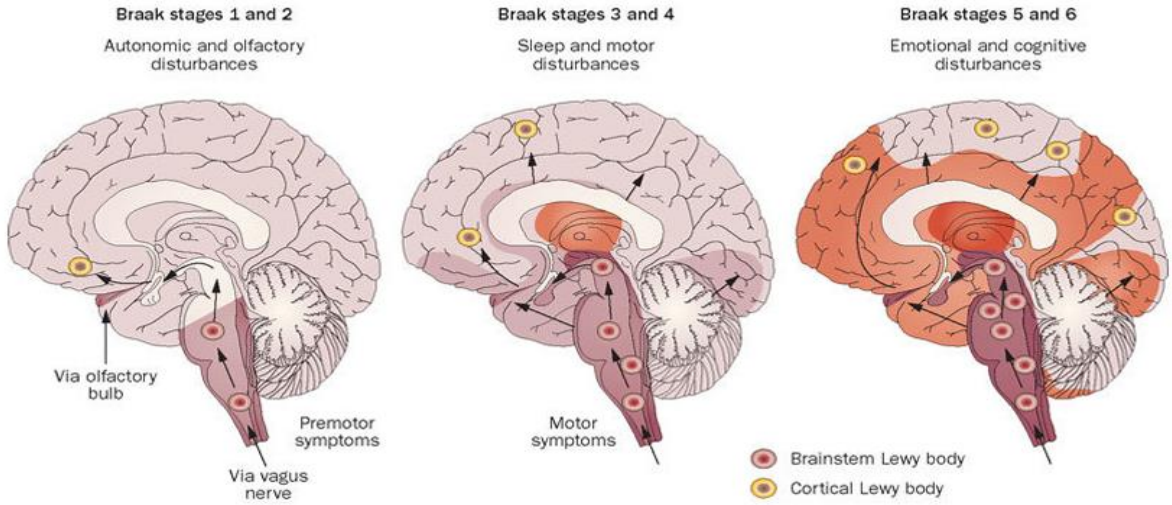

Figure 7: Stages of Parkinsons Disease [9].

Genetic Basis

Currently, over 20 genes responsible for diseases and 90 distinct variations associated with risk have been linked to PD. [10] About 5–10% of patients have forms of the disease caused by mutations in these genes. At least 11 autosomal dominant genes, including SNCA, PARK3, UCHL1, LRRK2, and VPS35, and nine autosomal recessive genes, including PRKN, PINK1, PARK7, and DJ-1, have been identified.[11] Among the genes known to be connected with Parkinson's disease pathology, the most common and closely associated include SNCA, LRRK2, PRKN, PINK1, and GBA1.

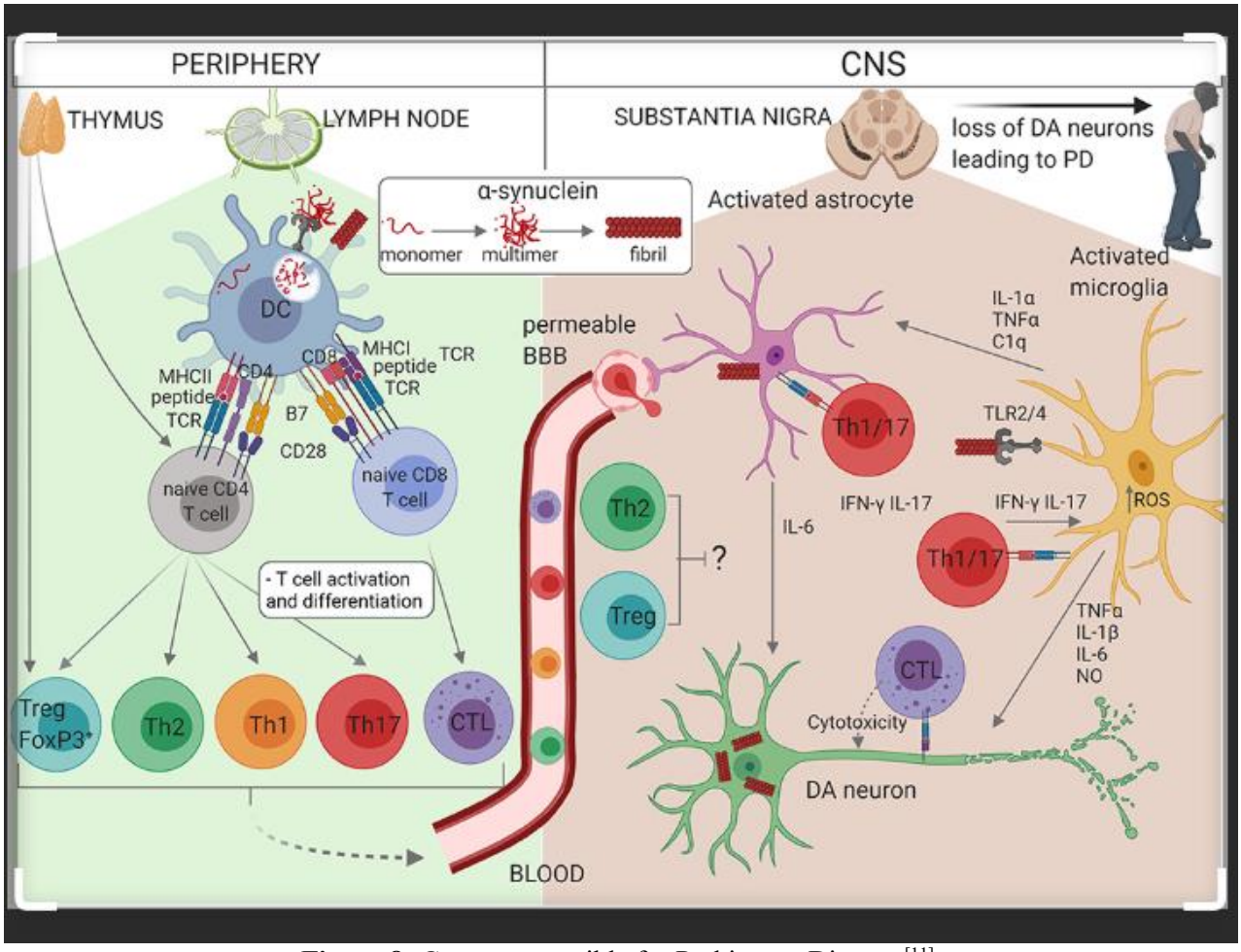

Figure 8: Genes responsible for Parkinsons Disease [11].

