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PARKINSON'S DISEASE

OVERVIEW AND LATEST UPDATES IN CLINICAL TRIALS

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ABSTRACT

Parkinson's disease is the second most common neurodegenerative disease in the elderly population, with a higher prevalence in men, independent of race and social class; it affects approximately 1.5-2.0% of the elderly population over 60 years and those over 80 years of age. Many factors such as environmental and genetic factors influence Parkinson's disease risk with different factors predominating in different patients. These factors are based on specific pathways including mitochondrial dysfunction, oxidative stress, protein aggregation, impaired autophagy, and neuroinflammation. Ultimately, treatment for Parkinson's disease may focus on targeted therapies for defined subtypes of PD patients. Even though effective medicines are available for Parkinson's disease there is no total cure.

Keywords: Parkinson's disease (PD), Substantia Nigra pars compacta (SNpc), Postural instability or gait difficulty (PIGD), Tremor-dominant [TD], Dopamine2 Receptor (D2R), SNCA-Synuclein Alpha.

1.INTRODUCTION

Parkinson's disease [PD] is one of the most common neurodegenerative disorders based especially on age [1]. It is associated with dopamine deficiency and both motor and nonmotor deficits [4]. Parkinson's disease is a chronic progressive disorder that affects the nervous system characterized by the cardinal features of rigidity, bradykinesia, tremor, and postural instability [1]. In addition, Parkinson's disease with medication-resistant properties is treated with deep brain stimulation [2]. It is a complex disease that has many different symptoms so not everyone with the condition suffers from the same problem. The disease was first described as a "shaking pulse" by James Parkinson in 1817. Although more than a century passed before the central pathological feature of Parkinson's disease was found to be the loss of neurons in the *Substantia Nigra pars compacta (SNpc)* [41].

SNpc neurons were responsible for the formation of the nigrostriatal dopaminergic pathway. First loss of SNpc neuron leads to striatal dopamine deficiency, which is responsible for the major symptoms of Parkinson's disease. The second replenishment of striatal dopamine through the oral administration of the dopamine precursor levodopa (L-3, 4-Dihydroxyphenylalanine) alleviates most of these symptoms.

Although the discovery of levodopa revolutionized the treatment of Parkinson's disease, the presentation can vary considerably across individuals with an identical toxic cause for their Parkinsonian signs, Such exposure to the neurotoxin *1-methyl-4 phenyl- 1,2,3,4 tetrahydropyridine (MPTP),* a heroin analog. There are over 6 million different variations of Parkinson's disease in the world [17].

2. TERMINOLOGY

Parkinsonism describes a syndrome characterized by rigidity, tremors, and bradykinesia, of which Parkinson's disease is the main cause. Parkinson's disease is lopsided and responsive to dopaminergic treatment. Pathological findings show that nigral dopamine neurons are greatly diminished and Lewy bodies are present in the remaining neurons [2].

3. EPIDEMIOLOGY

Parkinson's disease, which was first described in "An Essay on the Shaking Pulse" in 1817 by a London physician James Parkinson, has probably existed for thousands of years [41]. In India, the prevalence rate of Parkinson's disease per 100,000 population is 14 in Northern India, 27 in the south, and 16 in the east, while it is 363 for Paris and Mumbai. Parkinson's disease affects 1-2 per 1000 of the population at any time. Parkinson's disease prevalence is increasing with age and Parkinson's disease affects 1% of the population above 60 years [4, 19].

4. FACTORS INFLUENCING PARKINSON'S DISEASE

Both environmental and genetic factors influence Parkinson's disease risk with different factors predominating in different patients. These factors are based on specific pathways including mitochondrial dysfunction, oxidative stress, protein aggregation, impaired autophagy, and neuroinflammation.

10 to 20%of PD cases are usually due to genetic causes [40]

- Age: People with age between 60 and above are highly affected.
- Gender: Sex plays a major role in PD; This affects males more than females. However, females have a high death rate due to this disease.
- Genetics: Genetic mutations are one of the major causes of Parkinson's disease.
- Environmental cause: Clinical experts believe that environmental changes and conditions help to trigger Parkinson's disease. Exposure to radiation causes DNA damage, and exposure to farming chemicals like pesticides and herbicides, heavy metals, detergents and solvents, and other hazardous chemicals are also been a causes to develop PD [40].
- Head Trauma: Epidemiological studies prove that repeated blows to the head and traumatic head injury cause an increased risk of acquiring PD [12].

