

REVIEW OF INTEGRATED APPROACHES FOR THE TREATMENT OF PARKINSON'S DISEASE

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ABSTRACT

Parkinson's disease is the second most common neurodegenerative disease, and currently, there is no proper cure. A large number of pharmaceutical treatments, surgeries, and supportive therapies are designed to overcome the severity of symptoms. On the other hand, several latest, well-recognized emerging therapies are under trial phases to pinpoint the root cause of the disease. This review will discuss all the possible strategies, their benefits, and limitations. It will enable clinicians to select the most appropriate and suitable treatment strategies for their patients.

Key-words: Neurodegenerative disease, symptoms, therapies, review.

1. INTRODUCTION

Parkinson's disease (PD) was first described by the scientist James Parkinson in 1817 (Dorsey *et al.*, 2018; Parkinson, 2002). PD affects approximately 2–3% of the population over the age of 65 (Poewe *et al.*, 2017). It is the second most common neurodegenerative disease after Alzheimer's disease (Maiti *et al.*, 2017). PD is a neurodegenerative disorder characterized by the progressive degeneration of dopamine (DA)-producing neurons in a brain structure called the substantia nigra (SN), leading to various motor impairments and cognitive or mental disabilities (Armstrong and Okun, 2020; Simon *et al.*, 2020). Dopamine is a neurotransmitter through which nerve cells communicate. In PD, impaired communication occurs when the brain cannot send proper activation signals to the muscles due to reduced dopamine (DA) production (Björklund and Dunnett, 2007). The process leading to the destruction of dopaminergic (DAergic) neurons is still not fully understood; however, the deposition of alpha-synuclein into Lewy bodies within neurons has been reported in several studies (Kalia and Lang, 2015; Tolosa *et al.*, 2021; Villar-Piqué *et al.*, 2016). The symptoms of PD, such as rigidity, resting tremors, bradykinesia, abnormal posture, and mental disabilities, begin to appear after approximately 80% of dopaminergic neurons are destroyed (Burke, 2004; Jankovic and Tan, 2020). The root cause of PD remains unknown. However, several factors contribute to disease progression, including genetic factors, aging, sex, oxidative stress, and exposure to pesticides (Maiti *et al.*, 2017).

There is no cure for PD, however, medication provides symptomatic relief (Fox *et al.*, 2018). Pharmacological treatments for PD aim to increase dopamine levels, mimic the actions of dopamine, or counteract the excitatory effects of cholinergic neurons (Connolly and Lang, 2014). If a patient does not respond well to medication, a physician may recommend surgical treatments such as deep brain stimulation (DBS) (Armstrong and Okun, 2020a). In DBS, implanted electrodes deliver high-frequency electrical stimulation to the basal ganglia to improve motor symptoms such as tremor, bradykinesia, and rigidity, with effects comparable to those of L-DOPA therapy (Lee and Yanke, 2022). Ablative surgeries aim to alleviate symptoms such as tremor, rigidity, and hypokinesia by creating lesions deep within the brain. These procedures interrupt neural pathways that become overstimulated due to reduced dopamine production in PD; however, they may cause permanent side effects, including vision loss and swallowing difficulties (Lee and Yanke, 2022). Focused ultrasound (FUS) may be an option for patients who are unable to undergo surgical procedures due to cardiac or other medical conditions (Health Quality Ontario, 2018). High-frequency ultrasound waves are used to create a lesion in the brain, targeting areas responsible for reduced dopamine levels, and can temporarily open the putaminal blood–brain barrier (BBB) to enhance targeted drug

delivery (Foffani *et al.*, 2019). In advanced stages of PD, patients may experience fluctuations in symptoms due to variations in drug delivery. Therefore, continuous and stable methods of drug delivery are employed, such as subcutaneous infusion of apomorphine via a portable pump or intestinal infusion of levodopa. Continuous dopaminergic stimulation reduces fluctuations in motor symptoms (Senek and Nyholm, 2014). Novel therapeutic options—such as probiotics, psychobiotics, prebiotics, synbiotics, postbiotics, dietary modifications, and Chinese medicines—are being explored to address imbalances in the gut microbiota. Restoring a healthy gut microbiota balance may delay or even alleviate PD symptoms, as gut dysbiosis is thought to play a role in the initiation of PD (Zhu *et al.*, 2022). However, further research and development are required in this field. Gene therapy is based on replacing defective DNA with functional DNA in cells. Accordingly, genes encoding glutamic acid decarboxylase (GAD), aromatic amino acid decarboxylase (AADC), neurturin (NTN), tyrosine hydroxylase (TH), and guanosine triphosphate cyclohydrolase (GCH) have been introduced into different regions of the brain to reduce PD symptoms by activating specific enzymes and biochemical pathways; however, additional research is required in this field (Axelsen and Woldbye, 2018). Induced pluripotent stem cell (iPSC) technology is now preferred over fetal dopaminergic transplantation for the treatment of PD due to its promising results. Human embryonic stem cells and induced pluripotent stem cells are among the cell types that have been investigated in transplantation studies for PD treatment. Nevertheless, extensive research and larger-scale studies are still needed to evaluate the safety and effectiveness of these therapies (Mishima *et al.*, 2021). A number of neuroprotective agents, such as caffeine, coenzyme Q10 (CoQ10), creatine, and minocycline, are currently in clinical trial phases to reduce oxidative stress, mitochondrial dysfunction, protein aggregation, inflammation, excitotoxicity, cell death, iron accumulation, and to stimulate neurotrophic factors (Seidl and Potashkin, 2011). Machine learning approaches aid PD treatment by identifying new drug candidates, modeling disease progression from large clinical and biological datasets, enabling personalized therapies, and supporting continuous symptom monitoring through wearable devices (Chen *et al.*, 2013; Ju *et al.*, 2021).

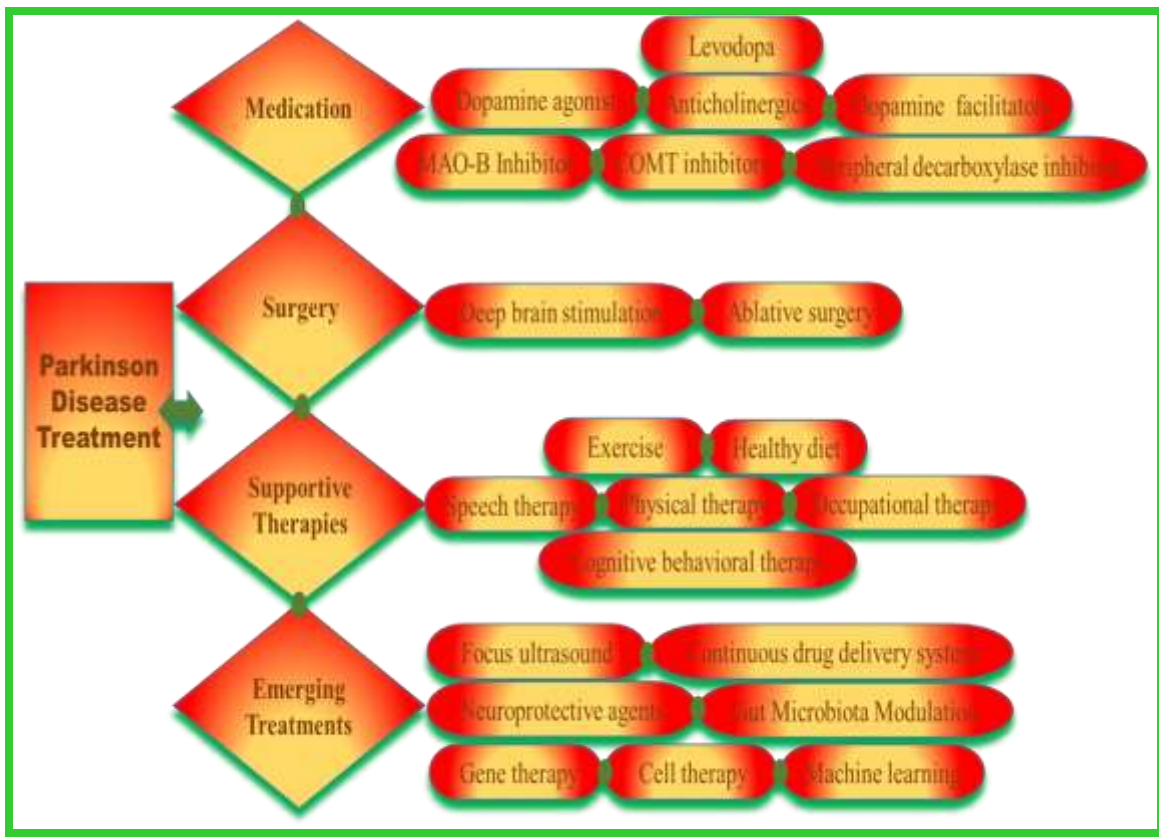


Fig. 1. Flow chart. Different available techniques for Parkinson disease treatment.