Research indicates that overproduction of α-Synuclein protein, produced by the SNCA gene in humans, leads to the degeneration of dopamine neurons.[12] The storage of dopamine is also affected by various mutations within the same gene, such as A53T, A30P, and E46K. These mutations mainly cause the formation of Lewy bodies (LBs), which result in the death of dopaminergic neurons in the substantia nigra pars compacta (SNpc). Mutations in the GBA1 gene, specifically L444P and N370S, represent the most prevalent genetic risk factors for sporadic early-onset Parkinson's disease, particularly in cases that are associated with a swift decline in cognitive function alongside Lewy bodies.[13]

Mitochondrial Dysfunction and Oxidative Stress

Mitochondrial dysfunction is crucial in the development of Parkinson's disease (PD). Accumulated evidence from diverse experimental models and patients with PD has underscored the disturbances in mitochondrial dynamics and energy production impairments associated with PD, which lead to elevated levels of reactive oxygen species (ROS) and intracellular calcium, reduced ATP production, and neuronal damage due to excitotoxicity. Imbalance, in mitochondrial dynamics influences processes such as mitochondrial fission, fusion, transport, mitophagy, and biogenesis.[14]

Autophagy-Lysosome System Dysfunction

Non-functional and abnormal proteins are eliminated through one of three mechanisms: the autophagy-lysosomal pathway, the ubiquitin-proteasome system (UPS), and molecular chaperones. Autophagy is essential in the development of Parkinson's disease (PD) as it facilitates the transport of misfolded proteins and damaged organelles to the lysosome for degradation through various pathways, including macro-autophagy, micro-autophagy, and chaperone-mediated autophagy. Disruptions in these pathways lead to the accumulation of protein aggregates, which is a prevalent pathophysiological feature of PD [2].

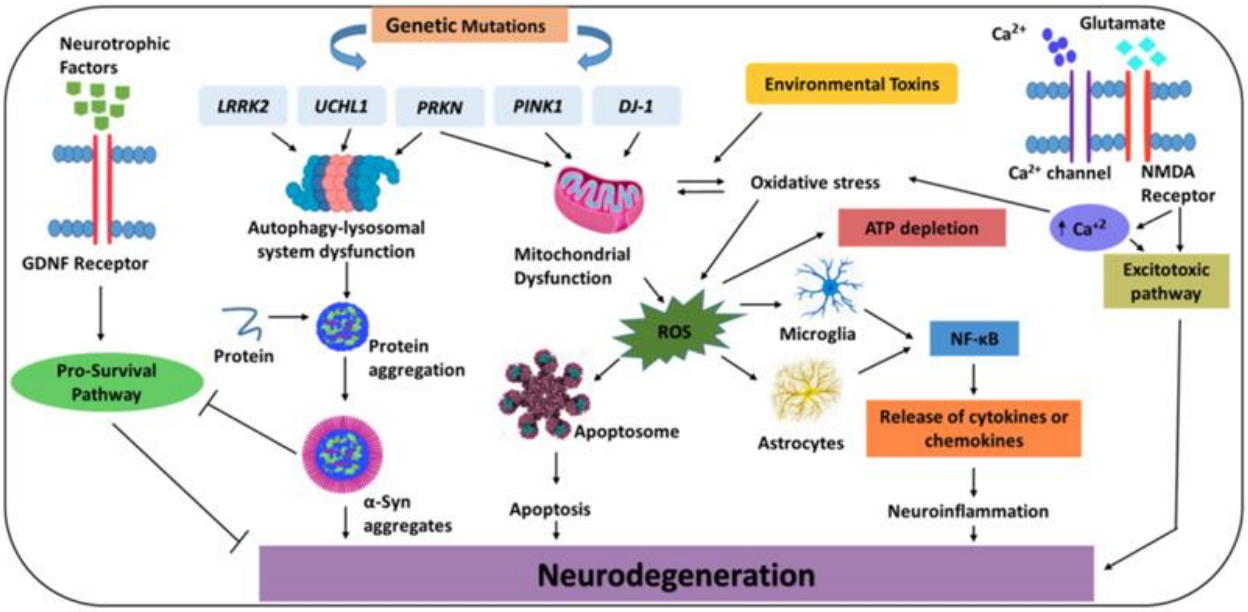

Figure 9: Genetic role in neurodegeneration [14].

Diagnosis

Imaging

The substantia nigra of Parkinson's patients through transcranial sonography and diffusion tensor magnetic resonance imaging (MRI). While transcranial sonography can reveal vulnerability to Parkinson's disease, PET and SPECT assessments of dopamine terminal function can identify dopamine deficiency in both symptomatic individuals and those at risk for Parkinsonian syndromes. Additionally, diffusion-weighted MRI and 18F-fluoro-deoxyglucose positron emission tomography (18F-FDG PET) can effectively differentiate atypical Parkinsonian syndromes from Parkinson's disease with a high degree of sensitivity.[15]

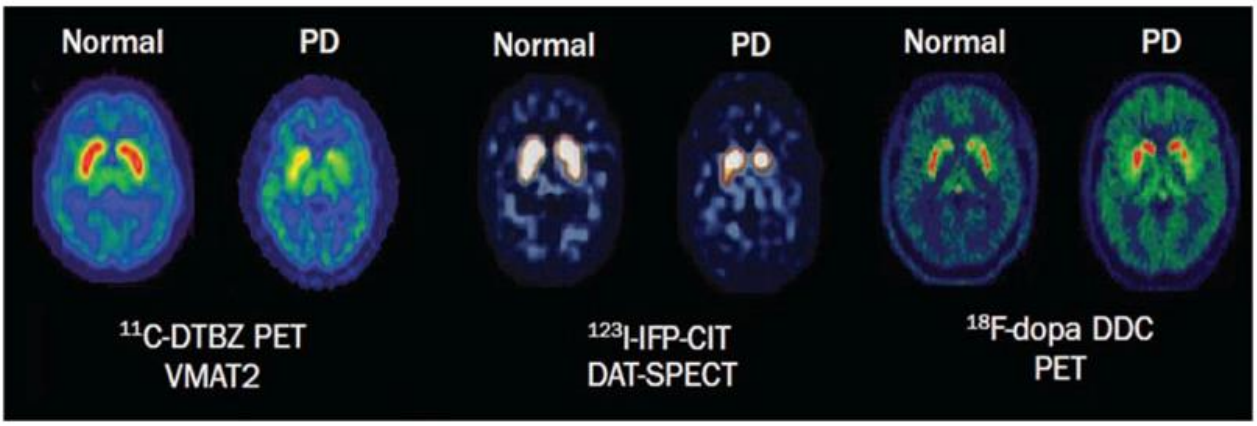

Figure 10: Diagnostic images of Brain [15].