5. CLINICAL FEATURES OF PARKINSON'S DISEASE IN MALE AND FEMALE

IN MALE

- High cholesterol level, Deficit in the functioning of the human body, Camptocormia, Drooling, Trembling of hands, legs, jaws, etc…

IN FEMALE

- Visual system dysfunction, Tremors, Pain in the right side part of the body, Dysphagia, Gastrointestinal dysfunction, Frequent falls

IN BOTH

- High urate level, Low physical activity, Anxiety, Depression, Insomnia, REM disorder

People above 65 years of age are mainly affected. Pathology of this disorder relies on the loss of midbrain ***dopaminergic neuron***s in ***Substantia Nigra Pars Compacta.***

The etiology of PD is not known well, in spite

PD is an idiopathic, multifactorial disease that can be due to genetic mutations and environmental factors [17, 20].

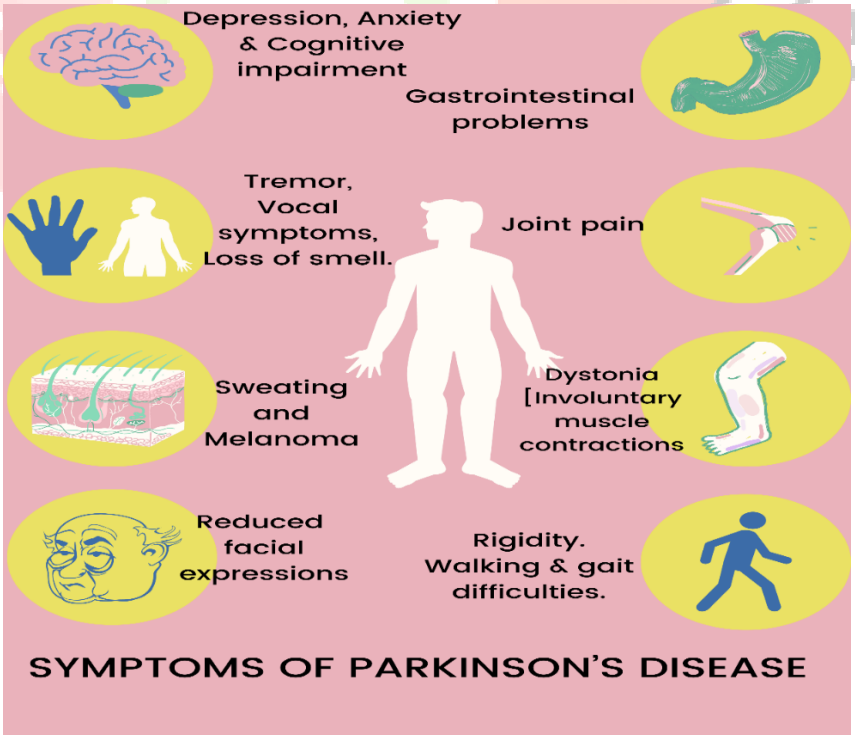

figure1: parkinson's disease symptoms (canva) [17,20]

6. MANAGEMENT OF NONMOTOR SYMPTOMS

In the early stages of PD, nonmotor symptoms are more common. These symptoms lower the risk to a patient's quality of life, and treating these symptoms improves the quality of life for patients.

Fatigue and Sleep disturbance:

One-third of patients with PD experience fatigue associated with the severity of the illness, less common in patients treated with carbidopa/levodopa. Methylphenidate increases fatigue in patients. Excessive sleepiness occurs with both PD and medications. Melatonin cannot improve sleep. Three Randomized small trials showed that modafinil improves sleepiness [3].

7. NEUROANATOMICAL CHANGES IN PD

In Parkinson's disease, understanding the cognitive impairment susceptibility is important for the diagnosis and treatment of PD.

Neuroanatomical changes in PD are as follows:

