Parkinson's Disease: New Clinical Trials and Emerging Therapies – A Review

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Abstracts: Parkinson's disease (PD) is a progressive neurodegenerative disorder characterized by the loss of dopaminergic neurons in the substantia nigra, leading to motor symptoms such as bradykinesia, tremor, rigidity, and postural instability, along with a wide range of non-motor manifestations. The etiology of PD is multifactorial, involving genetic, environmental, and aging-related factors. Despite significant advances in understanding the disease pathology, there is currently no cure, and treatment remains primarily symptomatic. Pharmacological approaches, particularly levodopa-based therapies, remain the gold standard for symptom management, while adjunctive medications and surgical interventions like deep brain stimulation offer additional benefit in advanced stages. Recent developments in neuroprotective strategies, gene therapy, and stem cell research offer hope for disease-modifying treatments. This review provides a comprehensive overview of the pathophysiology, clinical features, current therapeutic strategies, and emerging treatments for Parkinson's disease, emphasizing the need for continued research toward a cure and improved patient quality of life.

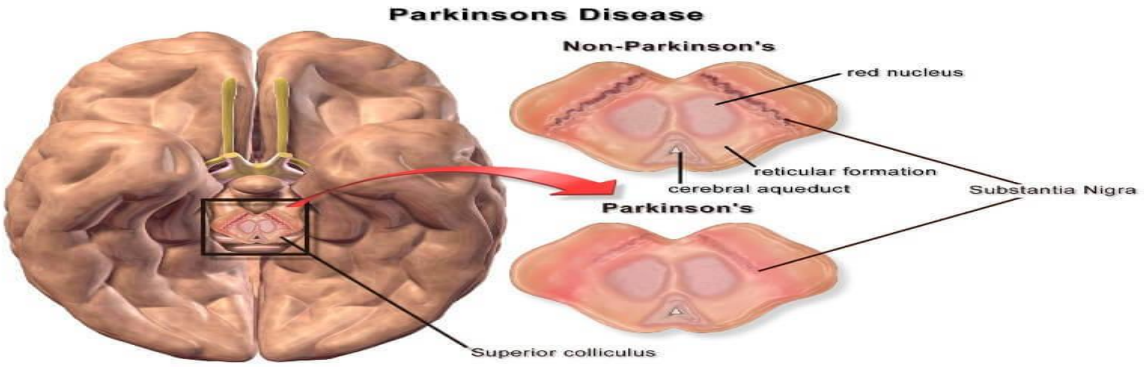
INTRODUCTION

Parkinson's disease is a progressive movement disorder of the nervous system. It causes nerve cells (neurons) in parts of the brain to weaken, become damaged, and die, leading to symptoms that include problems with movement, tremor, stiffness, and impaired balance. As symptoms progress, people with Parkinson's disease (PD) may have difficulty walking, talking, or completing other simple tasks.

Although many brain areas are affected in Parkinson's disease, the most common symptoms result from the loss of neurons in an area near the base of the brain called the substantia nigra. The neurons in this area produce dopamine. Dopamine is the chemical messenger that transmits signals in the brain to produce smooth, purposeful movement. Studies have shown that most people with PD have lost 60 to 80% or more of the dopamine-producing cells in the substantia nigra by the time symptoms appear.

People with PD also lose the nerve endings that produce the neurotransmitter norepinephrine—the main chemical messenger to the part of the nervous system that controls many automatic functions of the body, such as pulse and blood pressure. The loss of norepinephrine might explain several of the symptoms of Parkinson's that are not related to movement, such as fatigue and blood pressure changes.