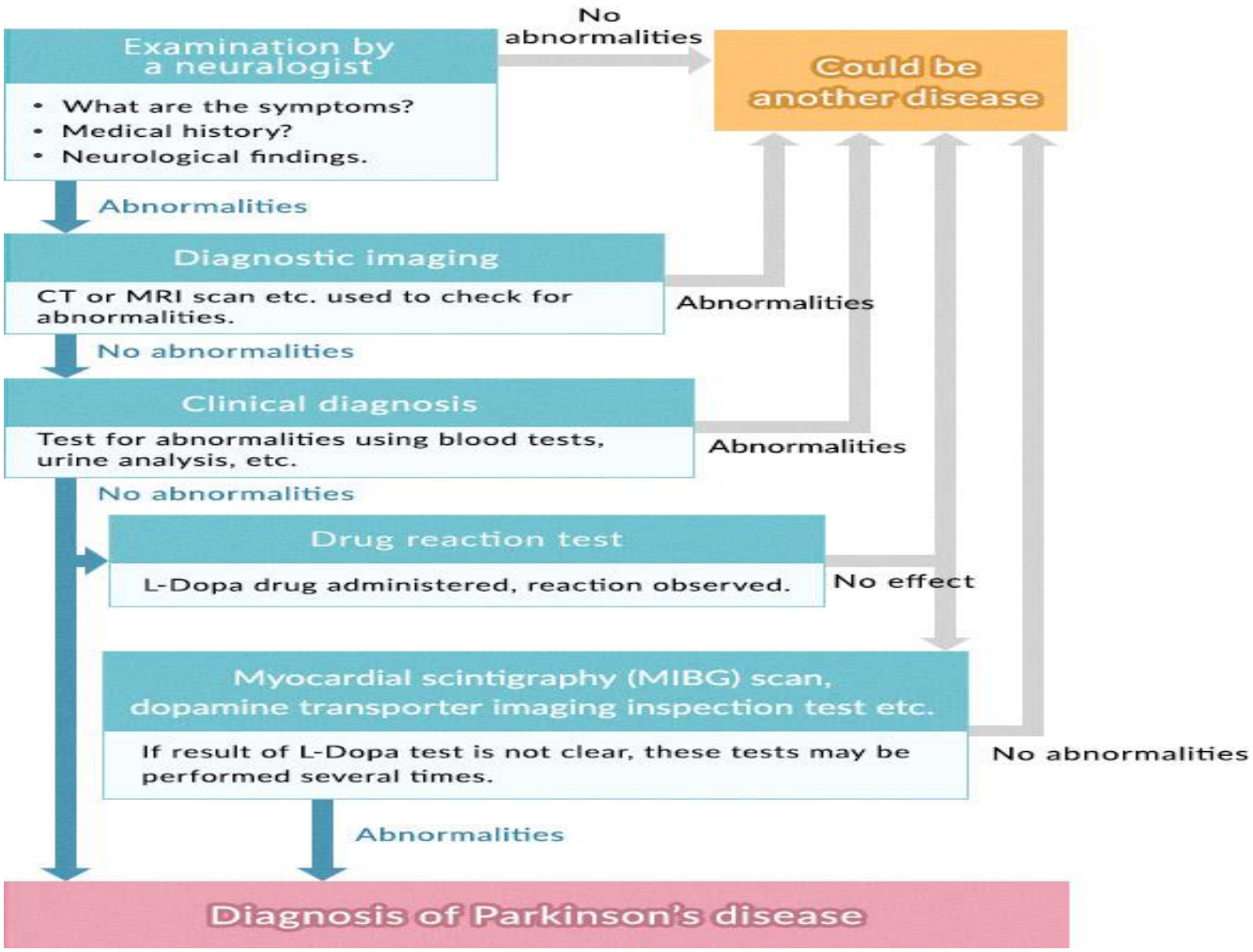

Figure 11: Examination stages of Parkinsons Disease [15].

Non-pharmacological treatments of PDs

The non-drug treatments for personality disorders encompass a range of methods such as physical therapy, occupational therapy, speech therapy, nutritional therapy, and exercise.[16]

Physical therapy aims to enhance mobility, balance, and strength through a variety of exercises, gait training, and the use of assistive devices. Occupational therapy supports patients in retaining their independence by enhancing their capacity to carry out daily tasks and suggesting adaptive methods and tools. Challenges related to speech and swallowing can be tackled through speech therapy. Speech therapy offers exercises to improve articulation, volume, and clarity of speech, along with techniques for managing dysphagia (difficulty in swallowing) [17]

Pharmacological treatments of PDs

Pharmacological interventions for Parkinson's Disease (PD) include

- ✓ levodopa and carbidopa
- ✓ dopamine agonists
- ✓ MAO-B inhibitors
- ✓ COMT inhibitors
- ✓ Anticholinergics
- ✓ Amantadine

Levodopa is a highly effective and frequently prescribed medication for PD, acting as a precursor to dopamine that can cross the blood-brain barrier (BBB) and is then converted into dopamine within the brain. Carbidopa is given alongside levodopa to prevent its premature conversion to dopamine outside the central nervous system, thus reducing side effects such as nausea and increasing the amount of levodopa that reaches the brain.

MAO-B is an enzyme that breaks down dopamine in the brain, which consequently results in increased dopamine levels and improvements in motor symptoms. Entacapone and tolcapone serve as COMT inhibitors, blocking catechol-O-methyltransferase. COMT is an

enzyme responsible for metabolizing levodopa.[10] MAO-A and MAO-B inhibitor drugs are primarily prescribed for the control of emotional behaviour (e.g. depression and anxiety disorders) and neurodegenerative diseases (e.g. Parkinson's disease, Alzheimer's, and possibly amyotrophic lateral sclerosis and Huntington's diseases) [18]

The identification of L-3,4-dihydroxyphenylalanine (L-DOPA) as a crucial treatment for Parkinson's disease (PD) has transformed the way this challenging condition is managed. L-DOPA, an amino acid that serves as a precursor to dopamine and can penetrate the blood-brain barrier, is converted into dopamine by the enzyme aromatic amino acid decarboxylase (AADC) within the presynaptic terminals of dopaminergic neurons. To enhance the efficacy of L-DOPA, medications like carbidopa or benserazide are typically employed to inhibit the peripheral metabolism of dopamine by blocking the enzyme AADC. [19]

Moreover, COMT inhibitors are paired with levodopa to extend its effects and diminish "off" periods. Benztropine and trihexyphenidyl are anticholinergic medications that assist in managing tremors and rigidity by reducing acetylcholine activity. Acetylcholine is a neurotransmitter that may become overly active in Parkinson's disease (PD). Reportedly, this medical treatment may lead to several side effects, including arrhythmia, gastrointestinal discomfort, and significant emotional fluctuations. Thus far, no drug has proven effective in delaying or halting the advancement of the disease, even after neuroprotective assessments. Additionally, effective biomarkers for PD are lacking, and some drugs can cause secondary hallucinations and delusions, along with the challenge of crossing the blood-brain barrier (BBB). All of these issues complicate the diagnosis and treatment of PD.

Dopamine agonists are categorized into two primary groups: ergot-derived and non-ergot-derived. Within the category of ergot-derived dopamine agonists, bromocriptine, sold under the brand name Parlodel, is given orally. Cabergoline and lisuride are also oral medications within this class, but their brand names are not mentioned. Pergolide, marketed as Permax, is another ergot-derived drug available in oral form.