Exercise has been shown to be beneficial for patients with PD. It improves balance and mobility, reduces glutamate levels, and increases dopamine availability. Additionally, exercise mitigates cortically driven hyper

excitability in the basal ganglia, which is commonly observed in the Parkinsonian state (Canning *et al.*, 2015; Petzinger *et al.*, 2010). Physical therapy can further improve gait and overall quality of life (Zhang *et al.*, 2022). Occupational therapy supports activities of daily living by improving and enhancing fine motor skills (Bloem *et al.*, 2015). Speech and voice impairments affect approximately 90% of individuals with PD; therefore, speech therapy is valuable for addressing communication and swallowing difficulties associated with the condition (Mahler *et al.*, 2015). A healthy and nutritious diet provides energy, maximizes the effectiveness of medications, and improves the overall health of patients with PD (Tosefsky *et al.*, 2024). Cognitive behavioral therapy is a commonly used psychotherapeutic approach and an effective option for reducing depression, mood swings, and anxiety; however, further research is needed in this area (Zhang *et al.*, 2020).

This review aims to discuss the progress of various techniques used in the treatment of PD. It includes an analysis of pharmacological approaches, surgical interventions, supportive therapies, and emerging treatment strategies. The review provides a comprehensive overview of these techniques, including their development, effectiveness, side effects, advancements, and future prospects. Furthermore, it aims to assist clinicians in selecting the most appropriate treatment strategies based on the severity and variability of symptoms in individual patients. (Fig.1).

2. Parkinson's disease treatments

2.1. Medication:

Two types of drugs are used. Drugs that are affecting the brain's dopaminergic system or used to increase dopamine level. Drugs that are affecting the brain's cholinergic system or decrease the level of Acetylcholine.

Table 1. List of anti-Parkinson drugs and their function.

S. No	Function of the Drug	Drug Name
1	Dopamine Precursor	Levodopa
2	Peripheral decarboxylase inhibitor	Carbidopa, Benserazide
3	COMT inhibitors	Entacapone, Tolcapone, Opicapone
4	MAO inhibitors	Selegiline, Rasagiline
5	Drugs mimic dopamine Dopamine agonists	Bromocripton, Rotigotine, Ropinitole, Apomorphine, Pramipexole
6	Anticholinergics	Benztropine, Biperiden, Procyclidine, Trihexyphenidyl
7	Dopamine facilitator	Amantadine

Levodopa:

Levodopa is a precursor and an inactive form of dopamine. Levodopa, a prodrug of dopamine, is the most effective drug; however, its long-term use is associated with side effects such as dyskinesia and motor fluctuations (Fig. 2) (Pandey and Srivanitchapoom, 2017).

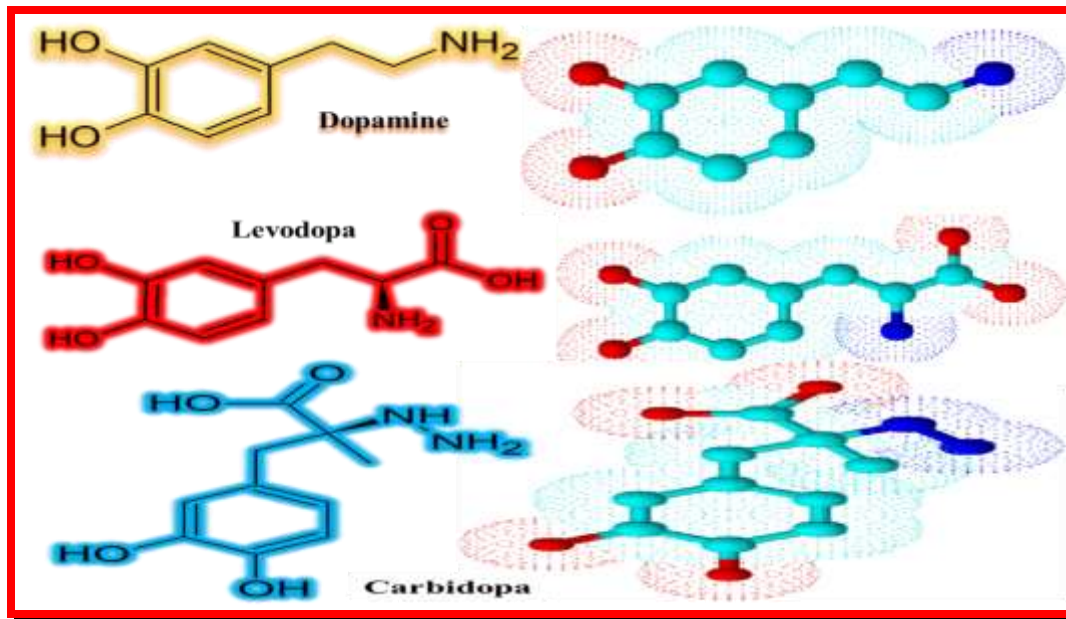


Fig. 2. Dopamine, levodopa and carbidopa. Chemical structure and 3D structures. Levodopa, a dopamine precursor, is the primary treatment for PD, while carbidopa inhibits dopamine decarboxylase to enhance its effectiveness (Mazloun-Ardakani *et al.*, 2011; Bannon *et al.*, 2020).

Levodopa is converted into dopamine by enzymes in the body to perform its function. The blood–brain barrier is a closely knit layer of endothelial cells that prevents the free movement of molecules between the bloodstream and the brain. Dopamine is one of the molecules that faces limitations in crossing this barrier. However, levodopa can pass through it with minimal assistance (Zahoor *et al.*, 2018). Levodopa faces a major challenge due to its peripheral metabolism. Two enzymes are involved in the degradation of levodopa before it reaches the brain. The first is peripheral dopa decarboxylase (DDC), which converts levodopa into dopamine. The second is catechol-O-methyltransferase (COMT), which converts levodopa into 3-O-methyldopa (3-OMD). Therefore, levodopa is administered along with carbidopa (Lorente-Picón and Laguna, 2021). Carbidopa inhibits dopamine decarboxylase, thereby reducing the peripheral metabolism of levodopa (Connolly and Lang, 2014).

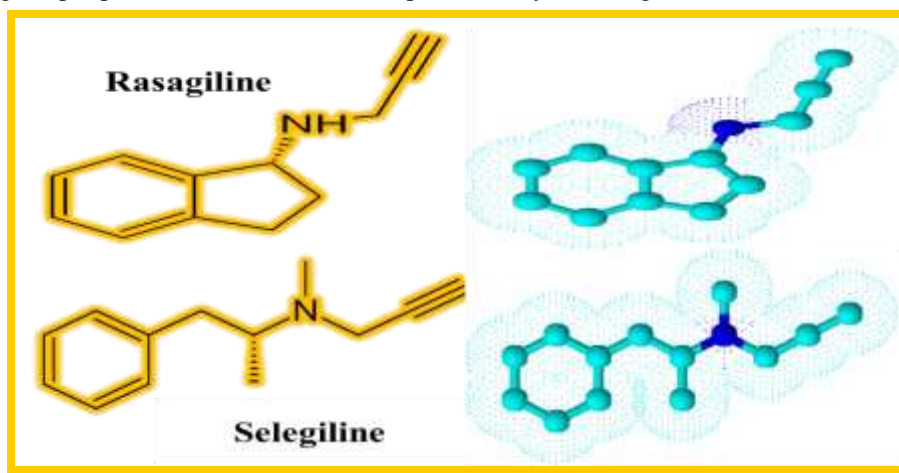


Fig. 3. Chemical and 3D structures of MAO-inhibitors, that include rasagiline and selegiline drugs used for the treatment of PD (Hoon *et al.*, 2017).

MAO-B Inhibitor: MAO-B enzymes are responsible for breaking down dopamine into 3,4-dihydroxyphenylacetic acid (DOPAC). Drugs like selegiline and rasagiline inhibit MAO-B, thereby increasing dopamine levels in the basal ganglia by reducing MAO-B enzymatic activity (Fig. 3) (Alborghetti and Nicoletti, 2019). However, these drugs

can cause gastrointestinal issues and other side effects, including joint pain, dry mouth, depression, insomnia, fatigue, dizziness, nightmares, indigestion, and headaches (Zahoor *et al.*, 2018).

Drugs mimic dopamine: Some drugs, such as bromocriptine, rotigotine, ropinirole, apomorphine, and pramipexole, act as dopamine agonists by directly stimulating dopamine receptors in the brain (Fig.4). Unlike dopamine, these drugs do not convert into dopamine but instead mimic its effects by binding to dopamine receptors (Zahoor *et al.*, 2018). Reduced dopamine levels lead to increased acetylcholine, which activates muscarinic receptors on dopaminergic neurons responsible for smooth motor control. Dopamine agonists are primarily used as initial therapy for motor symptoms of PD to delay the need for levodopa and the complications associated with it. Common side effects include sleepiness, hypotension, leg edema, and behavioral issues such as overeating, excessive shopping, and gambling (Jankovic and Tan, 2020).