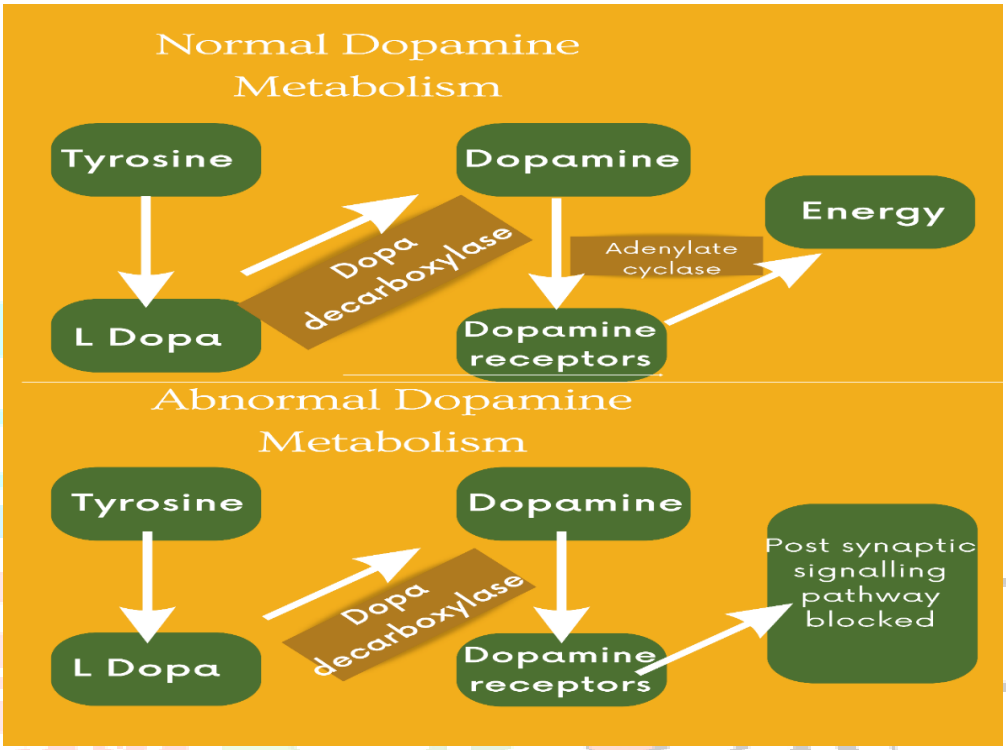

figure 2: normal vs pd brain function (canva) [15]

7.1 Changes in Basal Ganglia

Impulses from the cortex for execution of voluntary movements are controlled by Basal Ganglia, the most affected area in PD. 2 subtypes of PD are Tremor-dominant [TD] reduced fractional anisotropy within Substantia nigra have been reported and with Postural instability or gait difficulty [PIGD] microstructure within the substantia nigra is severely affected. High reduction in neuromelanin pigmentation, neuronal loss, and Lewy bodies have been observed in the substantia nigra. Volume reduction of the caudate nucleus, Thalamus, and white matter of the brain is the early sign of progression of disease [18].

The study called “The Importance of Early Identification for Parkinson's Disease Patients with Postural Instability and Gait Disturbance" proved that PIGD-PD has high disease severity, in this study 270 patients with PD were involved. This PIGD had more severe axial symptoms such as gait, bradykinesia, and other motor symptoms. In this study, TD-PD patients showed mild symptoms [48].

7.2 Changes in Cerebellum

Increased activity of the cerebellum during cognition is impaired during PD. Changes in the cerebellum such as reduction in the volume of grey matter of the brain in the right Quadrangular lobe with contraction in the left cerebellum. The cerebellum connection is reciprocal to the Basal ganglia.

7.3 Changes in Volume of Brain

Cognitive functions of the brain play a major role in describing the size and volume of the Brain. Atrophy of the brain in cortical and subcortical areas contributes to changes in the brain in PD-affected Patients. There are other reports like the increased volume of the Frontal lobe, Temporo parietal junction, parietal lobe, insula, cortex, ganglia, and thalamus.

7.4 Changes in Thalamus

Stimulation of the thalamus leads to improvement of cognition through the hippocampus and neocortex and changes in gene expression. Thalamic lesion formation affects cognition including 30-40% neuronal loss with a reduction in the volume of the brain. Depression in PD patients is due to changes in the mediodorsal thalamus.

7.5 Changes in Hypothalamus

Degeneration in the predominant area of the tuberomammillary nucleus lateral hypothalamic nuclei and posterior hypothalamic nuclei with neural degeneration in all 13 nuclei of the hypothalamus causes changes in brain function, thereby leading the way to PD. Decreased levels of neurotransmitters such as dopamine, melanin, serotonin, and hypocretin have been reported for PD in the hypothalamus.

7.6 Changes in the Limbic System

Changes in the Limbic system lead to atrophy of the grey matter of the brain with dopamine dysfunction affecting emotions and the creativity level of the brain. Cortical and central nuclei are affected during PD.

7.7 Changes in the Locus Coeruleus region of the brain

Dopaminergic neuronal loss in this region results in metabolic dysfunction in the cerebral cortex and impairment of cognitive functions.

7.8 Changes in Glial cells

Altered neuroglial interaction is the reason behind neurodegenerative disorders like PD. The altered neuroglial function causes changes in astrocytes and synaptic communication [18].

8. NEUROTRANSMITTERS IN PD

Neurotransmitters are chemical substances often referred to as Body's chemical messengers. The molecules are used by the nervous system to transmit messages between neurons, or from neurons to muscles. Communication between two neurons happens in the synaptic cleft [small gap between synapses of neurons].