In contrast, non-ergot-derived dopamine agonists include apomorphine, known by the brand name Apokyn, which is given via subcutaneous injection. Ropinirole, sold as Requip, comes in an oral form. Likewise, pramipexole, marketed as Mirapex, is also administered orally. Another important non-ergot-derived medication is rotigotine, which is available as a transdermal patch called Neupro.[20]

Current Treatment Options For Parkinson's Disease

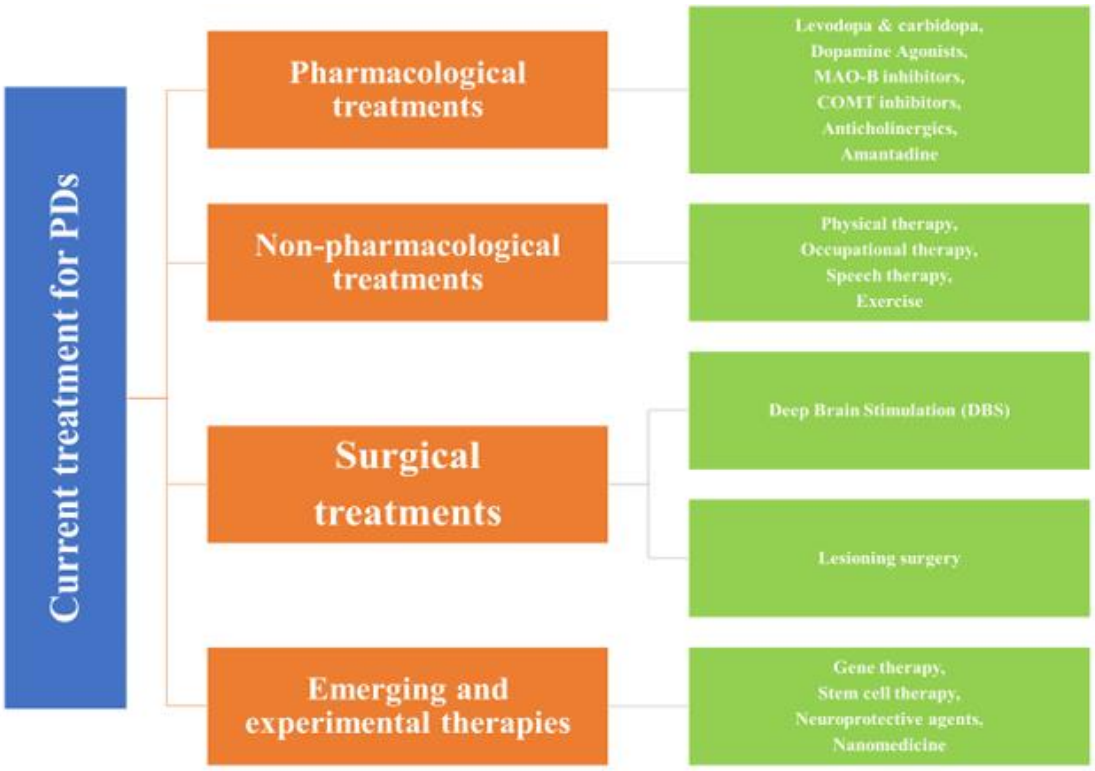

Figure 12: Current treatment of Parkinsons Disease [19,20].

The introduction of L-DOPA for systemic administration was a major milestone in the treatment of Parkinson's disease over 50 years ago, representing a groundbreaking advancement. Nevertheless, existing treatments for PD only address the manifestations of the condition. There are various potential pharmacological targets that could help modify Parkinson's disease, which include tackling neuroinflammation, mitochondrial dysfunction, oxidative stress, calcium channel activity, LRRK2 kinase activity, as well as α-synuclein build up, aggregation, and transmission between cells. Moreover, immunotherapy approaches could also be applied in this area. Additionally, surgical options such as targeted gene therapy, cell transplantation, and deep brain stimulation of the sub thalamic nuclei could be explored as viable strategies.[10]

- ✓ Currently, there are no treatments available that modify the disease progression of Parkinson's disease (PD), and management mainly relies on dopaminergic medications. The most frequently used of these are levodopa preparations, which serve as a dopamine precursor and are given in conjunction with a dopa-decarboxylase inhibitor to mitigate some side effects, like nausea.

Additionally, dopamine agonists, including ropinirole and rotigotine, are utilized. Monoamine oxidase B inhibitors, such as rasagiline and selegiline, along with catechol-O-methyltransferase (COMT) inhibitors like entacapone, can help to slow down the breakdown of natural dopamine. These therapies can enhance dopaminergic activity in the striatum, leading to improvements in the motor symptoms of PD. [19]

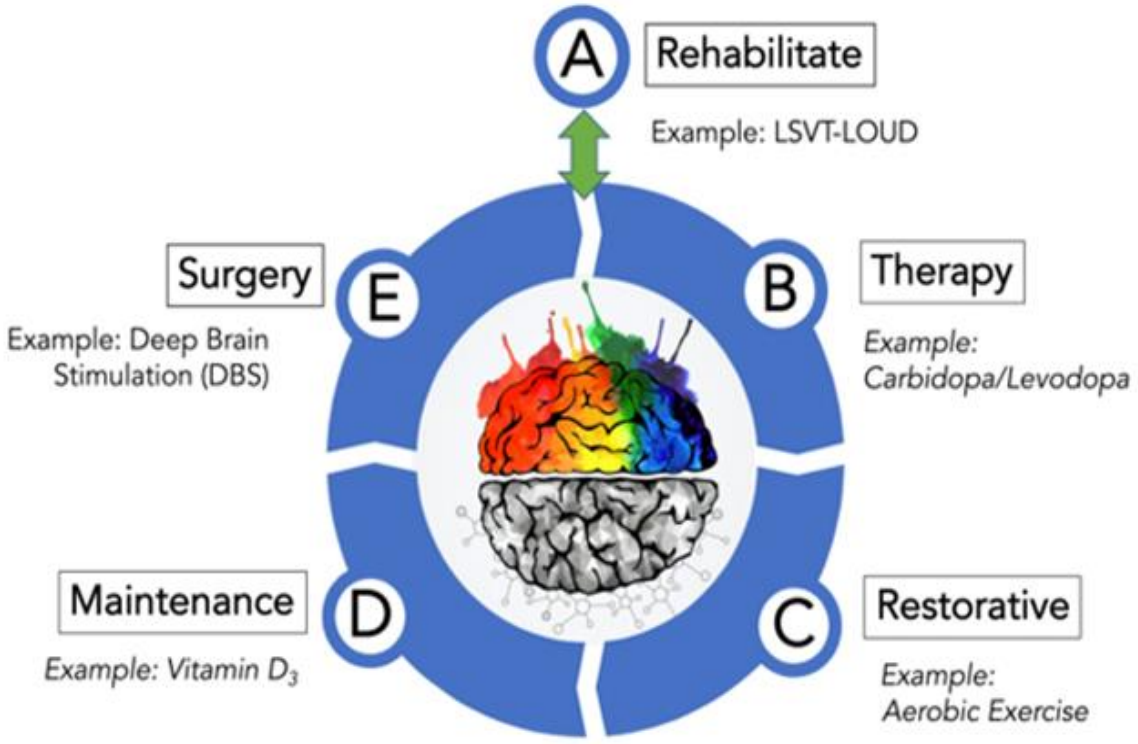

Figure 13: Management of Parkinsons Disease [19].