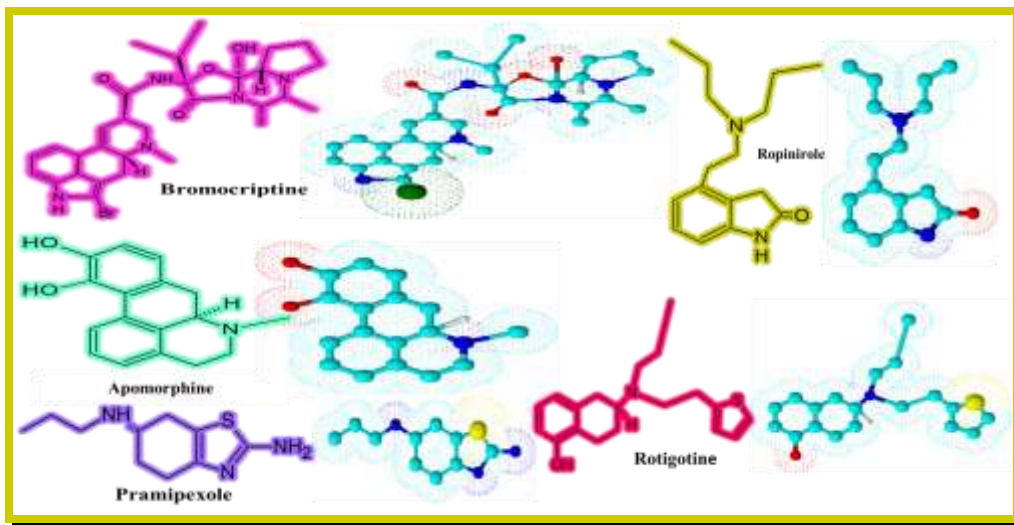


Fig. 4. Chemical and 3D structures of dopamine agonists, including bromocriptine, apomorphine, rotigotine, pramipexole, ropinirole (Luo *et al.*, 2020).

Anticholinergics:

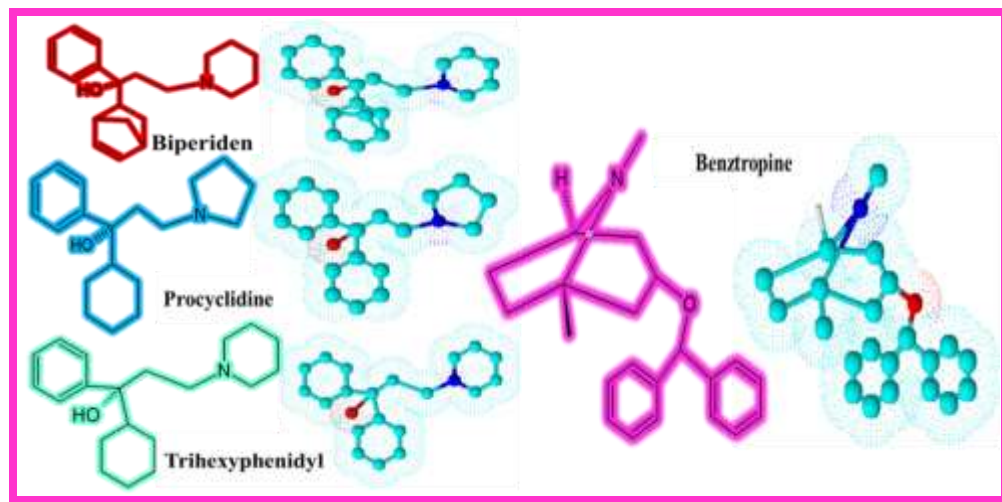


Fig. 5. Chemical and 3D structures of anticholinergic drugs for the treatment of PD, including biperiden, trihexyphenidyl, procyclidine, benzotropine (M. Timperley and Tattersall, 2015).

Anticholinergics are used to control tremors and rigidity, which are caused by the overactivation of dopaminergic neurons by acetylcholine. Therefore, anticholinergics are used to decrease acetylcholine neurotransmitter activity. Consequently, these agents help stabilize the balance between acetylcholine and dopamine

(Zahoor *et al.*, 2018). Improvements have been observed in patients treated with drugs such as biperiden, procyclidine, and trihexyphenidyl (Fig..5) (Connolly and Lang, 2014). However, anticholinergics are not recommended for elderly patients or those with cognitive impairment, as they increase the risk of confusion (Zahoor *et al.*, 2018).

Amantadine: Amantadine is recommended by healthcare providers during advanced stages of the disease to relieve symptoms such as dyskinesia. It works by preventing dopamine reuptake, facilitating presynaptic dopamine release, and blocking glutamate and NMDA receptors (Fig..6) (Sawada *et al.*, 2010).

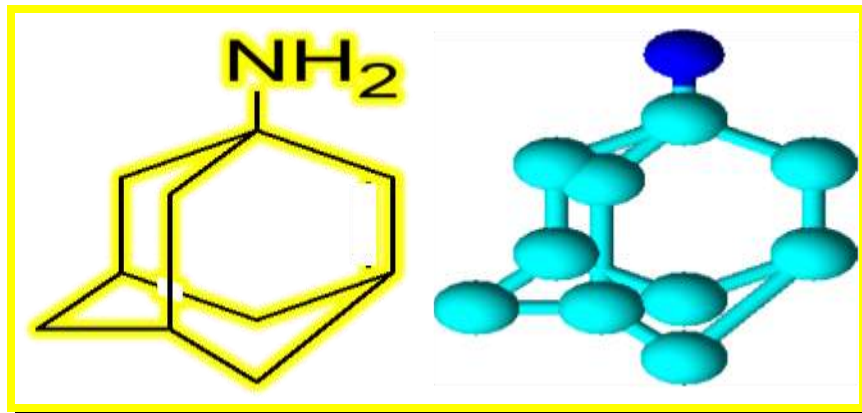


Fig. 6. Chemical and 3D structure of amantadine drug (Tsuruoka *et al.*, 2017).

COMT Inhibitors: Catechol-O-methyltransferase (COMT) is another enzyme that degrades levodopa before it crosses the blood-brain barrier (Bonifácio *et al.*, 2007). Drugs that inhibit COMT include tolcapone, entacapone and opicapone (Fig.. 7). Tolcapone can penetrate the blood-brain barrier more effectively, acting on both the central nervous system (CNS) and the periphery but it is associated with liver toxicity; therefore, continuous liver monitoring is advised (Zahoor *et al.*, 2018). Due to safety concerns, entacapone is now preferred for managing PD symptoms. A single pill combining entacapone, levodopa, and carbidopa has largely replaced separate entacapone tablets (Kaakkola, 2010).

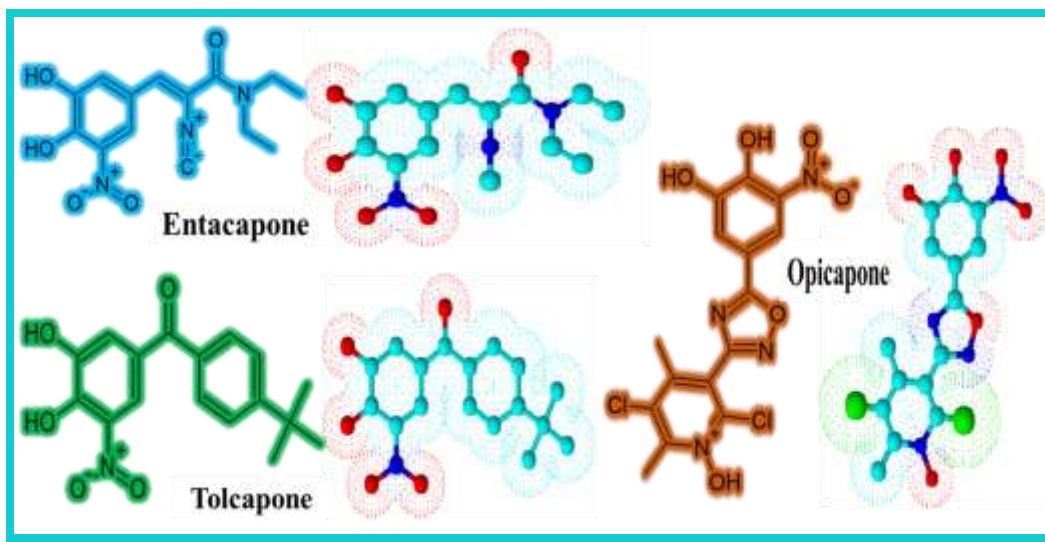


Fig. 7. Chemical and three-dimensional (3D) structures of COMT inhibitor drugs, including tolcapone, entacapone, and opicapone (Wermuth, 2003).

