# Review of Current Treatments for Parkinson's Disease

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## Abstract

This review paper comprehensively examines the current landscape of treatment strategies for Parkinson's Disease (PD). Parkinson's Disease is a progressive neurodegenerative disorder characterized by motor symptoms such as bradykinesia, tremors, and rigidity, along with non-motor symptoms including cognitive impairments and psychiatric disturbances. In this review, we cover several treatments that were reported in the literature, their efficacy, as well as how these treatments could be improved. The management of PD has evolved significantly over the years, driven by advancements in both pharmacological and non-pharmacological interventions. This paper provides an up-to-date overview of the various treatments available, ranging from levodopa therapy to dopamine agonists, monoamine oxidase-B inhibitors, and anticholinergics. Non-pharmacological interventions, including deep brain stimulation, physical therapy, and cognitive rehabilitation, are also discussed for their crucial roles in augmenting symptom management and improving quality of life.

**Keywords:**

Parkinson's, Dopamine, Deep brain stimulation, Blood-brain barrier, Neurotransmitter, Tremors, On-Off Cycles, Rehabilitation, Anticholinergics, Somatic stem cells

## Introduction

Parkinson's disease (PD) is characterized by muscle rigidity, slow movement, and imbalance within the limbs due to neurological loss in the brain. PD is the leading cause of neurological disease in the adult population, affecting 1.5 to 26 per 100,000 of the adult population (Xu 4). Approximately 8.7 million and 9.3 million people worldwide will be affected by Parkinson's disease by the year 2030 (Xu 7). Some risks of mortality with PD include cognitive impairment, old age, late age of onset, male gender, and gait disorder. All the current treatments increase the mortality rate of the patient by a significant amount making most treatments not ineffective to all patients. The current mortality rate of women with PD is age-dependent and in the US, it ranges between 28% and 44% (Xu 18). Longer duration of the disease is associated with a higher mortality rate, as can be seen by the high mortality rates in people over the age of 70, due to the progressive nature of PD.

### Parkinson's disease pathology

In a healthy brain, the cerebral cortex sends a signal to the basal ganglia, and the basal ganglia processes this signal and sends it forward to the motor cortex. The motor cortex can then send

these signals downstream to the spinal cord to initiate a movement by the body. The basal ganglia also aid with the subconscious control of sub-skeletal tone and the coordination of learned movement. This information will then be sent back to the thalamus, the cerebral cortex, and the spine and skeletal muscle in a loop. The first input from the cerebral cortex to the basal ganglia functions the same in PD, but the second step of output from the basal ganglia to the motor cortex is impaired in patients with PD. This causes an irregularity in the pattern and affects the ability of the muscles to perform smooth contractions. The basal ganglia consist of multiple areas, but the most relevant in PD are the striatum, globus pallidus interna, and thalamus because they make up the dopamine cycle. The initial step from the cortex to the basal ganglia is received by the striatum. The output of the striatum goes to the globus pallidus interna which separates the basal ganglia even further. However, the most important part of the basal ganglia is the substantia nigra which contains the dopaminergic neurons that release dopamine into the striatum. There are two types of receptors: D1 and D2. D1 is the dopamine that excites the nerve and allows it to function, but D2 inhibits the nerve to not be able to function (Xu 12). These two types of receptors allow for the action to be controlled and form a constant loop. But in PD, the patients have reduced dopamine within the substantia nigra because of their lack of dopamine-producing neurons.

A distinctive pathology in most cases of PD is the formation of clumps of misfolded proteins within the neurons. The most common type of these clumps is called Lewy bodies. Lewy bodies result from a misfolded protein called alpha-synuclein. These molecules can form small, repeated units called oligomers or longer fibrils. Extensive research points to these Lewy bodies being toxic to neurons and playing a key role in the progressiveness of the disease. Unwanted proteins are normally cleared by the cell's different protein-degrading functions, but within PD patients, these functions are overwhelmed by misfolded alpha-synuclein, which can kill the neurons. PD has also been linked to problems with mitochondria, organelles that usually provide the cell with energy and can be very malleable. They can move around and support cells that need energy and can migrate to support other cells. All of these functions, however, are impaired in PD, and the mitochondria are unable to sustain proper neuronal function. Mitochondria are normally replaced when they get old to help keep the energy flow steady. However, the neurons dying means the mitochondria do not get replaced, leaving the remaining cells lacking the energy they need. These cellular pathologies underlie the brutal effects of PD degeneration.