At present, or in the immediate future, advanced treatment alternatives for the motor symptoms of Parkinson's disease (PD) include or will include

- ✓ deep brain stimulation (DBS)
- ✓ levodopa-carbidopa intestinal gel (LCIG)
- ✓ Apo morphine
- ✓ magnetic resonance-guided focused ultrasound (MRgFUS)

Cell therapy, and gene therapy

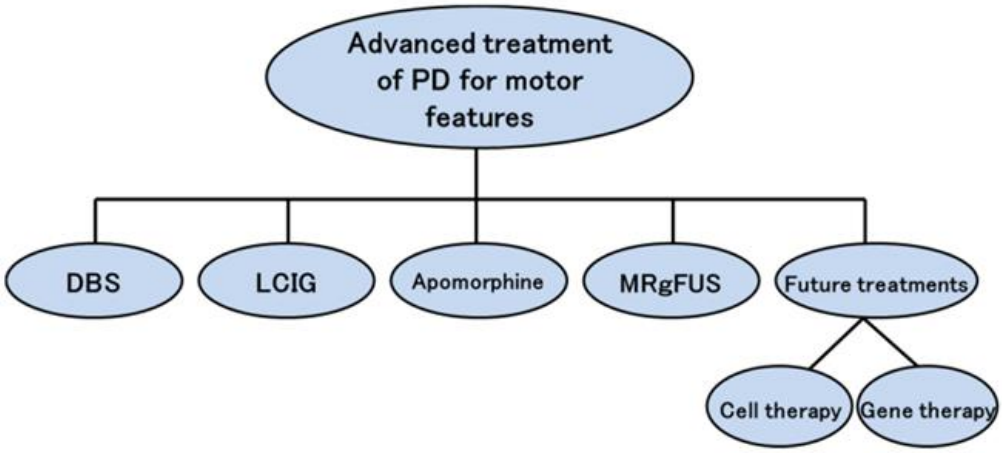

Figure 14: Advanced treatment in Parkinsons Disease [19].

Drugs used in Parkinson's disease

Table 1: Mechanism, Pharmacokinetics and ADR of Anti-Parkinson's drugs [19 to 29].

Category	Mechanism of action	Pharmacokinetic effect	ADR
1.levodopa and carbidopa	Levodopa crosses into the brain and is converted into dopamine by the enzyme DOPA decarboxylase, increasing dopamine levels in the striatum and improving symptoms such as bradykinesia, rigidity, and tremor. However, most Levodopa is normally converted to dopamine in the peripheral tissues, causing side effects like nausea and hypotension and reducing the amount reaching the brain. Carbidopa, a peripheral DOPA decarboxylase inhibitor that cannot cross the blood–brain barrier, prevents this premature conversion. As a result, more Levodopa reaches the brain, peripheral side effects are reduced, and lower doses of Levodopa are required for effective symptom control	**Absorption:** About 70% of an oral levodopa dose is absorbed in the small intestine, where much of it is converted to dopamine by the enzyme AADC. However, only around 1% of the absorbed levodopa actually reaches the brain by crossing the blood–brain barrier **Distribution:** levodopa binds to plasma proteins by about 20–30%, while carbidopa binds at roughly 36%. Although carbidopa cannot enter the brain, it enhances the delivery of levodopa into the CNS **Metabolism:** The combined levodopa–carbidopa regimen has an average half-life of about 1.5 hours. Levodopa is mainly metabolized through decarboxylation, but when this pathway is limited or inhibited, the COMT methylation pathway becomes more significant **Elimination:** Both medications are ultimately eliminated from the body as metabolites through the urine.	1.Nausea 2.Orthostatic hypotension 3. Worsen dyskinesia 4. Hallucination.
2.dopamine agonist	Dopamine agonists help in Parkinson's disease by directly stimulating dopamine receptors—mainly D2 and D3—in the striatum. Since Parkinson's involves	**Absorption** 1.Ropinirole: Well absorbed orally; bioavailability ~50%.	1.worsening dyskinesia

	degeneration of dopaminergic neurons in the substantia nigra and a resulting drop in dopamine levels, these drugs bypass the need for dopamine production and instead mimic its action on postsynaptic receptors. By activating these receptors, dopamine agonists restore signalling in the basal ganglia motor pathways, rebalance inhibitory and excitatory activity, and improve key motor symptoms such as bradykinesia, rigidity, tremor, and motor fluctuations.	2.Pramipexole: Rapid oral absorption; bioavailability >90%. 3.Rotigotine: Delivered via transdermal patch; steady absorption over 24 hours. 4.Apomorphine: Poor oral absorption; given subcutaneously for rapid onset. 5.Bromocriptine: Variable oral absorption due to first-pass metabolism. **Distribution:** Dopamine agonists are lipophilic, allowing good CNS penetration. 1.Protein binding varies: Ropinirole: ~40%, Pramipexole: <20%, Rotigotine: ~92% 2. Large volume of distribution due to high tissue uptake. Metabolism: 1.Ropinirole: **Extensively metabolized in the liver (CYP1A2).** 2. Pramipexole: Not significantly metabolized**; excreted unchanged.** 3. Rotigotine: **Undergoes hepatic conjugation (mainly glucuronidation).** 4. Apomorphine: **Rapid hepatic metabolism.** 5. Bromocriptine: **Extensive hepatic metabolism via CYP3A4.** **Elimination** 1.Pramipexole: Mostly excreted unchanged in urine (renal elimination). 2.Ropinirole: Excreted via urine as metabolites. 3.Rotigotine: Eliminated in urine and faeces as conjugates	2.nausea and vomiting 3.dry mouth and constipation 4. development of compulsive and impulsive behavioural problems (impulse control disorder [ICD]) 5. risk of dopamine agonist withdrawal syndrome (DAWS)
3. Monoamine Oxidase B (MAO-B) inhibitors	MAO-B inhibitors, such as selegiline, rasagiline, and safinamide, work in Parkinson's disease by blocking the monoamine oxidase-B enzyme responsible for breaking down dopamine in the brain. By inhibiting this enzyme, they slow dopamine degradation, increase dopamine availability in the striatum, and prolong its action on postsynaptic receptors. This enhanced dopaminergic activity helps improve motor symptoms like bradykinesia and rigidity, and also extends the therapeutic effect of Levodopa, reducing "wearing-off" episodes	**Selegiline** **Absorption:** Well absorbed orally; bioavailability ~10% due to strong first-pass metabolism. **Distribution:** Highly lipophilic; crosses the blood–brain barrier quickly. Protein binding: About 94%. **Metabolism:** Extensively metabolized in the liver via CYP2B6 and CYP2C19 to active metabolites (including amphetamine derivatives).	MAO-B inhibitors are usually well tolerated, with gastrointestinal discomfort being the most frequently reported issue. Other possible side effects include joint pain, mood changes such as depression, tiredness, dry mouth, sleep disturbances, dizziness, confusion, vivid dreams or nightmares,