8.1Dopamine

Pathology of PD is based on the loss of Dopaminergic neurons in substantia nigra pars compacta, which causes motor impairments. Amino acid tyrosine is further metabolized to form dopamine. Reduction in the level of dopamine or the inability of the D2 receptor to accept dopamine molecules causes PD [15].

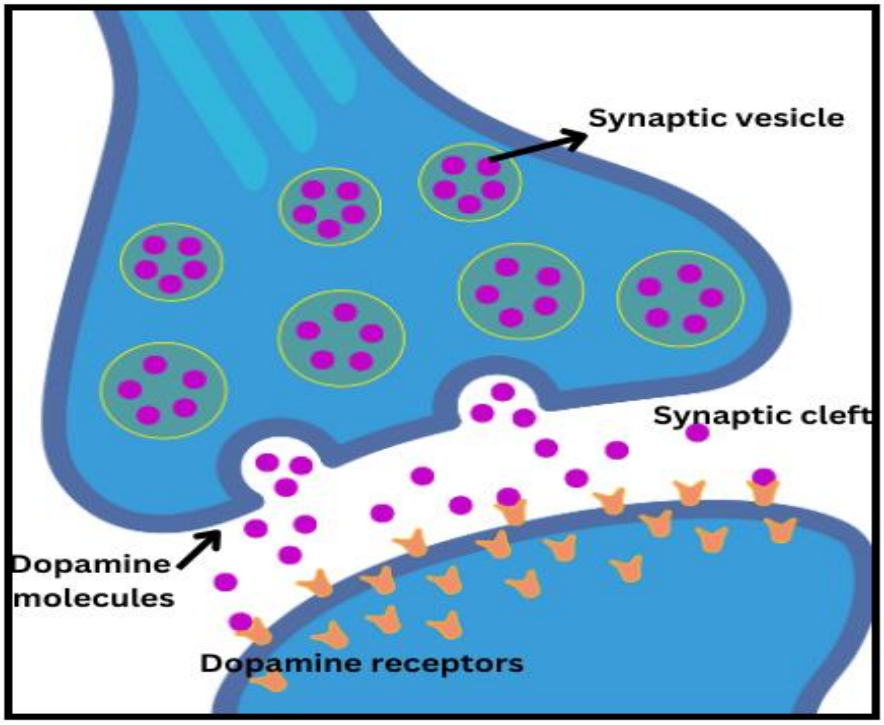

figure 3: dopamine metabolism (canva) [15]

8.2 Acetylcholine

The imbalance between Dopamine and acetylcholine transmission via D2 receptor and Muscarinic receptors mainly M4 receptors causes PD.

Auto inhibition of acetylcholine release by Autoreceptor is blocked leading to Surplus acetylcholine release.

8.3 Serotonin

Serotonergic neurons [5-HT] have interactions with all brain structures with a high degree of axonal branching. Dopamine loss can be covered by 5-HT hyperactivity.

Dopaminergic and serotonergic interaction in glutaminergic neurons via Dopamine and serotonin receptors.

8.4 GABA Gamma-aminobutyric acid

Gamma-aminobutyric acid acts as a primary inhibitory neurotransmitter for the Central Nervous System. Presynaptic inhibitory action of GABA in the striatum, Globus pallidus internus, and Globus pallidus externus via GABAα and GABAβ receptors. Dopamine loss is increased by GABA hypofunction with interaction between glutaminergic neurons and GABA α receptors. Has therapeutic value for PD.

8.5 Glutamate

An imbalance in GABAergic and glutaminergic neurotransmitters with a GABA deficiency and a glutamate hyperactivity compensates for GABA loss in PD [18].

9. DIAGNOSTIC CRITERIA AND DIFFERENTIAL DIAGNOSIS OF PARKINSON'S DISEASE

Accurate diagnosis of PD is a complicated process. Physicians must carefully weigh the symptoms, Family history, and other factors to conclude. There's no specific test for PD, Due to this, patients with very early stages may not be able to get proper treatment for the disease.

9.1 CONDITIONS THAT HAD TO BE CONSIDERED IN DIFFERENTIAL DIAGNOSIS OF PARKINSON'S DISEASE

Tremor: Neurological disorder which usually affects hands, this can be mistakenly diagnosed as PD but tremor does not cause other symptoms of PD.

Parkinsonism: Some antipsychotic drugs can cause this effect.

Multiple system atrophy [MSA]: Neurodegenerative disorder with some of the symptoms of PD like slow movements, and instability.

Progressive d+supranuclear palsy [PSP]: Rare neurodegenerative disorder that involves problems with balance, eye movements, and gait.

Dementia with Lewy bodies [DLB]: Associated with abnormal deposits of alpha-synuclein protein that affects brain functions [6, 21].