2.2. Surgical Treatments:

Ablative/Lesioning surgery: Ablative or lesioning surgeries (LS), such as pallidotomy, thalamotomy, and subthalamotomy, were once used to selectively destroy targeted brain tissue. However, their use declined after the

discovery of levodopa in the 1960s and deep brain stimulation (DBS) in the 1990s, as these treatments are more effective and safer. Reduced dopamine production leads to hyperactivity of the internal globus pallidus and the substantia nigra reticulata, resulting in increased inhibitory output that contributes to the symptoms of PD (Lee and Yankee, 2022). Ablative surgery is used to relieve PD symptoms by creating a lesion in the internal globus pallidus, thalamus, or subthalamic nucleus. It interrupts the overactive pathways caused by reduced dopamine production, either early in the pathway, as in pallidotomy, or later, as in thalamotomy. Although effective, these surgeries can cause permanent side effects, such as vision loss, hemiparesis, weight gain, speech and cognitive impairments, and swallowing difficulties. Therefore, ablative surgeries are typically reserved for cases in which medications are ineffective and deep brain stimulation (DBS) is either unavailable or not feasible (Walter and Vitek, 2004).

Deep Brain Surgery (DBS): If a patient does not respond well to medication, a doctor may recommend surgical treatments such as deep brain stimulation (DBS) (Armstrong and Okun, 2020a). DBS is a neurological procedure that uses implanted electrodes and electrical stimulation to treat several conditions including PD, essential tremors, dystonia, epilepsy, depression and obsessive-compulsive disorder (Chiken and Nambu, 2016). DBS is not recommended for all patients with PD, particularly those with unstable psychiatric conditions, gait dysfunction, or atypical parkinsonism—including corticobasal degeneration, dementia with Lewy bodies, progressive supranuclear palsy, and multiple system atrophy—as these patients show a poor response to treatment (Nabeel Muzaffar Syed *et al.*, 2020). Solid food intake is stopped eight hours before the procedure, and liquids are stopped at least two hours prior. An intravenous (IV) line is inserted to administer medications as needed. A stereotactic frame is then attached to the patient's head and MRI or CT scans are used to precisely target the area of the brain for electrode and wire placement. Proper placement of the electrodes in the specific region of the brain is the most important factor for the effectiveness of the treatment (Bötzel and Kraft, 2010; Pourahmad *et al.*, 2023). Two main targets of DBS for PD are globus pallidus internus (GPI) and subthalamic nucleus (STN) (Paff *et al.*, 2020). The ventral intermediate nucleus of the thalamus (VIM) is effective only for tremor and not for other symptoms of PD (Fang and Tolleson, 2017). DBS is performed with the patient awake throughout the procedure because it involves local anesthesia, allowing physicians to obtain real-time feedback from the patient (Nabeel Muzaffar Syed *et al.*, 2020). Physicians place one or two thin, wired leads with multiple electrodes at the tip into the brain. The number of leads and their placement depend on the individual case (Fig. 8). Since the brain lacks pain receptors, patients do not feel pain when the electrodes are inserted, experiencing only pressure. Local anesthesia is used to numb the scalp during the procedure, and the patient remains awake during electrode insertion. The second surgical step involves placing a pulse generator under the skin below the collarbone, which requires general anesthesia. (Nabeel Muzaffar Syed *et al.*, 2020). Leads are connected to the stimulator by wires that run under the skin and outside the skull. The implanted pulse generator (IPG) produces mild electrical impulses to stimulate specific areas of the brain, such as the subthalamic nucleus, and can be adjusted by patients and clinicians (Pycroft *et al.*, 2018). Patients can turn the device on and off using a special remote control, by a process called programming, which is done after surgery.

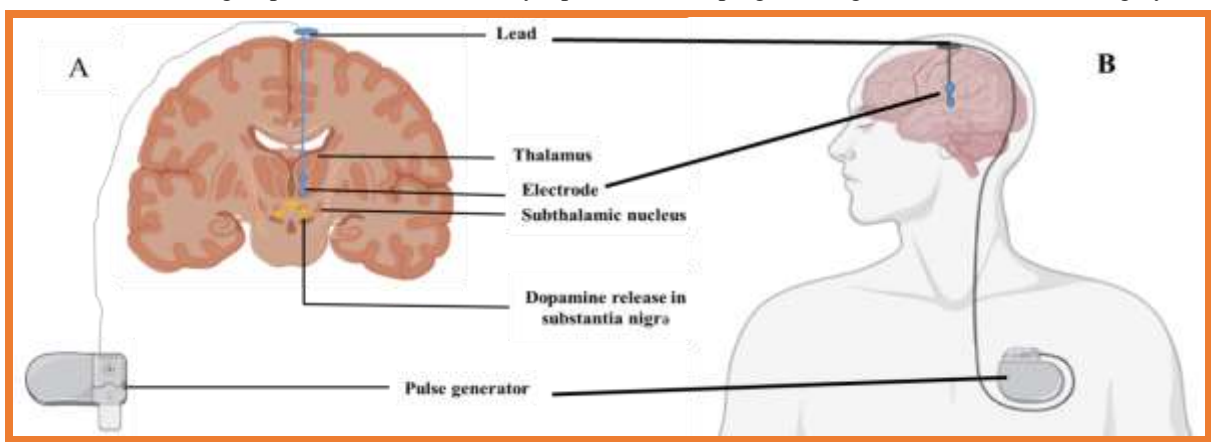


Fig. 8. DBS treatment for PD. (A) Thin, insulated leads with multiple electrodes are implanted into specific deep brain regions. (B) Connected to an implanted pulse generator (IPG), which delivers controlled electrical impulses for targeted stimulation. (Ramesh and Arachchige, 2023).

Doctors fine-tune the device to provide the correct level of stimulation, helping to alleviate PD symptoms by regulating overactive brain regions. While DBS significantly reduces motor symptoms by 70–80%, it is not a cure

for PD. There are risks associated with DBS, including a 1–3% risk of bleeding, which could lead to stroke, and a 3–5% chance of infection, as the electrodes are foreign bodies implanted in the brain (Rizek *et al.*, 2016). There is a 1–3% risk of fracture or migration of the lead, wires, or battery inside the body and a 1–2.5% risk of lead erosion (Hartmann *et al.*, 2019). After surgery, an unhealthy area of the brain is stimulated; however, other brain regions may also be affected or unintentionally stimulated. More research is needed to develop a clear understanding of the effects of these treatments on the brain.

2.3. Supportive Therapies:

Any kind of **physical activity/exercise** increases the level of brain- derived neurotrophic factor (BDNF) level, which protects the brain from neurotoxins and plays an important role in survival, development and proper functioning of neurons and neuroplasty (Ahlskog, 2011). Alternatively, it enhances mobility, mood, sleep, and memory (Ramaswamy *et al.*, 2018). Exercise not only improves motor symptoms (gait, balance, and strength) and non-motor symptoms (depression, fatigue, constipation, and mood swings), but also reduces secondary complications such as cardiovascular disease and osteoporosis (van der Kolk and King, 2013). **Physiotherapy** is another approach to managing PD symptoms. Physiotherapists plan physical therapy according to the type of symptoms and the severity of PD. Any kind of physical activity is associated with improved neuronal health and symptom alleviation by enhancing brain pathways and functions (Stillman *et al.*, 2020). Gait training and yoga poses improve posture and balance, while regular stretching can relieve muscle stiffness, which is a major cause of pain and sudden falls. Repetitive movements, such as arm swing during walking, can be improved by using an elliptical machine or cross trainer. **Occupational therapy** aims to enable patients to perform daily tasks independently. Occupational therapists help patients maintain full concentration and attention while walking to avoid frequent falls and recommend the use of assistive equipment such as shoulder bags, body belts, and trolleys. Sit-to-stand transfers from chairs, toilets, and beds can be facilitated with the help of chair risers or recliners. Therapists also assist with turning over, getting out of bed, and proper bed positioning. Fatigue is common in PD patients due to reduced movement and prolonged upright posture. Therapists assess daily routines and suggest physical therapies tailored to the patient's energy level, incorporating regular rest periods. **Speech and language** therapists design strategies and exercises to improve voice quality, speech rate, and pronunciation, and to address problems related to breathing, drinking, swallowing, and facial expressions. The Lee Silverman Voice Treatment (LSVT) is a four-week therapeutic exercise program that is easy to learn and effective in improving swallowing function, speech clarity, and vocal volume (Nozaki *et al.*, 2021).



Fig. 9. Mediterranean diet. The Mediterranean diet comprises a large proportion of whole-grain food items, leafy green vegetables, fruits, water, and unsaturated fatty acids for daily intake. It includes moderate consumption of dairy products and seafood (once per week) and very low intake of sugar and red meat (Bisaglia, 2022).

PD patients are advised to follow a **healthy diet** consisting of a large proportion of fruits, vegetables, and whole grains to ensure adequate intake of vitamins, minerals, fiber, carbohydrates, water, and fluids. Dairy products such as cheese and skim or low-fat milk, as well as processed and canned foods, lard, and butter, should be limited or avoided (Mischley *et al.*, 2017). Protein-rich foods such as meat are also recommended, while low intake of sugar, cholesterol, and saturated fats is advised. Recent studies suggest that the Mediterranean diet may have beneficial effects in the prevention and treatment of PD and its complications. This diet comprises fruits, vegetables, whole grains, and legumes; moderate intake of fish; regular use of unsaturated fatty acids such as olive oil; low intake of saturated fats and red meat; low to moderate consumption of dairy products, meat, and poultry; and moderate wine intake (Fig. 9) (Mazza *et al.*, 2021; Paknahad *et al.*, 2020). Plant-based, high-fiber diets, including the Mediterranean and low-fat diets, are associated with increased short-chain fatty acid (SCFA)-producing bacteria, faster gait speed, reduced inflammation, and improvement in both motor and non-motor symptoms in PD patients.