		Half-life: Parent drug: 1–2 hours; metabolites: longer (up to 20 hours). **Elimination:** Excreted mainly in urine (metabolites). **2. Rasagiline** **Absorption:** Rapid oral absorption; bioavailability ~36%. **Distribution:** Widely distributed; crosses the BBB easily. Protein binding: ~88–94%. **Metabolism:** Hepatic via CYP1A2; no amphetamine-like metabolites. Half-life: 1.5–3 hours, but MAO-B inhibition lasts much longer due to irreversible binding. **Elimination:** Primarily via urine as metabolites; small amount in faeces.	hallucinations, flu-like complaints, indigestion, and headaches. orthostatic hypotension, sleep disturbances and nervousness/agitation
4.COMT-inhibitor	COMT inhibitors, such as entacapone, tolcapone, and opicapone, work in Parkinson's disease by blocking the catechol-O-methyltransferase (COMT) enzyme, which normally converts levodopa into the inactive metabolite 3-0-methyldopa in the peripheral tissues. By inhibiting this enzyme, COMT inhibitors reduce levodopa breakdown, increase its plasma concentration, and allow more levodopa to cross the blood-brain barrier. This results in higher dopamine production in the brain, leading to improved motor control, reduced "wearing-off" episodes, and prolonged duration of "on-time" in patients receiving levodopa therapy.	Entacapone has a short half-life and low oral bioavailability, requiring multiple doses to maintain its therapeutic effect. Delivering entacapone continuously through infusion directly into the duodenum or jejunum enhances its bioavailability and overall effectiveness. Majorly it is excreted by fecal excretion due to extensive hepatic metabolism and it is also excreted by urine.	Gastrointestinal symptoms - e.g. diarrhoea, abdominal discomfort. Urine (or other bodily fluids) discolouration — often dark yellow, orange, or reddish (harmless but sometimes distressing), especially with entacapone. Dizziness, light headedness, orthostatic hypotension — due to dopaminergic and perhaps peripheral vascular effects. Neuropsychiatric effects: Hallucinations, vivid dreams, confusion, sleep disturbances — particularly in susceptible individuals or the elderly. Other dopaminergic side effects: nausea, vomiting, potential

			for increased impulse-control/compulsive behaviours (with some COMT inhibitor.
5. Anticholinergics	Anticholinergic medications work in Parkinson's disease by inhibiting muscarinic acetylcholine receptors in the brain, especially in the striatal region. The degeneration of dopamine-producing neurons creates an imbalance in which acetylcholine activity becomes disproportionately high. By suppressing this excess cholinergic signalling, these drugs help re-establish neural balance and reduce symptoms like tremor and stiffness. Despite their benefits, they tend to cause more side effects compared to other treatments, which restricts their broader use.	**Absorption:** Most anticholinergic drugs used for Parkinsonism are administered as hydrochloride salts, except for benztropine, which is available as a mesylate salt. With the exception of benztropine mesylate, these agents are rapidly absorbed after oral administration, typically reaching peak plasma concentrations within 2.5 hours. **Distribution:** ACPs have large volumes of distribution, slow post-distribution decline, and long half-lives. Procyclidine shows higher plasma levels due to its low clearance and Vd. Animal studies confirm extensive tissue uptake, especially in the brain, with high brain :plasma ratios and rapid brain entry (within minutes). Their high lipophilicity and possible lysosomal trapping promote this distribution. Plasma protein binding is not well defined in humans, but in animals, ethopropazine is over 95% bound, and orphenadrine and biperiden are approximately 90% bound. **Metabolism and excretion:** Anticholinergic Parkinsonism drugs undergo extensive metabolic processing, primarily through N-dealkylation, N-oxidation, and hydroxylation, with benztropine metabolized in a similar manner. Their relatively low clearance indicates that hepatic first-pass metabolism is limited. Although some ACPs are chiral compounds, the stereo selective aspects of their metabolism are not well explored. Orphenadrine and its metabolite are known to influence cytochrome P450 activity. Both the parent drugs and their metabolites are eliminated through urinary and biliary excretion.	Peripheral ADRs: Blurred vision (impaired accommodation) Dry mouth and dry mucous membranes Urinary retention Constipation Nausea Reduced sweating (risk of overheating) Dental issues such as gingivitis and dental caries Contraindicated in: narrow-angle glaucoma, tachycardia, prostatism Central Nervous System ADRs Confusion and disorientation Hallucinations Sedation Short-term memory impairment Worsening of frontal lobe dysfunction Higher risk in elderly patients and those with dementia Other Important ADRs: Can induce or worsen dyskinesia's (alone or with levodopa). Abrupt withdrawal may cause rebound worsening of Parkinsonism

Deep Brain Stimulation (DBS)

Currently, DBS has emerged as one of the most effective surgical options for treating advanced stages of PD, with numerous patients around the globe having undergone the procedure. In DBS, electrodes are placed deep within the brain, a pulse generator is positioned in the chest wall, and an electric current is transmitted via a connected lead wire to stimulate the targeted area of deep brain tissue. Presently, DBS is recognized as one of the most effective surgical interventions for advanced PD, having been conducted on many individuals worldwide. In addition to selecting the DBS target and the parameters for stimulation, modern technologies have facilitated a personalized treatment strategy for PD. When it comes to brain targets, the subthalamic nucleus (STN) and globus pallidus internus (GPi) are frequently selected for DBS in PD patients.[30]

To focus on particular areas of the brain for electrical stimulation and regulation during Deep Brain Stimulation (DBS), an electrode is inserted into designated brain regions, and high-frequency electrical stimulation (100–200 Hz) is applied to replicate the impact of a lesion while preserving brain tissue.[10]

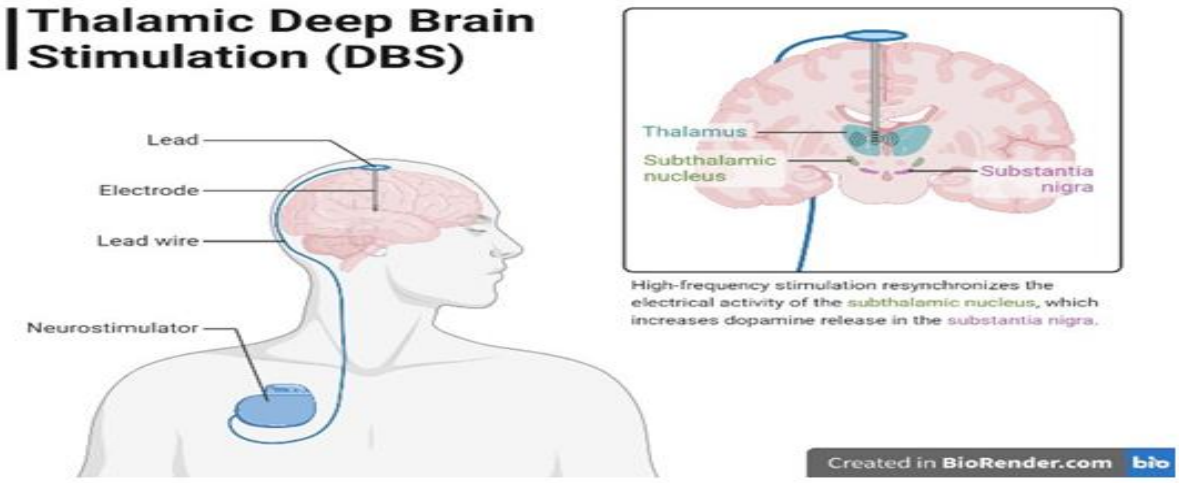

Figure 15: Deep Brain stimulation [30].