Wilson's disease: Genetic disorder that causes accumulation of copper in various organs such as the brain, liver, etc. This also has similar symptoms of PD.

Normal pressure hydrocephalus [NPH]: Excess buildup of cerebrospinal fluid in the ventricles of the brain.

Stroke or Vascular parkinsonism: Affects movement control [1, 7].

10. PROGNOSIS

Patients with PD suffer a progressive decline in motor and cognitive impairment with a high mortality rate showing bradykinesia, tremor, and rigidity at diagnosis. Community-based cohort studies in Norway have identified that men with PD at the age of 70 had a life expectancy of eight years and women at 70 had a life expectancy of 11 years [3].

11. NEUROIMAGING:

Neuroimaging of PD includes Magnetic Resonance Imaging, Positron Emission Tomography, or Single Photon emission, Computed Tomography.

Changes in Neurotransmitters in various regions of the brain and their influence on the brain network are the reason for symptoms of PD.Imaging data were classified into 3 types based on their differences

1. Anatomical
2. Functional
3. Metabolic differences.

Biomarkers are measured and evaluated to indicate normal vs pathogenic or pharmacological responses to therapeutic intervention.There's no specific biomarker currently available to predict the onset of PD.PD biomarkers of SN neurons include

- Prodormal, preclinical, promotor stage biomarkers – Development stage biomarkers.
- Biomarkers of risk or susceptibility
- Motor stage biomarkers

Examples of biomarkers

Fluid and tissue biomarkers include; Alpha-synuclein.

Genetic biomarkers include; the SNCA gene [5, 7, 8, 9, 42].

Transcranial Sonography is a test that is not based on invasive methods used to reveal structural changes in SNpc. The study named "Substantia Nigra Echogenicity Signal Correlated with Clinical Features in Patients with Parkinson's Disease in Xinjiang" investigated the relationship between SN and clinical features of PD in China. A total of 147 people had undergone TCS [Transcranial Sonography] and both motor and nonmotor symptoms were analyzed [46].

12. BIOMARKERS OF PARKINSON'S DISEASE IN VARIOUS STAGES

table 1: biomarkers in various stages of parkinson's disease [5, 10, 18, 42]

Predormal Parkinson's Disease	Preclinical Parkinson's Disease	Clinical Parkinson's Disease
Hyposmia (olfactory deficits)	Molecular imaging, DAT SPECT	Akinesia, Bradykinesia, Hypokinesia.
Depression, Anxiety	Florodopa PET scan, MRI	Instability, Rigidity.
Anhedonia, sleep disorders, urogenital dysfunction.	Transcranial sonography, Optical Resonance Tomography.	Gait impairment
Mood disorders and Neurobehavioural abnormalities.	Biochemical and genetic biomarkers	Stiffness of arms and legs.

12.1 Predormal Parkinson's Disease:

This starts with nonmotor and subtle motor symptoms with the pathology of Parkinson's Disease. Premotor symptoms may show pathogenic processes in the development of PD.

12.2 Preclinical Parkinson's Disease:

In this stage, there are no clinical symptoms.

12.3 Clinical Parkinson's Disease:

Motor stage biomarkers serve to chart disease progression and aid in determining the efficacy of various therapies given in the period when motor symptoms are readily apparent due to marked degeneration of SN neurons. Classical motor manifestations are present [18,42]

13. CAUSES AND PATHOGENESIS

PD neuropathology depends on selective loss of dopaminergic neurons in the substantia nigra pars compacta, involved in Central nervous system and peripheral tissues. Pathogenesis is based on genomic, epigenetic, and environmental factors that lead to trembling and instability. Conventional treatments for PD are the dopamine precursors [Laevodopa, I- DOPA, 1-3,4 Dihydroxifenilalanina] and other treatments including dopamine agonists (amantadine, apomorphine, bromocriptine, cabergoline, lisuride, pergolide, pramipexole, ropinirole, rotigotine), monoamine oxidase inhibitors (MAO) such as selegiline, rasagiline and catechol-*O*-methyltransferase inhibitors (COMT) such as entacapone, tolcapone.

Administration of Antiparkinsonian drugs induces the "wearing off phenomenon of PD". Since biochemical and therapeutic outcomes are highly dependent on the genomic profiles of PD patients, personalized treatments should rely on pharmacogenetic procedures to optimize therapeutics.

PD is due to the loss of nerve cells in the part of the brain called the substantia nigra. Nerve cells in this part of the brain are responsible for producing a chemical called dopamine [12].