Glia is another cell type that may contribute to PD pathology. Glial cells surround neurons and provide physical and chemical support to them by maintaining their environment. There are five types of glial cells: astrocytes, oligodendrocytes, microglia, ependymal, and radial glia. The type that is most involved in PD is the microglia, tiny glial cells that act as the brain's dedicated immune system. The brain needs its immune system because the blood-brain barrier (BBB) isolates the brain from the rest of your body. Microglia are alert to signs of injury and disease.

When they detect a problem, they charge in and take care of it—whether it means clearing away dead cells or getting rid of a toxin or pathogens. When microglia respond to an injury, it causes inflammation as part of the healing process. When the neurons have died the microglia will take up the remaining cellular debris and release the inflammatory cytokines which activate another type of glial cell called the astrocyte. With both glial cells active the neighboring neurons start to die, due to all the cytokines being released.

## Non-motor symptoms of PD

The first set of symptoms occurs with the patient's mental health. PD increases the risk of developing anxiety because of many associated fears and worries. One is a fear of being unable to function independently, especially when the medication is less effective ("off" period). This further develops into the fear of isolation and social embarrassment. The neurological pathways and chemical signals impacted by PD overlap with those influenced by anxiety. Individuals with PD often exhibit irregular levels of the neurotransmitter Gamma-aminobutyric acid (GABA). Low GABA levels are also associated with anxiety, which can be alleviated by certain anti-anxiety medications designed to increase GABA levels. In certain instances, anxiety is directly connected to fluctuations in motor symptoms. During "off" periods, people may experience intense anxiety, sometimes leading to full-blown anxiety attacks. Over 40% of people with PD will experience an anxiety disorder, displaying the prevalence of anxiety within PD patients. Anxiety could be treated with psychotherapy but is most often treated with psychiatric medication.

Another mental health symptom that affects PD patients is apathy, a lack of interest or motivation, which can hinder symptom management as patients become less inclined to exercise and follow medication schedules. Alongside apathy, depression, and fatigue are common experiences for people with PD, but apathy is distinct from depression and may be associated with cognitive decline. A combination of apathy and depression can lead to reduced energy and difficulty distinguishing their respective effects on mood. Coping with apathy is crucial for enhancing the quality of life and maintaining positive relationships with caregivers, family, and friends. Apathy does not have any effective treatments but can be overcome through structured activities and opportunities for socialization.

Depression is different from temporary sadness, as it can persist for weeks or longer and is linked to changes in brain chemistry caused by PD. PD affects brain regions responsible for dopamine, norepinephrine, and serotonin production, which regulate mood, energy, motivation, appetite, and sleep. Despite its common occurrence in PD, depression is often overlooked and undertreated, even before the official diagnosis. Recognizing and treating depression is essential to reduce disability and improve the overall quality of life for individuals with PD.

Depression symptoms may fluctuate over time and can intensify both motor and cognitive PD symptoms, but medications used to manage Parkinson's movement symptoms can also help alleviate depression.

Clear speech relies on proper respiration, phonation (vocal fold closure), and precise articulation & and resonance involving tongue and throat muscles. PD can affect these systems, leading to soft and difficult-to-understand speech. PD symptoms like a frozen or masked face may hinder emotional expression during communication, causing others to misinterpret the speaker's emotions as disinterest, aloofness, depression, or anger. Additionally, some individuals with PD may struggle to find words, resulting in slow speech, while others may experience rapid speech that resembles stuttering. These symptoms may worsen with fatigue and may not always be noticed by the person with Parkinson's. Dysphagia refers to difficulty in swallowing, and it typically begins with mild signs like extended mealtime or coughing while eating. Over time, it can develop into a significant symptom of PD. Silent aspiration is where a person does not cough or choke, which increases the risk of aspiration pneumonia, which is the primary cause of death in PD. Moreover, experiencing discomfort during swallowing or being unable to enjoy favorite foods and beverages can significantly reduce one's quality of life.