Continuous intra-jejunal administration of levodopa (LCIG/LECIG)

Continuous intra-jejunal administration of levodopa (LCIG/LECIG) involves delivering levodopa as a gel directly into the jejunum through a percutaneous endoscopic jejunal tube (PEJ). This method bypasses swallowing and stomach passage, leading to more stable and effective drug levels. A benefit of LCIG therapy is the ability to assess its effectiveness using a nasojejunal tube before PEJ insertion. However, it requires ongoing effort for cartridge changes and pump connections/disconnections.[31]

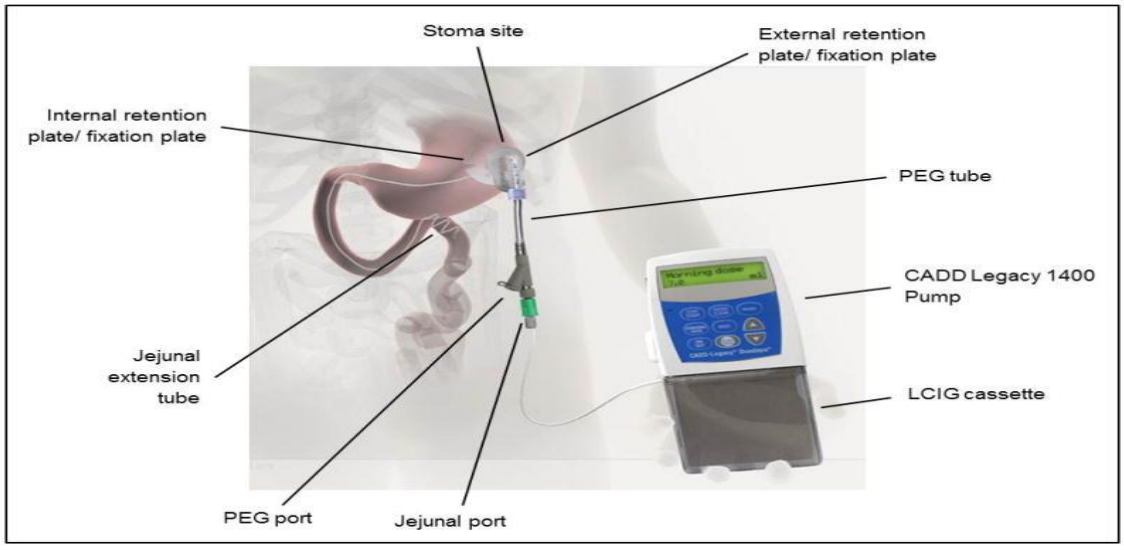

Figure 16: Intra jejunal administration levodopa [31].

Continuous application of subcutaneous apomorphine (CS)

Continuous application of subcutaneous apomorphine (CSAI) Apomorphine, which acts as a dopamine D1- and D2-receptor agonist, has been utilized in the treatment of Parkinson's disease for numerous years. Due to its pronounced first-pass effect, its administration is limited to parenteral methods. Consequently, subcutaneous application is employed, either intermittently through a pen to manage delayed-on phenomena or sudden-offs, or continuously via a pump to control fluctuations. Recently, sublingual administration of apomorphine has been introduced. Similar to LCIG, the continuous subcutaneous infusion of apomorphine (CSAI) bypasses the gastrointestinal tract, facilitating ongoing drug administration and absorption, which leads to more stable plasma drug levels.[31]

Parkinson's disease gene therapy

Over the years, several gene therapy approaches have been used in clinical trials. The tactics can be divided into several main groups:

- Increasing the synthesis of dopamine:
- Promoting dopamine neurons' survival
- Assisting dopamine neurons in surviving
- Counteracting genetic mutations that contribute to PD risk

Stem cell-based methods

Stem cells may develop into any form of cell in the body and have the ability to self-renew through limitless reproduction. Therefore, an infinite number of cells could be employed for neural grafting if the fate of these cells could be changed to become dopaminergic neurons. The most promising stem cell types for treating Parkinson's disease (PD) are induced pluripotent stem cells (iPSCs) and embryonic stem cells (ESCs).[32]

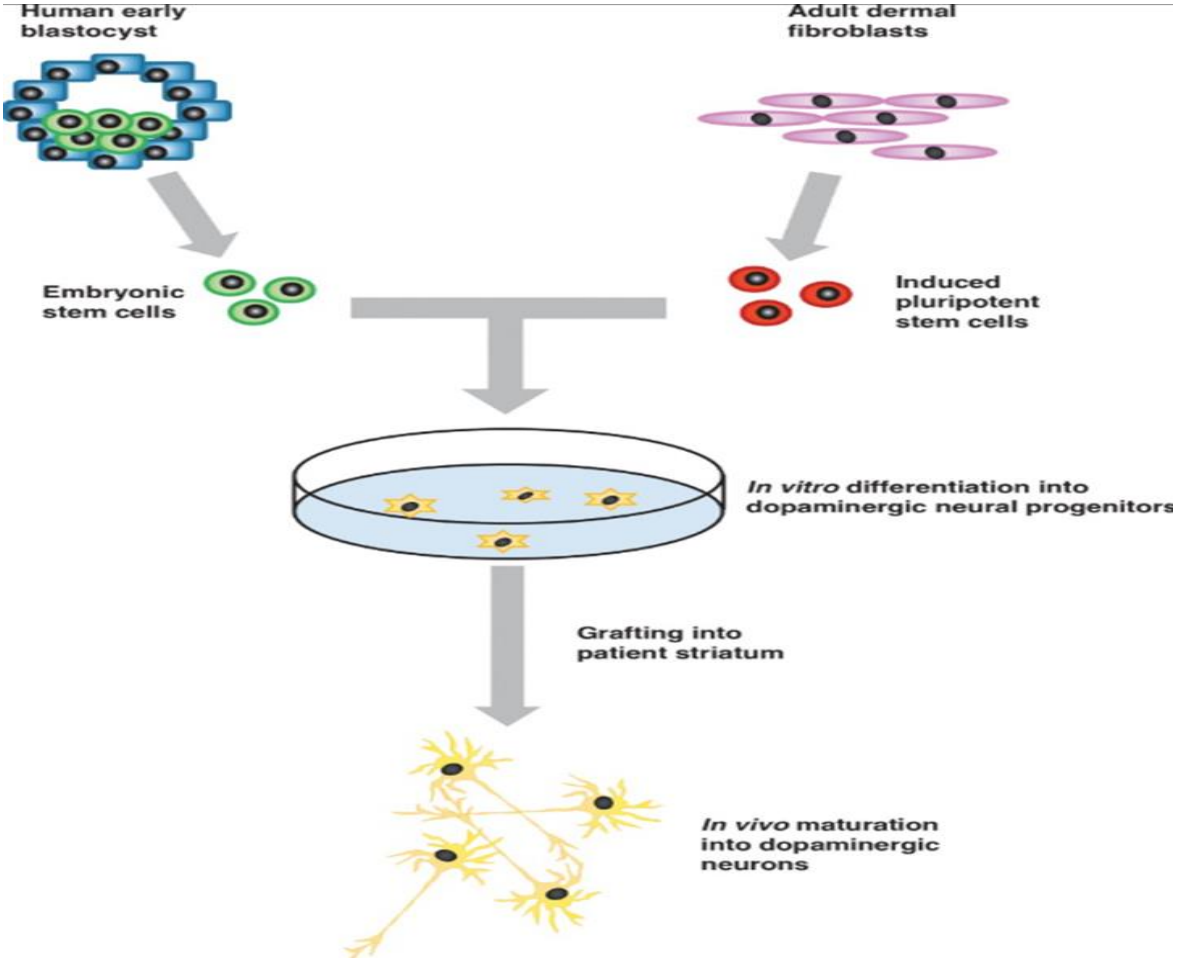

Figure 17: Pluripotent stem cell method [33].