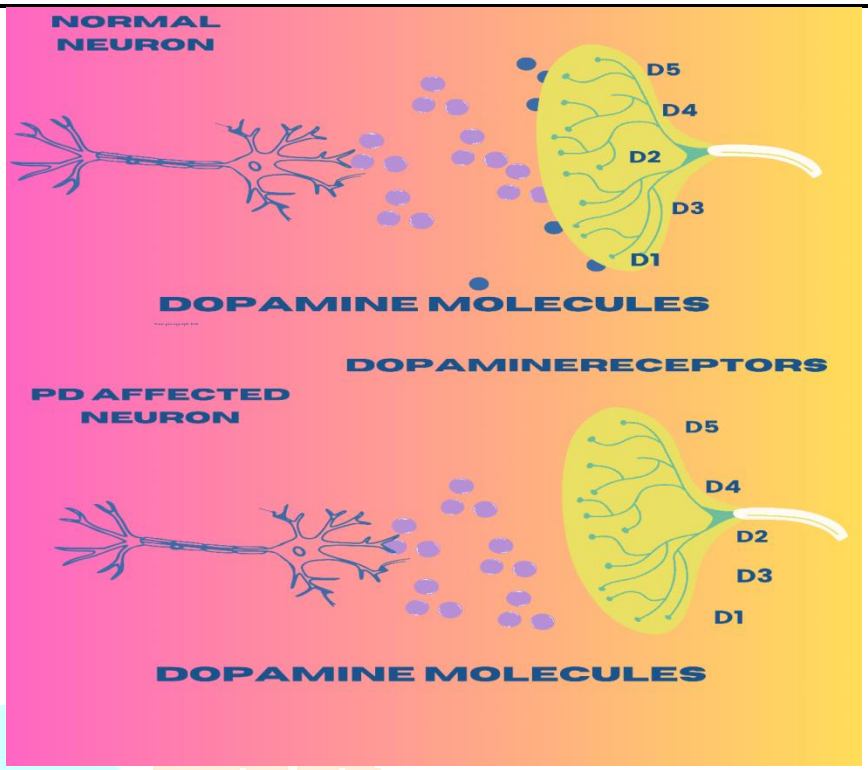

Figure 4: Normal vs PD affected neuron (Canva) [15.41]

14. MEDICAL TREATMENT

There's no cure for Parkinson's disease, but medicines can help to control its symptoms.

Physicians suggest lifestyle changes, especially aerobic exercise. Physical therapy helps to reduce the effects of PD.

14.1Early Medical Therapy:

Once a patient experiences functional disability, he/she should initiate taking treatments, as recommended by The American Academy Of Neurology. For initial treatment, Levodopa – dopamine agonists and monoamine oxidase-B inhibitors can be used. Levodopa along with carbidopa can also be used, this has no adverse effects and is most effective against motor symptoms. Pramipexole and ropinirole – dopamine agonist has the ability to directly stimulate dopamine receptors but are less effective than levodopa. For the first–line treatments Ergot –derived agonists like cabergoline, bromocriptine, lisuride, and pergolide should not be used, If used ECG [Echo Cardio Graphy] and certain renal function tests should be performed [3, 22].

14.2 Late Medical Therapy

Due to the progression of PD, initial therapy becomes less effective. For later stages, several other medications with levodopa help to reduce motor fluctuations. Catechol O- methyl transferase inhibitors decrease the level of the levodopa metabolism, allowing for more levodopa to reach the brain, this is associated with fatal hepatotoxicity and should be avoided. These treatments may cause adverse effects, including nausea, vomiting, hypertension, hallucinations, and insomnia. A study called Cochrane that indirectly compared drugs concluded that dopamine agonist is considered more effective [3, 22].

15. MEDICATIONS FOR PD

PD medications for Motor symptoms come under 5 general categories:

Table 2: Medications and their functions [45]

Medications	Functions
Carbidopa-levodopa(L-dopa)	Crossing the blood-brain barrier gets converted into dopamine makes normal transportation to the brain.
Dopamine Agonists such as Ropinirole, Apomorphine, and Pramipexole	Mimics the effects of Dopamine.
Catechol-o-methyltransferase inhibitors like Entacapone and Tolcapone	Inhibits degradation of dopamine.
Monoamine oxidase B inhibitors like Selegiline	Selegiline inhibits the enzymes that break down L-dopa.
Anticholinergics	Enhances the activity of Acetylcholine.

Miscellaneous drugs are also prescribed such as

- Rivastigmine tartrate – Reduces the breakdown of Acetylcholine, which helps to treat mild dementia
- Droxidopa – An artificial norepinephrine precursor that helps to raise blood pressure [45].