Cognitive behavioral therapy (CBT) is used to manage depression, anxiety, and mood swings in PD patients. CBT aims to address dysfunctional beliefs and negative behaviors by replacing them with realistic, cognitive, and encouraging ideas through structured sessions and home assignments. Patients are encouraged to attend sessions regularly for motivational support. Future research could explore cost-effective approaches, such as group therapy or internet-based therapies (Moonen *et al.*, 2021).

2.4. Emerging Therapies:

Focus Ultrasound (FUS): Initially, ultrasound was used primarily for diagnostic purposes, such as echocardiography for cardiac examinations and the detection of tremors and stones in organs like the kidneys, liver, and gallbladder (Quadri *et al.*, 2018). More recently, it has also been applied as a therapeutic modality, employing high-frequency sound waves for treatment. Focused ultrasound (FUS) is used not only for tremor-dominant PD but also for essential tremor, psychiatric conditions, chronic pain, and epilepsy (Meng *et al.*, 2021). FUS for PD treatment is a painless procedure that requires no incision, no anesthesia, and no hospital stay (Fiani *et al.*, 2020). Patients often experience better improvements and are able to walk immediately after the treatment. FUS is performed within an MRI scanner and does not damage the surrounding healthy tissues. Its mechanism of action is similar to that of a magnifying glass, which converges sunlight to a single point, generating heat at that focal point (Quadri *et al.*, 2018). First, the patient's head is fitted with a transducer helmet. A highly focused, high-intensity ultrasonic beam (typically 1–3 MHz, 100–10,000 W/cm²) is emitted from the transducer system and directed deep into the targeted brain region (Fig. 10). The mechanical energy of the ultrasonic waves is converted into heat (>56°C), leading to protein denaturation and cell death (Franzini *et al.*, 2020). This allows the targeting of small clusters of neurons associated with voluntary movements. Thermal heating induces cell death in a manner in which cells retain their overall shape, but intracellular proteins coagulate, rendering the cells nonfunctional (Fig.10) (Quadri *et al.*, 2018). Within 48 hours, these treated areas become clearly distinguishable from healthy tissue, creating a small lesion without affecting surrounding cells. Damaged cells begin to separate from their basement membrane and from one another. A chronic inflammatory phase lasting up to three months follows, during which tissue remodeling occurs. In this phase, damaged cells regenerate, proliferate, migrate, rebuild connective tissue through fibroblast activity, and remove cellular debris from the damaged site (Quadri *et al.*, 2018).

FUS treatment offers several advantages. It does not involve harmful ionizing radiation and allows the creation of precise, well-defined lesions. Patients often experience immediate improvements, and MRI provides real-time monitoring during the procedure. However, there are some limitations associated with the treatment. The procedure can be time-consuming, and variations in skull thickness may affect its effectiveness. (Sharma *et al.*, 2020). FUS targets the thalamus to treat PD tremors, a procedure known as thalamotomy. For PD dyskinesia, the target is the globus pallidus (pallidotomy), while for PD tremor, akinesia, or dyskinesia, the target is the pallidothalamic tract.

FUS treatment can temporarily open the BBB, therefore it prevents many substances from entering the brain (Fig 10). This temporary disruption of BBB allows desired drugs to reach the brain; moreover, it also allows the toxic waste products and harmful substances to exit from the brain more easily.

Continuous drug delivery system: During the advanced stages of PD, there are insufficient dopaminergic neurons remaining to produce and store dopamine; therefore, patients require higher doses of levodopa to maintain adequate dopamine levels in the brain. Additionally, PD-associated gastric dysfunction leads to delayed or impaired gastric emptying, which can delay or prevent the absorption of oral medication from the small intestine into the bloodstream. Importantly, the effect of oral levodopa may wear off during the night, causing patients to awaken with severe motor symptoms. In such cases, patients may be unable to turn over in bed or go to the toilet without a significant risk of falling. Consequently, there is a clear need for a non-oral, continuous drug delivery system to

improve quality of life. Levodopa–carbidopa intestinal gel (LCIG; Duodopa, containing 20 mg/mL levodopa and 5 mg/mL of the dopa decarboxylase inhibitor carbidopa), supplied in cassettes and administered into the duodenum or upper jejunum via a portable pump, represents an effective method for continuous drug delivery (Timpka *et al.*, 2016). **Subcutaneous apomorphine infusion** is a minimally invasive, device-aided therapy for PD that is used when oral medications fail to adequately control motor fluctuations. Apomorphine is a dopamine agonist with proven antiparkinsonian efficacy; it is rapidly absorbed and has a short half-life (T. van Laar *et al.*, 2023). If the therapeutic response is unsatisfactory, apomorphine infusion can be easily discontinued. Common adverse effects associated with this therapy include pruritic subcutaneous nodules at the infusion site, local discomfort, and erythema (Katzenschlager *et al.*, 2018).

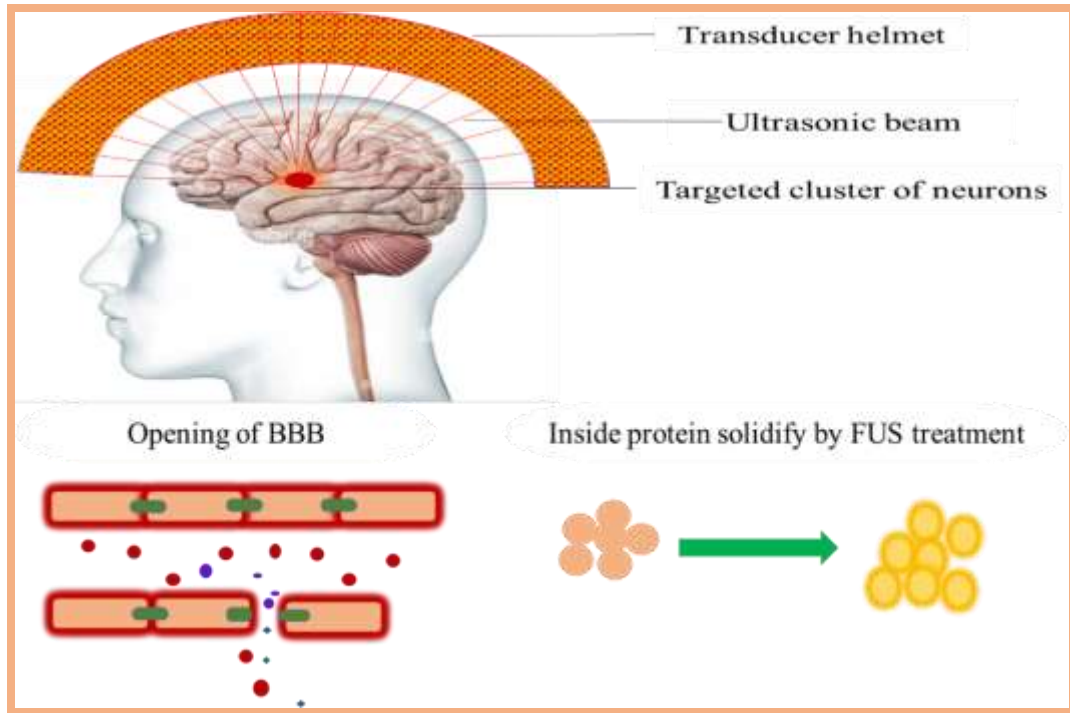


Fig. 10. FUS uses ultrasonic waves to target deep brain regions, generating heat that solidifies intracellular proteins without damaging surrounding tissue, thereby creating a precise lesion without surgery. Additionally, it temporarily opens the blood–brain barrier (BBB), allowing therapeutic drugs to reach the brain. (Bok *et al.*, 2022; Rao *et al.*, 2023).

Gene Therapy: Gene therapy represents a promising emerging treatment strategy for PD, however, no gene therapy has yet been approved for clinical use in PD, and further research is required. The primary aim of gene therapy is to enhance the expression of key enzymes involved in dopamine biosynthesis within the nigrostriatal pathway, including tyrosine hydroxylase (TH), aromatic L-amino acid decarboxylase (AADC), and GTP cyclohydrolase 1 (GCH1). In addition, gene therapy seeks to restore neurotrophic support essential for the maintenance and survival of dopaminergic pathways, such as neurturin (NRTN) and glial cell line–derived neurotrophic factor (GDNF) (Fig. 11). Overall, gene therapy is an important therapeutic approach under investigation for promoting neuronal survival and preserving dopaminergic function (A. D. Van Laar *et al.*, 2021).