Pluripotent stem cells

When the method for producing iPSCs was first described in 2007, it opened up a new possibility for the creation of a stem cell-based therapy for Parkinson's disease (and several other illnesses) . By expressing several transcription factors that may induce pluripotency, such as c-myc, klf-4, sox2, and oct4, an adult somatic cell (like a dermal fibroblast) can be reprogrammed into a stem cell, producing iPSCs. By following procedures akin to those employed with ESCs, the iPSCs generated in this manner can differentiate into dopaminergic neurons, potentially forming the foundation of a beneficial cell-based therapy for Parkinson's disease.

The potential benefit of iPSC-derived grafts over ESC-derived grafts is that autologous grafts could be created by using the patient's own fibroblasts to create a neural grafting product, obviating the need for immunosuppression that ESC-derived grafts require. The iPSC approach does, however, present additional biological and practical difficulties, which are covered below.

With encouraging outcomes, iPSC-derived neural grafts have been tested in primates with nigral toxicity brought on by MPTP. At two years, the neural progenitors that were grafted improved motor function, did not develop any tumors, and eventually extended neurites into the striatum. Human clinical trials are anticipated to start in the coming years, similar to the ESC-approach.[33]

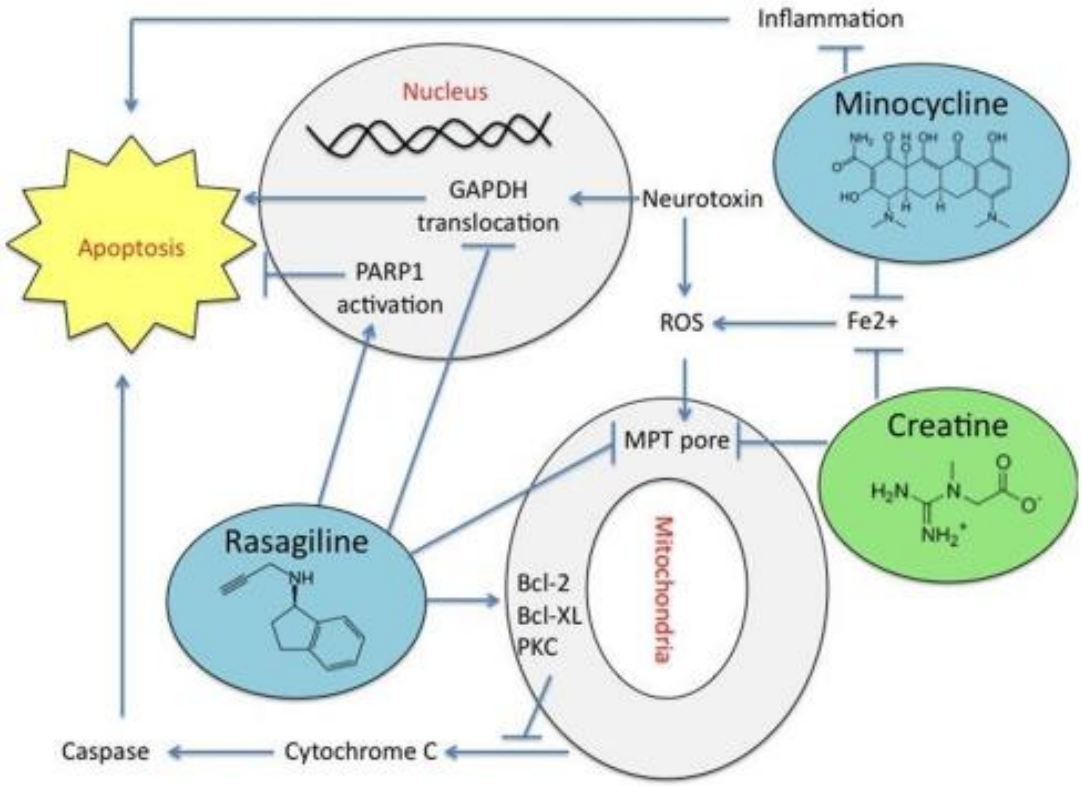

Figure 18: Cell death process involved in PD [25].

Conclusion

Parkinson's disease (PD) is a progressive, multifactorial neurodegenerative disorder in which genetic predisposition, environmental exposures, and aging collectively drive the degeneration of dopaminergic neurons and widespread α-synuclein pathology. The disease extends far beyond its characteristic motor symptoms, involving significant non-motor manifestations that often appear years before clinical diagnosis, highlighting the importance of recognizing the prodromal phase. Advances in understanding the molecular mechanisms—such as mitochondrial dysfunction, oxidative stress, impaired autophagy–lysosomal pathways, and neuro inflammatory processes—have deepened our insight into the biological basis of PD and identified key therapeutic targets. Although current treatments remain largely symptomatic, ongoing research into disease-modifying strategies, including gene therapy, neuroprotective agents, and immunomodulation, holds substantial promise. Emerging diagnostic tools, such as α-synuclein seed amplification assays and advanced

neuroimaging techniques, may enable earlier detection and personalized intervention. As scientific progress continues to bridge the gap between mechanistic understanding and therapeutic innovation, a more precise and effective management approach for PD is becoming increasingly attainable. Continued interdisciplinary research and early identification efforts will be crucial in altering the course of this complex disorder and improving patient outcomes. Current treatments such as levodopa, dopamine agonists, MAO-B and COMT inhibitors, and deep brain stimulation provide significant symptomatic relief but do not halt disease progression. However, emerging evidence highlights promising disease-modifying strategies targeting the root mechanisms of PD, including α-synuclein aggregation, mitochondrial dysfunction, oxidative stress, and impaired autophagy–lysosomal pathways. Gene therapies aimed at restoring dopaminergic function, enhancing neurotrophic support, or correcting genetic mutations such as those in SNCA, LRRK2, and GBA1 are advancing into clinical trials. Additionally, novel immunotherapies, small-molecule inhibitors, and neuroprotective agents show potential in reducing neuroinflammation and preserving neuronal integrity. Improved delivery systems, such as viral vectors and nanoparticle-based carriers, are enhancing the precision and safety of these approaches. Parallel advancements in early diagnostics—particularly α-synuclein seed amplification assays and advanced neuroimaging—may allow therapeutic interventions to begin during the prodromal phase, when disease-modifying treatments are most likely to be effective. Together, these innovations represent a transformative shift toward personalized, mechanism-driven care that aims not only to manage symptoms but to slow or prevent the progression of Parkinson's disease.

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Conflict of Interest

None declared.

Author Contributions

All the authors contributed to the study.

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