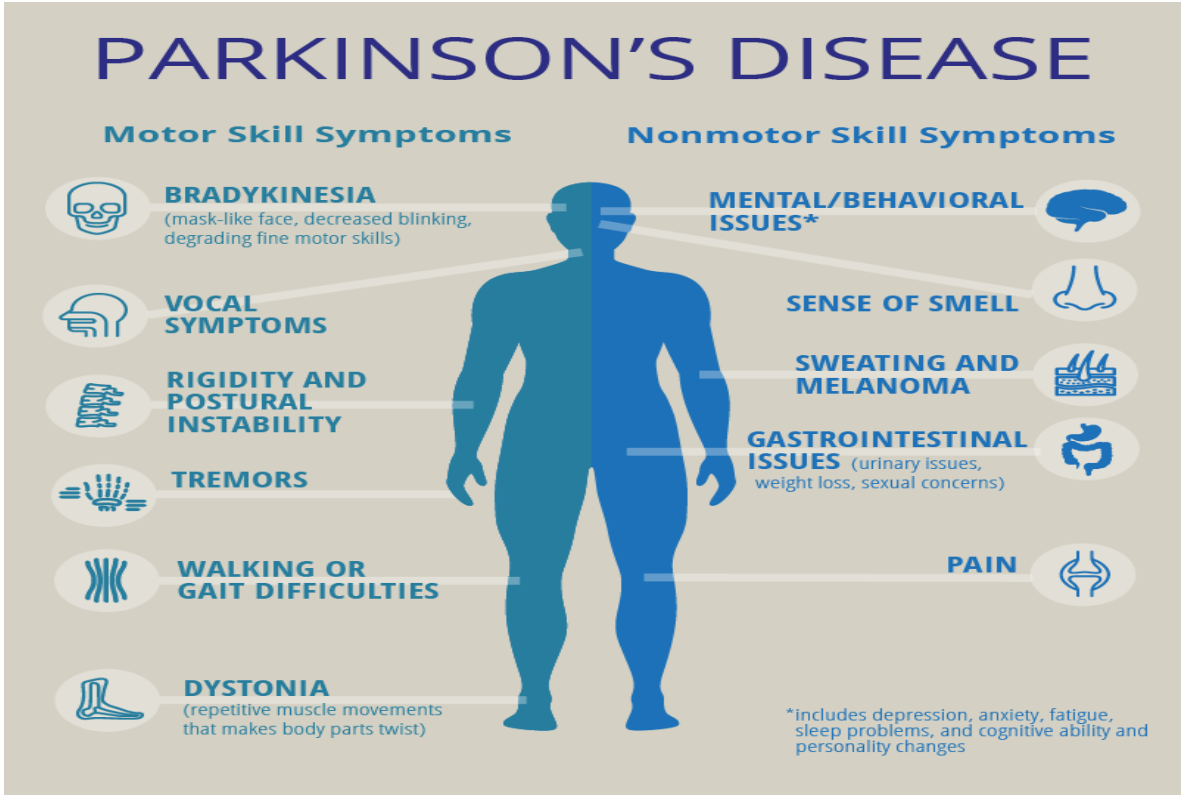
The affected brain cells of people with PD contain Lewy bodies—deposits of the protein alpha-synuclein. Researchers do not yet know why Lewy bodies form or their role in the disease. Some research suggests that the cell's protein disposal system may fail in people with PD, causing proteins to build up to harmful levels and trigger cell death. Additional studies have found evidence that clumps of protein that develop inside the brain cells of people with PD may contribute to the death of neurons.



Symptoms of Parkinson's disease:

PD affects different people in different ways. The rate of progression and the particular symptoms differ among individuals. PD symptoms typically begin on one side of the body. However, the disease eventually affects both sides, although symptoms are often less severe on one side than on the other. The four primary symptoms of PD are:

1. Tremor (shaking) often begins in a person's hand, although sometimes the person's foot or jaw is affected first. The particular tremor associated with PD has a rhythmic back-and-forth motion. Often, the tremor will cause the person to rub their thumb and forefinger together, which may appear as "pill rolling." It is most obvious when the hand is at rest or when a person is under stress. This tremor usually disappears during sleep and may improve when the person makes a purposeful, intended movement.
2. Rigidity (muscle stiffness), or resistance to movement, affects most people with PD. The muscles stay tense and tight so the person aches or feels stiff. If another person tries to move the individual's arm, it will move only in short, jerky movements (known as "cogwheel" rigidity).
3. Bradykinesia is a slowing down of spontaneous and some automatic movement. It can make simple tasks more difficult, and activities the person could once perform quickly and easily—such as washing or dressing—may take much longer. The person's face may be less expressive (known as "masked face").
4. Postural instability, such as balance problems and changes in posture, can increase the risk of falls.