16. SURGICAL TREATMENT FOR PD

There are three surgical procedures available to treat Parkinson's disease:

- Ablative or destructive surgery
  Ablative surgery is a procedure used to locate, target, and destroy or ablate a targeted area [abnormal tissue that produces abnormal chemical or electrical impulses that cause tremors] of Parkinson's disease [38].

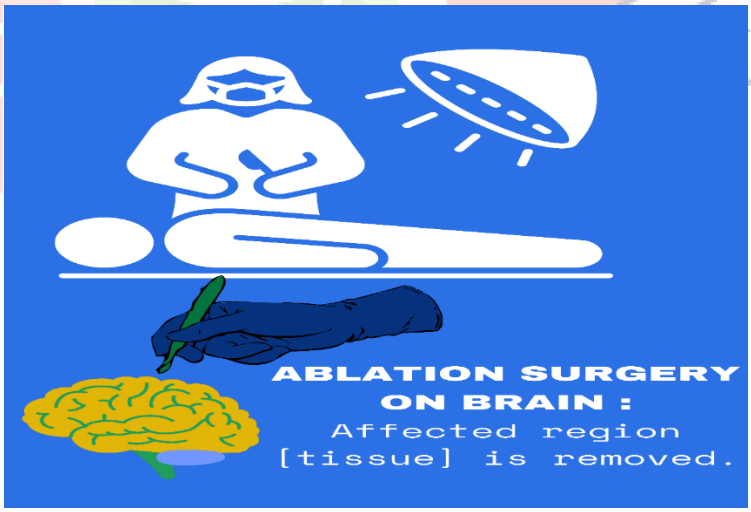

Figure 5: Ablation surgery on the brain (Canva) [38]

- Stimulation surgery or deep brain stimulation [DBS]

  Deep brain stimulation is an elective surgical procedure, in this, electrodes like lead are used to generate electrical impulses that control abnormal brain activity after implantation [11].

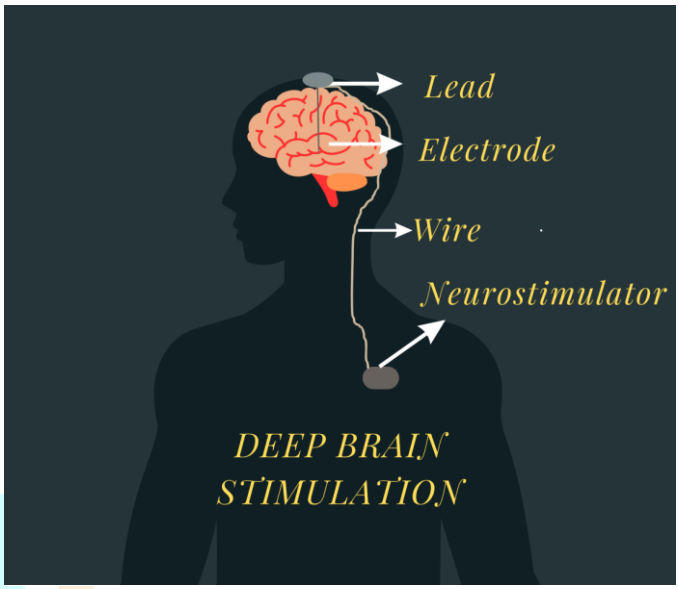

Figure 6: Deep brain stimulation (Canva) [11]

- Transplantation or restorative surgery.
  Stem cells are implanted into the abnormal nerve cells [11].

17. TRANSPLANTATION

On 13th February 2023, a transplant of nerve cells derived from stem cells was transplanted to a person with PD at Skane University Hospital, Sweden.

The transplant product replaces the dopamine nerve cells which are lost in the Parkinsonian brain.

The STEM-PD trial is currently testing a new investigational therapy aimed at replacing lost dopamine cells with healthy cells manufactured from stem cells. After being transplanted, cells are expected to mature into new and healthy dopamine-producing cells within the brain [13].

18. Parkinson – Pandemic

Though PD is not an infectious disease, PD exhibits numerous characteristics of the Pandemic due to reasons like aging and industrialization. This can be similar to the pandemic of non-communicable diseases as articulated by Allen [49]. Various factors like Ultra-processed foods, drinks, alcohol, tobacco products, and wider environmental changes may increase the risk of a PD pandemic. No one is immune to a pandemic, so the pandemic of Parkinson's disease is preventable but not evitable [50].

19. Latest update on clinical trials in Parkinson's disease

Plant-derived therapies or nutritional supplements are mostly preferred methods nowadays because they cause no adverse effects. Many kinds of Preclinical extracts were identified in plant-based databases. There are more than 56 formulations proven to have Neuroprotective activity, most of them protect the dopaminergic cells against neurotoxin that reduces the risk of degeneration.