Cell Therapy: Stem cell therapy has shown high therapeutic potential in treating certain diseases associated with cellular degeneration and dysfunction; however, it has not yet cured any patients with PD. At present, stem cell–based therapy for PD remains in the early stages of clinical trials, as transplanted stem cells possess the ability to differentiate into multiple cell types, raising concerns regarding safety and precise functional integration. The primary objective of stem cell therapy is to repair, replace and regenerate damaged neuronal populations.

Stem cells are typically derived from two principal sources: human embryonic stem cells (ESCs) or induced pluripotent stem cells (iPSCs) (Fig. 12). The next step involves selecting the appropriate target region of the brain, such as the putamen, substantia nigra, or other components of the nigrostriatal pathway. Subsequently, the specific cell type to be transplanted is determined, including neuronal progenitors or midbrain glial cells. The fourth step

requires selection of the transplantation source—xenogeneic, allogeneic, or syngeneic—to achieve optimal compatibility and therapeutic outcomes. Finally, continuous post-transplantation monitoring of the grafted cells is essential, including the management of immunosuppression.

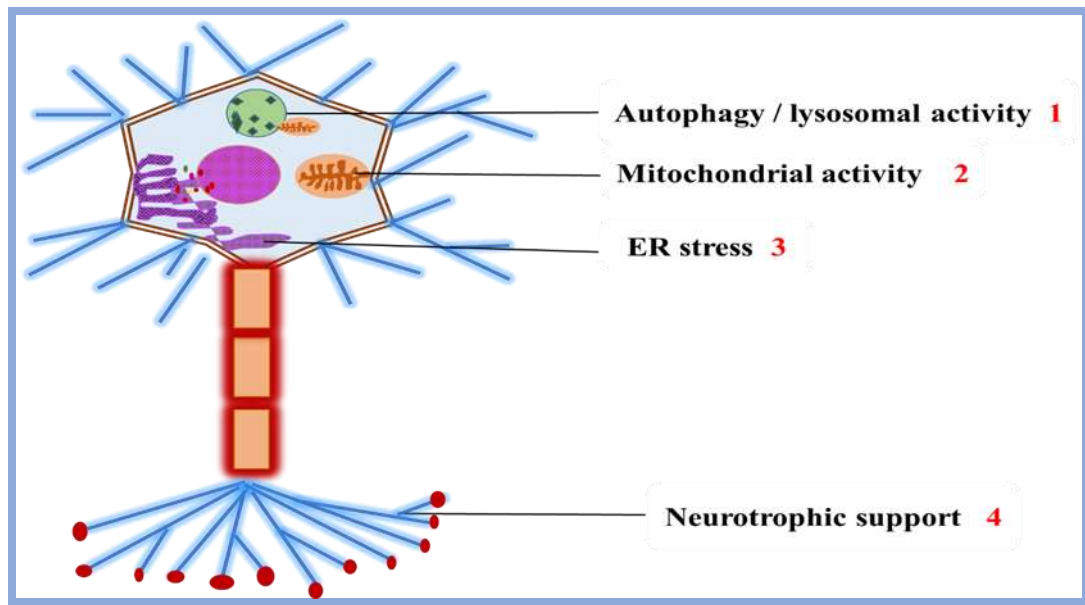


Fig. 11. Proposed gene therapies for neuroprotection against PD. (1) Gene therapy can modulate autophagy–lysosomal pathways, thereby providing neuroprotection against α -synuclein aggregation and deposition. (2) Gene therapy has the potential to mitigate mitochondrial dysfunction and toxin-induced damage by replacing or repairing defective mitochondrial DNA. (3) Gene therapy may reduce endoplasmic reticulum (ER) stress and regulate the unfolded protein response (UPR), contributing to improved cellular homeostasis. (4) Delivery of neurotrophic factors via gene therapy promotes increased dopamine synthesis, axonal sprouting, and the formation of new synaptic connections, which collectively enhance motor function (Valdés and Schneider, 2016).

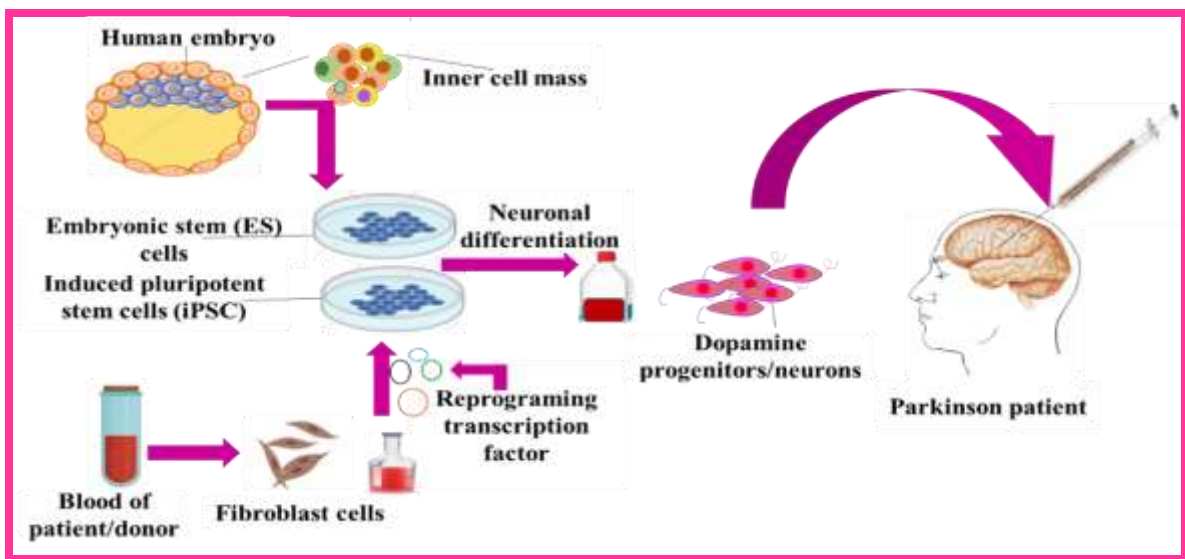


Fig. 12. Stem cell therapy for PD. **Induced pluripotent stem cells (iPSCs)** and **human embryonic stem cells (ESCs)** are the principal sources used to derive stem cells and expand them in large numbers. These cells are carefully and safely differentiated into dopaminergic progenitors or neurons, which are subsequently transplanted into the brains of patients with PD via stereotactic injection (Barbuti *et al.*, 2021).

Researchers found stem cells highly effective to treat some illnesses, involved in cell destruction and dysfunction but it has not yet cured any PD patient. Stem cells have the potential to convert in different parts of the body. First, stem cells are carefully generated from two main sources: human embryonic stem cells (ES) or induced pluripotent stem cells (iPSC) (Fig. 12). The second step is to select the target region of the brain, such as the putamen, substantia nigra, or another area along the nigrostriatal pathway. The third step involves selecting the type of cells to graft, whether neuronal cells or mid-brain glial cells. The fourth step is to decide the type of source to use for the transplant, such as xenogeneic, allogeneic, or syngeneic, to achieve the best and most accurate results. Finally, continuous monitoring of the grafted cells is essential post-transplantation, including immunosuppression management (Barbuti *et al.*, 2021). The main safety concerns associated with stem cell therapy for PD include the risk of infection or malignancy related to surgical procedures, tumor formation due to uncontrolled graft overgrowth, and complications arising from invasive neurosurgical interventions. (Li *et al.*, 2016).

Table 2. Neuroprotective agents and their functions for PD treatment.