Fatigue is a common and significant issue for many individuals with PD. It is characterized by a deep and persistent feeling of tiredness that doesn't improve with rest, affecting about half of people with PD, and one-third consider it their most disabling symptom. Unlike sleepiness, fatigue doesn't necessarily prompt a desire to sleep. It can occur at any stage of PD, regardless of the severity of movement symptoms, and may be accompanied by other issues like sleep disturbances, pain, or depression. The exact cause of fatigue in PD is not fully understood, and it may not solely be linked to motor symptoms. Identifying other potential causes outside of PD, such as other illnesses or medications, is essential. Fatigue's impact can be severe, leading to social withdrawal, reduced work hours, or early retirement. Managing fatigue effectively is essential for enhancing the overall quality of life for individuals with PD.

Sleep is crucial for overall health, particularly for individuals with PD as their bodies require additional time for restoration and repair. PD-related brain changes can lead to sleep difficulties even before movement symptoms appear. More than 75% of people with PD report sleep-related symptoms, with some medications causing disruptions in sleep while others induce daytime sleepiness. Poor sleep can negatively impact health, mood, and quality of life for both individuals with PD and their caregivers, highlighting the importance of restful sleep for everyone involved.

Some individuals with Parkinson's disease (PD) may experience mild cognitive impairment, which can manifest as distraction, disorganization, and difficulty planning, and accomplishing tasks. Cognitive changes may also lead to trouble focusing on situations that demand divided attention or remembering information and finding the right words when speaking. While

cognitive impairment can affect many people with PD to some extent, it may not always interfere significantly with daily life. Stress, medication, and depression can contribute to these changes. Cognitive impairment in PD is distinct from dementia, but some individuals may eventually develop mild dementia as the disease progresses, typically years after the initial diagnosis.

The combination of movement and cognitive impairments can present challenges, hindering social participation and basic activities. Care partners of individuals with PD-related dementia must prioritize self-care, as dementia can also cause caregiver stress. Accurate diagnosis is crucial, as mood, sleep, medication, or other medical issues can mimic dementia symptoms in PD. There are two types of dementia which are both caused by the alpha-synuclein protein: Parkinson's disease dementia (PDD) and Dementia with Lewy Bodies (DLB). Both have the common symptoms of disorientation, confusion, and short/long-term memory impairment. The difference in the types of dementia is determined by the onset of dementia. If cognitive decline is recognized early, then it is DLB. When a person has had a year of more motor symptoms and experiences cognitive decline after this year, it is considered PDD. Exelon (rivastigmine tartrate) is a medication that can treat dementia in PD, with other treatments under study.

Between 20-40% of people with PD experience hallucinations or delusions, and this percentage tends to increase as the disease progresses. However, it is important to note that these statistics may also include temporary symptoms due to medication adjustments, infections, or misinterpretations of real stimuli (illusions). Antipsychotic medications may not be prescribed for minor hallucinations, but more significant psychosis may develop over time. The prevalence of hallucinations and psychosis in PD varies and changes as the disease advances, making it essential to understand the complexity of PD and its symptoms.

A sensory issue within PD is the reduced sense of smell, known as hyposmia, which can occur years or decades before a PD diagnosis and may even precede other symptoms. This loss of smell can impact individuals with PD and may lead to a decreased enjoyment of food and a reduced appetite since the sense of taste is closely linked to the ability to smell.

PD can impact the vision system in several ways. Double vision may occur due to difficulties with eye muscle coordination, particularly for close-up vision (convergence insufficiency). Dry eyes, caused by reduced blinking, can lead to blurry vision. Additionally, some PD medications, particularly anticholinergics, may also cause blurry vision. In advanced stages of PD, visual disturbances in the form of hallucinations can be experienced by some individuals, although they are less common in the early stages.

Changes in physical sensation are common in PD, with the sense of touch sometimes leading to pain instead of being decreased like other senses. This pain can be attributed to peripheral neuropathy, a condition where nerves, often in the feet and legs, are damaged, and it occurs at a higher rate in people with PD, though the exact reasons are not fully understood. Neuropathy

can cause numbness, sensitivity, and various types of pain, while restless leg syndrome (RLS) can create discomfort in the legs, with an irresistible urge to move for temporary relief. Medications used to manage motor symptoms of PD can also help alleviate RLS, and anticonvulsant drugs like gabapentin or pregabalin can be beneficial for both painful peripheral neuropathy and RLS.

## Current treatments

### Pharmacological treatments

Medications can assist in the management of issues related to walking, movement, and tremors. These drugs work by either boosting dopamine levels or acting as dopamine substitutes. Individuals with Parkinson's disease experience reduced dopamine levels in the brain. Yet, direct administration of dopamine is not feasible due to its inability to penetrate the blood-brain barrier (BBB). Upon initiating treatment for Parkinson's disease, notable symptom enhancement is possible. Nonetheless, as time passes, the effectiveness of medications often declines. Despite this, maintaining effective symptom control is generally achievable.