Hence, the study called The Neuroprotective Effect of Isotetrandrine on Parkinson's Disease via Anti-Inflammation and Anti apoptosis *In Vitro* and *In Vivo*", proved that a compound called "Isotetrandine (ITD) obtained from Berberis species is considered as an analgesic, antimicrobial, immunosuppressive and antimalarial agent is also called as Cell -permeable PLA2 inhibitor has the ability to inhibit α 1 adeno receptor but it's activity as neuroprotective activity has not been investigated yet [47].

20. Latest Therapies in Clinical Trials of Parkinson's Disease: A 2021 Update

Food and Drug Administration had approved the drug "Levodopa" as a dopamine replacement to manage PD motor symptoms, Levodopa - carbidopa became commercialized after 1975. After all these years, the use of Levodopa is still the gold standard for PD treatment. Unfortunately, Levodopa-based therapy including dyskinesia and OFF symptoms remains unresolved. Therefore, Need for analyzing each latest clinical trial's status and therapeutic strategy is important to discover new therapeutic approaches for PD treatment.

After excluding levodopa/carbidopa derivative add-on therapies, there are 47 trials currently going on for PD treatment with drugs and therapies identified.

- 19 trials are in phase 1[41%]
- 25 trials are in phase 2 [53%]
- 3 trials are in phase 3 [6%]

The therapeutic strategies are the use of small molecules, monoclonal antibodies, plasma therapy, cell therapy, gene therapy, and herbal extract, respectively [14].

20.1 CLINICAL TRIALS

20.2 PRECLINICAL TRIALS

- Phenserine tartrate targets Acetylcholine esterase hydrolysis Acetylcholinesterase.
- S32504 Dopamine D2 receptor catalysis dopamine pathway and controls movement and emotions [44].

20.1.1 PHASE 1

- KM-819 is a drug that targets FAS Associated Factor [FAF1] which is a ubiquitin-binding protein required for the progression of DNA replication fork.
- NPT200-11 is a drug that targets Synuclein alpha which is a neuronal protein that plays a major role in synaptic activity and neurotransmitter release [44].

20.1.2 PHASE 2

- Pardoprunox – Dopamine d2 receptor acts as a target, whose activity is mediated by G proteins which inhibit adenylyl cyclase.
- Pardoprunox has been used in trials studying the treatment of early-stage PD and Advanced PD.
- VY-AADC – Aromatic L – amino acid decarboxylase, catalysis the decarboxylation of L-3,4 dihydroxyphenylalanine (DOPA) to dopamine, L-5-hydroxytryptophan to serotonin and L-tryptophan to tryptamine.
- Adeno-associated viral vector serotype 2 encoding human aromatic L amino acid decarboxylase infusion into the brain.
- DT-1687[Foliglurax] is a drug that targets Metabotropic Glutamate receptor 4[mGluR4] which controls adenylate cyclase activity.
- E2027[Irsenontrine]is a drug which is novel and potent inhibitor of Phosphodiesterase which is involved in the hydrolysis of cAMP and cGMP.
- PRX002 is a drug that targets Synuclein alpha which is a neuronal protein that plays a major role in synaptic activity and neurotransmitter release [44].

20.1.3 PHASE 3

- ABBV-951 is a drug that targets Dopamine receptors catalysis the dopamine pathway and controls movement and emotions [44].

20.1.4 PHASE 4

- Neupro is a drug that targets Dopamine receptors catalysis the dopamine pathway and controls movement and emotions [44].

20.3 APPROVED DRUGS

- Istradefyline targets the Adenosine A2a receptor.
- Opicapone targets Catechol o methyl transferase.
- Safinamide mesylate targets Monoamine oxidase type B
- Biperiden, Benztropine, Metixene, and cycrimidine target Muscarinic acetylcholine receptor M1 [44].

21. CONCLUSION

There's still no diagnostic test for Parkinson's disease, many trials are ongoing to find a diagnostic method to easily identify the presence of this disease.

We hope that our future scientists will find a proper and effective treatment for this disease. Many investigational products are under investigation, that will reach the market soon.

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The University of California, San Francisco Medical Center is a research and teaching hospital in San Francisco, California and is the medical center of the University of California, San Francisco

[12] Mayo Clinic, Medical Center in Rochester, MinnesotaMayo Clinic is a nonprofit American academic medical center focused on integrated healthcare, education, and research.

[13] Lund University
Public university in Lund, Sweden
Lund University is a public research university in Sweden and one of Northern Europe's oldest universities. The University is located in the city of Lund in the province of Scania, Sweden. It traces its roots back to 1425 when a Franciscan stadium general was founded in Lund.

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