S. No.	Neurotrophic factor	Function related to PD
1	Coenzyme Q10 Co-Q10	Coenzyme Q10 (Co-Q10) is an antioxidant that neutralizes free radicals. Decreased levels of Co-Q10 have been reported in the blood and platelet mitochondria of PD patients (Shults, 2005).
2	Creatine	Creatine, an energy booster for the brain, is converted to phosphocreatine in cells, which helps in ATP synthesis from ADP, activates cell signaling and transcription, reduces oxidative stress, inhibits central inhibitory transmission, strengthens excitatory transmission, improves cognitive function, and has therapeutic potential against epilepsy, depression, and PD (Kanekar, 2024).
3	Caffeine/smoking	Caffeine possesses antioxidant, anti-inflammatory, and anti-apoptotic properties, reduces striatal dopamine loss, and is effective in PD treatment for men, but its effect in women is controversial due to caffeine's competition with estrogen for the estrogen-metabolizing enzyme CYP1A2 (Kolahdouzan & Hamadeh, 2017). Coffee and smoking decrease neurodegeneration, as they reduce the release of pro-inflammatory cytokines from the gut into the bloodstream (Vidal-Martinez <i>et al.</i> , 2020).
4	Iron chelators	Deposition of iron in the glial cells of SN causes protein misfolding and deposition of Lewy bodies, which triggers the PD symptoms. Iron chelators like deferiprone has the ability to slow down the disease progression (Dusek <i>et al.</i> , 2016).
5	Uric acid, Inosine	Oral administration of inosine is safe for early PD patients, as it maintains urate levels in the serum and cerebrospinal fluid in a dose-dependent manner and slows down the progression of PD. Inosine is a precursor of uric acid, which is a natural antioxidant and free radical scavenger. Further research is required to determine its therapeutic potential for PD (de Lau <i>et al.</i> , 2005).
6	Kynurenic acid KYNA	Abnormalities in the kynurenine pathway, including increased 3-OH-L-KYN and QUIN concentrations, cause oxidative stress, neurotoxicity, and neurodegeneration. The kynurenine metabolite KYNA could serve as a promising anti-excitotoxic agent with minimal side effects, and may have a beneficial effect against depression and PD. However, there is a major need to improve its pharmacokinetics (Zádori <i>et al.</i> , 2011).
7	Vitamins	Vitamin D regulates nerve growth and activity and reduces the risk of falls and fractures (Pignolo <i>et al.</i> , 2022). Vitamin C increases antioxidants and reduces oxidative stress, while deficiencies of vitamins B and C are associated with depression (Kumar <i>et al.</i> , 2022). Higher levels of vitamin B12 are associated with a lower risk of dementia in PD patients (McCarter <i>et al.</i> , 2020).
8	Ginseng polysaccharide	GP possesses immunity-enhancing activity, inhibits inflammation, acts as an antioxidant, and enhances signaling, as it is rich in neutral and acidic polysaccharides. Further research is required (Wang <i>et al.</i> , 2021).
9	Ginkgo biloba leaf extract	It reduces the loss of striatal dopamine and neurodegeneration of the nigrostriatal pathway, as it possesses antioxidant properties and contains high levels of flavonoids and terpene trilactones (Yu <i>et al.</i> , 2021).
10	Scutellaria baicalensis	Baicalin, a flavonoid isolated from it, increases dopamine and serotonin levels in the striatum, inhibits oxidative stress and astroglial responses, exerts a protective effect against 6-hydroxydopamine, and prevents α -synuclein oligomerization (Yu <i>et al.</i> , 2021).

Neuroprotective Agents: Neurotrophic factors are small proteins with molecular weights ranging from 10 to 35 kDa that support the development, maturation, plasticity, and survival of neurons (Bondarenko and Saarma, 2021). Several neurotrophic agents, including antioxidants, vitamins, omega-3 fatty acids, coenzyme Q10, enzyme inhibitors, and natural products, have demonstrated neuroprotective effects in PD (Table.2) (Marsili *et al.*, 2017).

Gut Microbiota Modulation: An imbalance in gut microbiota composition leads to dysbiosis, which has been associated with several neurological and psychiatric disorders, including depression, autism, anxiety, and PD. Studies have reported a higher abundance of *Bifidobacteriaceae*, *Ruminococcaceae*, *Verrucomicrobiaceae*, and *Christensenellaceae*, along with a reduced abundance of *Prevotellaceae*, *Faecalibacterium*, and *Lachnospiraceae* in patients with PD (Table.3) (Shen *et al.*, 2021).

Probiotics are beneficial microorganisms that inhibit the growth of pathogenic bacteria and enhance the production and absorption of essential vitamins and minerals. They modulate gastrointestinal inflammation and may reduce the degeneration of dopaminergic neurons in the substantia nigra by increasing butyrate production. Butyrate, in turn, suppresses nigral inflammation and enhances the expression of neurotrophic factors (Gazerani, 2019). Probiotics are commonly prescribed by healthcare providers to restore gut microbiota balance, particularly following illness or antibiotic use. They are also present in smaller amounts in fermented foods such as yogurt, cheese, and pickles (Fig. 13). Patients with PD are advised to look for products labeled “live and active cultures,” as food processing and canning can destroy naturally occurring probiotics.

Prebiotics are nonviable food materials that enhance the growth/activity of microorganisms. In PD patients, low abundance of short chain fatty acid (SCFA) can be corrected by prebiotic fibers, as they impact the inflammatory processes, gut barrier integrity and peristalsis, which in turn improve motor functions, neurotransmitter system and dopaminergic neuroprotection (Fig..13) (Dong *et al.*, 2020).

Symbiotics are a combination of probiotics and prebiotics, in which the prebiotic promotes the growth or activity of the probiotic microorganism, thereby providing a beneficial effect on the host's health.

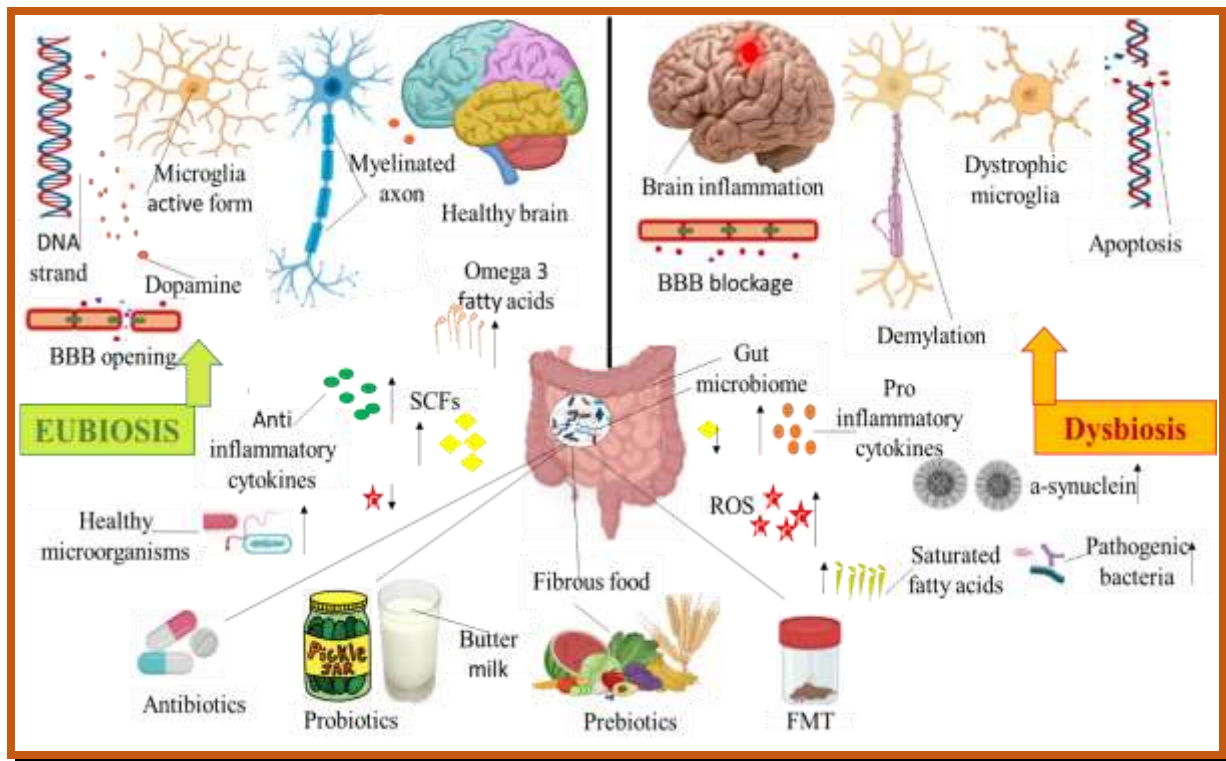


Fig. 13. Microbiome and PD: Microbial therapies, including probiotics, prebiotics, antibiotics, and fecal microbiota transplantation (FMT), can increase beneficial microbiota while reducing pathogenic bacteria. Dysbiosis in the gut is associated with brain inflammation, neuronal damage, apoptosis, and abnormal aggregation of α -synuclein fibrils, all of which contribute to the development of PD symptoms. Conversely, a healthy gut microbiome is associated with proper dopamine release and overall brain health. (Boehme *et al.*, 2023; Mayer *et al.*, 2015; Ratsika *et al.*, 2023).

Table 3. Gut microbiota and their role in PD.