Carbidopa-levodopa, often referred to simply as "levodopa," is a frequently prescribed medication for addressing the motor-related symptoms characteristic of PD. It is widely regarded as the benchmark treatment for this ailment. PD is typified by a scarcity of dopamine, a neurotransmitter pivotal in governing movement and coordination. Levodopa functions as a precursor to dopamine and, upon crossing the BBB, undergoes conversion into dopamine within the brain. Levodopa originates as a naturally occurring amino acid endowed with the capacity to transform into dopamine within the brain. Once it enters the brain, this transformation takes place, leading to a replenishment of dopamine levels that have become deficient.

Consequently, the lines of communication between nerve cells responsible for motor control are enhanced. This culminates in a reduction of hallmark motor symptoms of PD, such as tremors, rigidity, and bradykinesia (slowed movement). Carbidopa, a medication frequently paired with levodopa in a single tablet, assumes a pivotal role in the therapeutic regimen. In instances where levodopa is administered in isolation, a significant proportion is transformed into dopamine within the bloodstream before reaching the brain. This can result in undesirable effects like nausea and lowered blood pressure. Carbidopa counteracts this conversion of levodopa into dopamine outside the brain, facilitating a larger portion of levodopa to access the brain and undergo transformation into dopamine where its effects are needed. The synergy of carbidopa with levodopa serves to enhance the therapeutic impact of levodopa while concurrently minimizing peripheral side effects.

Carbidopa-levodopa substantially alleviates the motor-related symptoms of Parkinson's disease. Numerous individuals experience enhanced mobility, diminished tremors, and an overall boost in motor function. The administration of carbidopa-levodopa can be tailored to cater to individual requirements. This adaptability empowers healthcare professionals to precisely tailor treatment regimens to manage symptoms optimally. As the disease advances, certain individuals may encounter fluctuations in their responsiveness to carbidopa-levodopa, leading to periods of heightened mobility (termed "on periods") alternating with intervals marked by exacerbated symptoms (dubbed "off periods"). Common side effects linked to carbidopa-levodopa encompass nausea, vomiting, low blood pressure, and involuntary movements termed dyskinesias. Frequently, these side effects can be ameliorated through dose adjustments or the inclusion of complementary medications.

Dopamine agonists stand as another efficacious class of medications aimed at addressing these symptoms, rendering them valuable assets in the management of PD. Within the spectrum of PD treatment, dopamine agonists play an instrumental role through their direct activation of dopamine receptors in the brain. Diverging from levodopa, which transforms into dopamine, dopamine agonists emulate the effects of the neurotransmitter directly. This distinctive mechanism contributes to the restoration of dopamine equilibrium, consequently mitigating motor symptoms. The prescription of dopamine agonists involves tailoring dosages and treatment regimens to accommodate individual variables, encompassing factors such as disease progression, specific medication selection, and patient characteristics. Typically, therapy commences with a conservative dose, progressively escalating to achieve an optimal level of symptom control. This methodical strategy not only aids in minimizing potential side effects but also enhances patient tolerance to the medication. The versatility of dopamine agonists is reflected in their various administration forms, spanning from oral tablets to extended-release formulations. The frequency of dosing can vary, ranging from once a day to multiple times a day, contingent on the formulation and medication.

While dopamine agonists offer notable advantages, they are not exempt from potential adverse effects. Common manifestations include nausea, dizziness, and headaches, often ameliorating as the body adapts to the medication. However, certain individuals might encounter more substantial concerns like compulsive behaviors, hallucinations, or disruptions in sleep patterns. The judicious oversight of healthcare professionals remains pivotal in promptly identifying and managing these effects. Dopamine agonists represent a valuable augmentation to the therapeutic repertoire for PD, particularly in its early stages or as a complementary adjunct to levodopa. Customizing medication choices, dosages, and treatment schedules to accommodate the unique requisites of each patient, including age, disease progression, and concurrent medical conditions, is imperative. Regular and open lines of communication between patients and healthcare providers are essential in optimizing treatment outcomes and attenuating side effects. In summation, dopamine agonists offer a focused and effective avenue for addressing

the motor symptoms inherent to PD. While their direct engagement with dopamine receptors yields discernible relief, a cautious approach to dosing and vigilant monitoring emerges as pivotal measures in minimizing adverse effects and ensuring optimal outcomes for individuals grappling with Parkinson's. As the realm of medical knowledge advances, the significance of dopamine agonists as a cornerstone within the comprehensive care of PD becomes increasingly evident.

Within the realm of pharmacological strategies designed to alleviate the multifaceted symptoms of this condition, MAO-B inhibitors have emerged as a significant asset in elevating the quality of life for individuals grappling with PD. MAO-B (Monoamine oxidase-B) inhibitors represent a class of medications specifically designed to target and restrain the activity of the enzyme MAO-B within the brain. This enzyme plays a pivotal role in the breakdown of dopamine, the neurotransmitter profoundly compromised in PD. By inhibiting the action of MAO-B, these medications actively contribute to sustaining elevated levels of dopamine in the brain. This augmentation facilitates improved communication among nerve cells governing motor control, culminating in enhanced motor function and a reduction in the hallmark symptoms of PD, including tremors, rigidity, and bradykinesia.

The dosing and treatment regimen of MAO-B inhibitors are contingent on individual patient attributes and the precise medication prescribed. Typically, treatment commences with a conservative dosage, incrementally augmented to achieve the intended therapeutic outcome. Among the common MAO-B inhibitors employed in PD treatment, selegiline, and rasagiline stand out. These medications are typically administered orally, once or twice daily, with the timing and dosage adjustments overseen by healthcare professionals to ensure both optimal symptom management and minimal adverse effects. While generally well-tolerated, MAO-B inhibitors, like any medications, can instigate potential side effects. Routine manifestations may encompass gastrointestinal disturbances, headaches, or episodes of dizziness. More profound interactions might manifest if MAO-B inhibitors are concomitantly used with certain medications, such as antidepressants, given their impact on neurotransmitter levels. Moreover, some individuals might encounter behavioral shifts or hallucinations. The vigilance of healthcare providers in closely monitoring and swiftly addressing any untoward effects is pivotal in upholding the safety and efficacy of the medication. MAO-B inhibitors stand as a substantial stride forward in the management of PD, extending targeted relief through the preservation of dopamine levels and the augmentation of motor functions. These medications furnish an additional treatment avenue, often employed in tandem with other therapeutic modalities such as levodopa or dopamine agonists. The dosing regimen is personalized to the specific requirements of each patient, and vigilant monitoring serves to curtail potential side effects. As ongoing research continues to unravel the intricacies of PD, the role of MAO-B inhibitors remains indispensable in the holistic strategy of treating and enhancing the lives of those impacted by this condition.

Amidst the array of medications employed to alleviate these symptoms, anticholinergics have surfaced as a therapeutic avenue presenting distinctive advantages for individuals grappling with PD. Operating by impeding the activity of acetylcholine, a neurotransmitter orchestrating signals in the brain, anticholinergics assume a crucial role. The intricate balance between dopamine and acetylcholine, disrupted in PD due to the degeneration of dopamine-producing neurons, is targeted by anticholinergics. Their action dampens the influence of acetylcholine, consequently alleviating specific motor symptoms of PD, including tremors and muscle rigidity. Tailoring the dosage and treatment regimen of anticholinergics to align with individual patient requirements, symptom severity, and potential interactions with concurrent medications is paramount. A comprehensive assessment accounts for variables such as age, overall health status, and pre-existing medical conditions. Ordinarily, treatment is inaugurated with a conservative dose that is subsequently calibrated based on the patient's response. The mode of administration may vary, with oral ingestion or patch application for certain anticholinergic medications, facilitating personalized and adaptable management. While anticholinergics undeniably furnish symptomatic relief, they are accompanied by potential side effects that necessitate prudent consideration. Among the common manifestations are dry mouth, compromised vision clarity, and challenges in urinary retention. Cognitive impairments and moments of confusion are also within the realm of possibility, particularly among older individuals. The propensity for adverse effects tends to escalate with escalated doses or extended usage periods. Notably, elderly patients are often more susceptible to these side effects due to age-related alterations in metabolic processes.