S. No.	Specie, Family, Genera	Role in gut dysbiosis and Parkinson disease	References
1	<i>Prevotellaceae</i>	Its deficiency leads to increased gut permeability and exposure to bacterial endotoxins, which in turn leads to α -synuclein deposition in the colon.	(Scheperjans et al., 2015)
2	<i>Lachnospiraceae</i>	An increased abundance of <i>Lachnospiraceae</i> has been reported in the gut microbiota of patients with Parkinson's disease compared with controls. Its deficiency can cause gastrointestinal inflammation, as some short-chain fatty acids (SCFAs) are associated with reduced inflammation.	(Vidal-Martinez et al., 2020)
3	<i>Butyricoccus</i>	Its increased abundance is associated with cognitive impairment.	(Wang et al., 2021)
4	<i>Akkermansia muciniphila</i>	Its abundance destroys the mucin layer, causes gut permeability, and leads to α -synuclein fibril deposition in the intestine.	(Lorente-Picón & Laguna, 2021)
5	<i>Faecalibacterium</i> / <i>Roseburia</i>	It is associated with butyrate production, which possesses anti-inflammatory properties; thus, its deficiency can lead to PD symptoms.	(Lorente-Picón & Laguna, 2021)
6	<i>Lactobacillaceae</i> / <i>Bifidobacteriaceae</i>	These probiotics are used to treat constipation and bloating, upregulate mucus secretion, and reduce the binding of enteric pathogens to mucosal epithelial cells.	(Mack et al., 1999)
7	<i>Enterobacteriaceae</i>	Its increased abundance causes gut inflammation through the production of endotoxins, such as lipopolysaccharide (LPS). LPS induces the production of inflammatory cytokines, which cause neuro-inflammation.	(Lorente-Picón & Laguna, 2021)
8	<i>Collinsella</i>	It is a hydrogen-reducing bacterium, commonly present in individuals on a low-fiber diet. Its abundance leads to intestinal hyper-permeability and microglial activation in PD patients.	(Huang et al., 2023)
9	<i>Romboutsia</i>	Its lower abundance leads to the worsening of cognitive function and depression.	(Kwon et al., 2024)
10	<i>Parabacteroides</i> / <i>Escherichia</i>	They are related to the expression of GABA-producing pathways; their increased abundance is negatively/inversely associated with depression and mood swings.	(Strandwitz et al., 2018)
11	<i>Clostridium ramosum</i>	Its decreased abundance causes inhibition of serotonin secretion in the intestinal tract. PD patients exhibit low plasma levels of serotonin (5-HT) and its metabolite 5-hydroxyindoleacetic acid (5-HIAA), which are associated with non-motor symptoms such as depression, pain, fatigue, and sleep disorders.	(Wang et al., 2021)

Antibiotics are prescribed by healthcare providers to treat specific pathogenic bacteria; however, they can also disrupt beneficial gut microbiota. This disruption may lead to gut dysbiosis, impairing the gut mucosal barrier and exposing the host to pathogens, toxins, and inflammation, which can trigger overexpression and aggregation of α -synuclein (Table 4). Conversely, antibiotic administration can also have beneficial effects; for example, eradication of *H. pylori* not only improves gastrointestinal symptoms but may also enhance levodopa pharmacokinetics and clinical efficacy in PD. Nevertheless, it remains unclear whether antibiotic therapy can slow disease progression or broadly improve PD symptoms (Brown and Goldman, 2020).

Fecal microbiota transplantation (FMT) involves the transfer of fecal material from a healthy donor to a patient, which can be administered via oral capsules, gastroduodenal endoscopy, colonoscopy, or enema. Studies have reported significant improvements in constipation as well as motor and non-motor symptoms (such as depression and anxiety) in patients with PD. However, these effects often diminish after several months, as the gut microbiome gradually returns to its original composition, which can lead to a recurrence of PD symptoms (Brown and Goldman, 2020).

Table 4. List of antibiotics and their role in gut dysbiosis and PD.

S. No.	Antibiotic	Role in gut dysbiosis and Parkinson disease	Reference
1	Minocycline	It has the ability to inhibit microglial activation and reduce oxidative injury and inflammation.	(Cankaya et al., 2019)
2	Doxycycline (DOX)	DOX possesses anti-inflammatory and anti-apoptotic properties, reduces dopaminergic neuron loss in the substantia nigra (SN), and increases striatal dopamine levels.	(Varesi et al., 2022)
3	Rifampicin	It prevents α -synuclein fibrillation and neuronal death by increasing fibril solubility. It also prevents reactive oxygen species (ROS) production and reduces α -synuclein-induced microglial cell activation.	(Acuña et al., 2019)
4	Rifaximin	Reduced motor fluctuations have been reported in patients with PD.	(Varesi et al., 2022)
5	Ceftriaxone	It binds to α -synuclein and inhibits its in vitro polymerization.	(Varesi et al., 2022)

Machine Learning (ML):

Diagnosis: ML enables the detection of PD at early stages, allowing patients to maintain a better quality of life. In one approach, short audio samples of approximately 10 seconds are collected from individuals with and without PD. These data are then analyzed and classified using four ML algorithms: support vector machine (SVM), random forest, K-nearest neighbors (KNN), and logistic regression. Among these, a reliable diagnostic model, such as the random forest classifier, can identify PD with an accuracy of 91.83% based on audio data (Govindu and Palwe, 2023). Similarly, patients may be asked to write or draw various patterns, which can be analyzed using low-cost machine learning methods such as optical pattern recognition (OPF), support vector machines (SVM), and Bayesian classifiers (Bernardo *et al.*, 2019). Organic fluorescent compounds are used in diagnostics because they emit light upon excitation. They are non-invasive, easy to use, and provide accurate spatial and temporal information. For example, specially designed organic fluorescent compounds can selectively bind to disease-associated biomarkers, such as α -synuclein aggregates or dopamine receptors. By analyzing their fluorescent signals, early diagnosis of the disease can be achieved. (Li *et al.*, 2020).

Monitoring: Machine learning (ML) can be applied to mobility or gait measurements to monitor the progression of PD. Biomarker-based diagnostics for PD are currently under clinical investigation, as they have the potential to diagnose the disease, monitor its progression, and guide safe, personalized treatments (Delenclos *et al.*, 2016). Organic fluorescent compounds can also be used to monitor different stages of PD by tracking protein aggregates and detecting early neurological changes. These compounds can be further optimized for therapeutic purposes; by following their distribution, points of attachment to aggregates, and neuroimaging signals, clinicians can enhance their specificity to interact only with disease-related targets. Additionally, ML-based classifier models are under development to enable detailed image-based cell profiling and to predict toxicity in dopaminergic neurons (Monzel *et al.*, 2020).

Designing new Organic compounds: New organic compounds with desired fluorescent properties for the treatment of PD can be designed using machine learning (ML) approaches (Chen *et al.*, 2013). ML algorithms can analyze large datasets to predict potential drug candidates. In addition to identifying novel compounds, machine learning can also be used to optimize the properties of existing compounds for therapeutic applications.

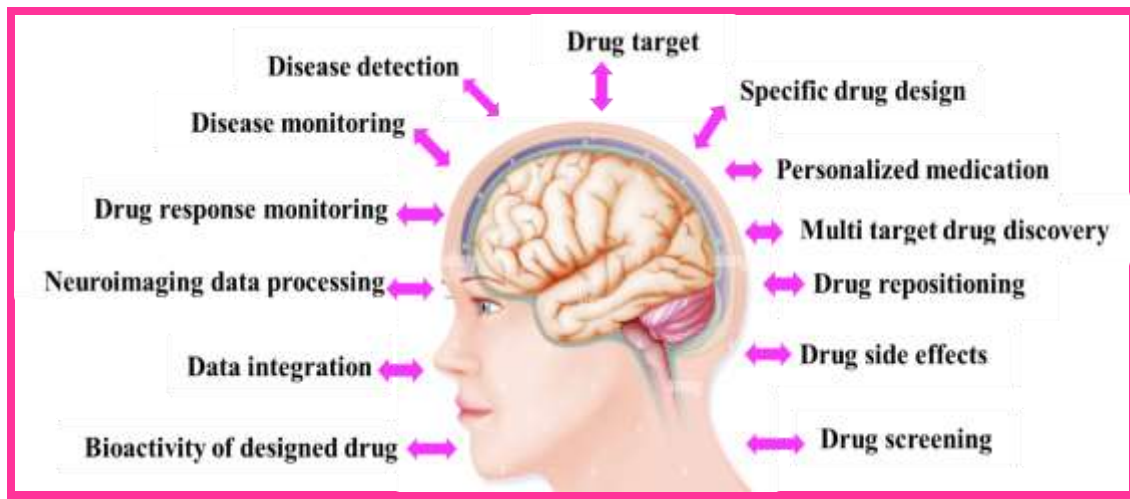


Fig. 14. Application of ML in disease treatment (Vatansever *et al.*, 2021).

This includes optimizing properties such as brightness, binding affinity to specific targets, and spectral characteristics. Machine learning (ML) can also facilitate the development and adoption of the latest technological approaches. By analyzing the molecular structures of organic compounds and understanding cellular mechanisms, ML can generate predictive models that describe the relationships between organic compounds and disease progression. Organic fluorescent compounds provide valuable insights for visualizing protein aggregates in the neurons of patients with Alzheimer's disease and PD (Li *et al.*, 2020).

Personalized medicine: The symptoms of PD vary among patients. ML can be used to design compounds tailored to the severity and profile of individual symptoms; however, extensive research is still required in this area.

3. Conclusion and Future Expectations: Looking ahead, the future of PD treatment lies in a multidisciplinary approach that integrates pharmacological, surgical, supportive, and emerging therapies tailored to individual patient needs. Advancements in biotechnology and artificial intelligence are expected to pave the way for more effective treatments and, potentially, a cure. In conclusion, although significant progress has been made in the management of PD, the search for a definitive cure continues. The integration of emerging therapies with existing treatment modalities offers hope for improved outcomes, but extensive research is required to address this complex disease. Overall, the future of PD treatment is promising, with the potential to provide more comprehensive and personalized care for patients.

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