Anticholinergics occupy a substantial position within the pharmacological toolkit directed at treating PD. Their role involves rectifying specific motor symptoms through the recalibration of neurotransmitter activity. The underlying mechanism of action, coupled with personalized dosing and versatile administration options, renders them invaluable, particularly in scenarios where alternative treatments may not be feasible. However, meticulous oversight is imperative to monitor potential side effects and make necessary adjustments to the treatment regimen. As the trajectory of PD research advances, and our comprehension of its treatments deepens, anticholinergics continue to retain their significance as a viable therapeutic approach. Their nuanced impact, harmonized with attentive medical supervision, can significantly contribute to elevating the quality of life for individuals navigating the intricate challenges posed by PD.

CMOS sensor-controlled dopamine injection

The main goal behind the CMOS sensor is to protect and repair the damaged neurons within the brain that are being affected by Parkinson's. This treatment is different from the rest since most other treatments as covered later, will not repair or even protect the neurons but instead try to negate the effects of Parkinson's not solving the root of the disease. The reason solving the root of the problem is important, is so people can understand why the disease is prevalent and to take steps to focus on early preventative care. CMOS was also created to try and limit the amount of different side effects that were laid out in other treatments. These side effects include a lack of control over infusion rate, GDNF dosage, a strong immune reaction, and a gene mutation. The proposed CMOS's main method of repairing neurons is by maintaining the therapeutic levels of dopamine concentration within the body. The way the CMOS circuit works is by using a CMOS-controlled novel sensor. The standard levels are inputted within the circuit and the sensor detects any variation and injects the appropriate amount of dopamine needed. The electrochemical sensor was selected as it provided a reliable way of gauging the levels of dopamine (Poustinchi 4). Electrode over-polarization during the operation of the closed feedback loop introduces the risk of electrode material delamination. Over-polarization was prevented using a three-electrode system, which incorporates a separate reference electrode to which no current is passed.

The two parts of the chassis were the low-power noise-immune current conveyor and the comparator with offset cancellation. The goal for the current conveyor was to measure the electrochemical current with low amounts of power which can be used with stability and high return. Wide swing folded cascade amplifiers were used for lower power consumption and returns with great accuracy and precision. The comparator with offset calculation was the function used to compare the dopamine values with the standard (the standard dopamine is 0.39 nmol/L) (Poustinchi 6). A low-power version of this item was found, and with a digital patch, was ready to be implemented within CMOS. In conclusion, a working CMOS circuit has been built with some of the side effects being cured. However, there are still multiple side effects not viewed including the GDNF dosage and the lack of control over the infusion rate.

## Deep brain stimulation

Deep brain stimulation (DBS) was implemented into modern treatments due to the lack of response to medications after certain time frames (5 years). DBS is a surgery that sets an implant within the brain and stimulates the basal ganglia through multiple high-frequency electrical currents. An impulse generator is used to control impulses sent through to the brain. The most common spots for the implant to be in are the subthalamic nucleus and the internal segment of the globus pallidus.

DBS can change the firing rate of neurons and change the pattern of individual neurons within the basal ganglia to inhibit certain motor symptoms that might appear due to PD. The pattern of individual neurons within the basal ganglia has been changed due to the electrical current which allows for change to the motor symptoms due to PD. The current also replicates the synapse of the human body and releases neurotransmitters, allowing neurons to communicate with each other more efficiently, which can alleviate both motor and non-motor symptoms. DBS also has established treatments for advanced forms of PD, in which usually the medication has been rendered ineffective. This is also furthered because DBS surgery benefits can last 10+ years in some individuals. DBS was discovered due to an observation although it is not fully understood, so the closed-loop DBS can be investigated further to reduce side-effects and allow improved feedback.

Clinical trials conducted with DBS show that it is very effective in patients with PD and can be represented through the patient's Parkinson's Disease Questionnaire (PDQ). PDQ scores represent the amount of disease that has overtaken the patient, so the lower the score the better. For the first trial, the DBS group had a 31.8 PDQ average while the control (medication) had an average of 40.2 PDQ (Okun 3). This initial trial displays some form of DBS working effectively while the second trial had far more conclusive results. The patients undergoing DBS had an average PDQ of 28.3 while the control had a 46.0 PDQ. This massive jump could have been due to several factors, but the difference in the scores in both trials points to the effectiveness of the treatment.

DBS was approved by the Food and Drug Administration (FDA) in 2002 as it was a responsive treatment and allowed PD patients who "are not adequately controlled by medication" to gain treatment options. Most PD patients can undergo DBS but some candidates are not able to, due to problems like severe dementia, severe autonomic dysfunction, atypical parkinsonism, and unstable psychiatric disease. The costs of DBS vary, but most range from $28,000 to $50,000 with an additional cost of $3,000 per year for programming and attunement of the impulse generator. Some adverse effects of DBS include infection which occurs in 1.2% to 15.2% of patients, and intracranial hemorrhage which occurs in 5% of patients (Okun 6). Some side effects of the treatments include cognitive impairment and electrode relocation.

Due to conventional DBS being an open-loop system and not allowing for feedback and patient adjustment, adjustive deep brain stimulation was put into creation (aDBS). aDBS can recognize spikes in symptoms and only stimulate, when necessary, unlike the traditional DBS, thus improving patient comfortability and happiness. Some problems with this device are that the feedback signal must be perfect or the DBS might not activate at all. This paired with wanting the neurosurgical intervention to be small, the readings could be taken from the local field potential (LFP). The LFP can be consistently picked up from the subthalamic nucleus which is one of the most common spots to plant the electrode in the brain for DBS, and the local field potential being so close to the surgical entry could eliminate the need for invasive surgery.

STEM cell therapy

Stem cells possess a unique quality due to their ability to specialize in a wide range of cell types. Stem cells are perceived as inherent assets within the body. Whenever the body necessitates a specific kind of cell, whether it's bone cells or brain cells, an undifferentiated stem cell can adapt and fulfill that requirement.

There are three primary categories of stem cells. The first is embryonic stem cells which are pluripotent, signifying their ability to differentiate into numerous cell types present in your body. These cells are found in embryos. The second category of stem cells is the somatic stem cells, which are also called adult stem cells. These stem cells usually perform repair functions, but they are still able to transform into other cells. However, these cells are different because they cannot turn into as many cell types as embryonic stem cells. The third and final stem cell category is the induced pluripotent stem cell (iPSCs). These stem cells are made by genetically changing cells that have already matured. Since they are not able to transform as a cell function, the genetic modifications alter the cell and turn it into a different cell. Stem cell therapy involves utilizing stem cells, typically obtained from a donor but occasionally sourced from your own body, to address a disorder. Given that PD results in the demise of brain cells, researchers are endeavoring to employ stem cells to replace the affected brain cells in PD-affected regions. This approach holds the potential to alleviate the symptoms associated with PD.

The current concept involves directly introducing stem cells into the affected regions of the brain, where they can transform functional brain cells. These newly generated brain cells might contribute to the regulation of dopamine levels, ultimately leading to a reduction in disease symptoms. It's crucial to emphasize that experts view this approach as a potential treatment for PD rather than a definitive cure. While stem cell therapy holds the promise of replenishing the brain cells lost due to PD, it's important to acknowledge that the disease itself would persist. The implanted stem cells could eventually die at a higher rate due to the progression of PD.

Before the discovery of the method for generating iPSCs, the sole stem cell treatments available for PD necessitated the utilization of embryonic stem cells. This approach was accompanied by ethical and practical complexities, which added challenges to the research process. Following the introduction of iPSCs, stem cells have been employed in clinical trials for various conditions involving neural damage, yielding somewhat varied outcomes. The initial clinical trial involving iPSCs for PD was conducted in 2018 in Japan, encompassing a small group of merely seven participants (Pinjala 12). Other experiments have been conducted employing animal models. To date, these trials have demonstrated reductions in symptoms related to movement and non-motor symptoms like bladder control. Nevertheless, certain issues do arise concerning the origin of stem cells. Analogous to organ transplants, stem cell therapy can be likened to the process of harvesting organs. If iPSCs are sourced from a donor, it might be necessary to administer immunosuppressant drugs to avert the rejection of the cells by your body. On the

other hand, if the iPSCs are derived from your cells, the likelihood of rejection might be lower. However, experts anticipate that this approach could extend the timeline for stem cell therapy, as the iPSCs would need to be created in a laboratory. This method is likely to be more costly compared to utilizing a well-established and tested line of iPSCs from a donor.

Stem cell therapy presents a novel and experimental method of treating PD, differing from conventional treatment alternatives in various aspects. One comparison that we look at is the difference between medication and stem cell therapy. Stem cell therapy aims to replace or mend dopamine-producing cells that have been lost or harmed in the brain, while conventional PD medications like Levodopa therapy and dopamine agonists seek to elevate dopamine levels in the brain or imitate dopamine's effects. For surgery, the transplantation of stem cells into the body is involved in stem cell therapy, whereas established surgical approaches for PD, such as deep brain stimulation (DBS), encompass the insertion of electrodes into the brain to emit electrical impulses to specific affected brain regions. Traditional rehabilitation methods like speech, occupational, and physical therapy can complement the impacts of stem cell treatment. Research has indicated that an active lifestyle and rehabilitation can enhance the outcomes of stem cell therapy. The efficacy of stem cell therapy for PD is still under investigation, and further research is essential to validate the findings from preliminary laboratory and clinical investigations. In contrast, conventional PD treatments have been in use for an extended period, establishing their effectiveness.

**Current Clinical Trials**

| Clinical Trial | Trial Number | Start Date - End Date | Outcomes |
|---|---|---|---|
| Prosthetics In PD | (NCT03103919) | 03/16/2017 - 01/02/2018 | A decrease from the baseline score indicated an improvement in symptoms. |
| Safinamide Medication in PD | (NCT03841604) | 04/19/2019 - 05/03/2021 | Substantial improvements were identified after the administration of safinamide treatment. |
| Voice Treatment in PD | (NCT03700684) | 09/19/2018 - 11/30/2022 | Among the group of ten speakers, six showed improved temporal coordination between the |

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| | | | laryngeal and subpharyngeal mechanisms. |
| Low-Frequency DBS with Freezing of Gait in PD | (NCT02549859) | 08/01/2015 - 05/01/2017 | Notably, these positive changes persisted consistently over the entire 6-week duration of the study. |
| Carbidopa/Levodopa Medicine in PD | (NCT00391898) | 10/01/2006 - 06/01/2008 | In conclusion, patients diagnosed with Parkinson's disease who exhibit either minimal or no motor complications witnessed improvements in their motor function. |

The research about prosthetics within PD centered on assessing the impact of a novel medication called Neupro on the symptoms of Parkinson's Disease. A decrease from the baseline score indicated an improvement in symptoms. The study tracked Neupro dosage, modifications, treatment discontinuation, and any adverse events. Over the 12 weeks, noteworthy enhancements in motor scores and specific Kinesia-ONE variables were observed, implying the potential efficacy of Neupro in managing Parkinson's Disease symptoms. Instances of adverse events were duly recorded. The research about safinamide medication in PD was shown to have substantial improvements identified in UPDRS IV, KPPS item 5 (specifically addressing dystonia during "off" periods in a specific region), KPPS domain 3 (covering items 4 to 6 related to pain during fluctuations), and the overall KPPS score after the administration of safinamide treatment. To conclude, our findings suggest that safinamide could potentially have a positive influence on managing pain, which stands as a notable unmet requirement for individuals dealing with PD and its fluctuating symptoms.

Voice treatment research delves into how both groups and individual participants responded to the treatment, examining the outcomes in depth. Notably, individuals with Parkinson's disease who were capable of speaking demonstrated a noteworthy increase in sound pressure level (SPL) in response to the treatment. Among the group of ten speakers, six showed improved temporal coordination between the laryngeal and subpharyngeal mechanisms, as evidenced by enhanced interarticular timing resulting from the treatment. However, by the conclusion of the treatment, four out of these ten speakers exhibited a decrease in the timing coordination between these two mechanisms. Furthermore, following the treatment, there was a significant

increase in the group's speech intelligibility scores compared to their scores before receiving the treatment.

In the research about low-frequency DBS comparison to the standard 130 Hz stimulation, the utilization of 60-Hz stimulation resulted in a significant improvement in the ability to swallow, reduction in freezing of gait (FOG), and alleviation of symptoms associated with axial movement and Parkinson's disease in individuals who received bilateral deep brain stimulation (STN-DBS) targeting the subthalamic nucleus as part of their Parkinson's disease treatment. Notably, these positive changes persisted consistently over the entire 6-week duration of the study.

In conclusion, the trials about carbidopa/levodopa patients who were diagnosed with Parkinson's disease and exhibited either minimal or no motor complications witnessed improvements in their motor function and daily activity scores when undergoing treatment with LCE, as compared to the LC treatment. Incorporating entacapone into the early stages of dopaminergic therapy in combination with LC not only alleviates functional limitations but also upholds a positive safety and tolerability profile.

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