People with PD often develop a "parkinsonian gait." This includes a tendency to lean forward, taking small, quick steps as if hurrying (called festination), and reduced swinging in one or both arms. They may have trouble initiating movement (called "start hesitation") and stop suddenly as they walk, freezing in place.

In addition to the characteristic symptoms noted above, people with PD may experience other problems related to the disease. These may include:

- Mental and emotional health problems, including depression or anxiety, may occur during the early stage of the disease, even before the onset of movement issues.

- Difficulty with swallowing and chewing. Problems with swallowing and chewing may occur in later stages of the disease. Food and saliva may collect in the mouth and back of the throat, resulting in choking or drooling. It can be difficult for people in the later stages of PD to get enough nutrients.

- Speech changes. Most individuals with PD have speech difficulties, which may include speaking quietly or in a monotone. Some people may hesitate before speaking. They may also slur or speak too quickly.

- Urinary problems or constipation. In PD, the autonomic nervous system, which controls movements and functions we don't have to think about, doesn't function normally. This can cause bladder and bowel problems.

- Skin problems. People with Parkinson's may have increased facial oils, particularly on the forehead and at the sides of the nose. The scalp may become oily, too, resulting in dandruff. In other cases, the skin can become very dry, or the person may experience excessive sweating.

- Sleep problems. Common sleep problems in PD include difficulty staying asleep at night, restless sleep, nightmares and emotional dreams, and drowsiness or suddenly falling asleep during the day. Another common problem is REM sleep behavior disorder, in which people act out their dreams. This may result in injury to themselves or their bed partners. Medications used to treat PD may contribute to some sleep issues.

- Dementia or other cognitive problems. Some people with PD develop memory problems and slowed thinking. Cognitive problems become more severe in the late stages of PD, and some people are diagnosed with Parkinson's disease dementia. Memory, visuospatial skills, attention, language, reasoning, or other mental and cognitive skills may be affected.

- Orthostatic hypotension. Orthostatic hypotension is a sudden drop in blood pressure when a person stands up from a lying down or seated position. This may cause dizziness, light headedness, and, in extreme cases, loss of balance or fainting.

- Muscle cramps and dystonia. The rigidity and lack of normal movement associated with PD often causes muscle cramps, especially in the legs and toes. PD can also be associated with dystonia—sustained muscle contractions that cause forced or twisted positions.

- Pain. People with PD may have aches and pains in their muscles and joints because of the rigidity and abnormal postures with the disease.

- Fatigue and loss of energy. Many people with PD often have fatigue, especially late in the day. Fatigue may be associated with depression or sleep disorders, but it may also result from motor control issues such as trouble initiating or carrying out movement, tremors or stiffness.

- Sexual dysfunction. Because it affects nerve signals from the brain, PD can cause sexual dysfunction. PD-related depression or use of certain medications may also cause decreased sex drive and other problems.

DIAGNOSIS

Currently, there isn't a specific test to diagnose Parkinson's disease. A diagnosis is made by a doctor trained in nervous system conditions, known as a neurologist. A diagnosis of Parkinson's is based on your medical history, a review of your symptoms, and a neurological and physical exam.

It can take time to diagnose Parkinson's disease. Healthcare professionals may recommend regular follow-up appointments with neurologists trained in movement disorders to evaluate your condition and symptoms over time and diagnose Parkinson's disease.

Your healthcare team may order some of these tests and procedures:

- Physical and neurological exam. This includes taking your medical history and doing a neurological exam that tests your thinking and mental abilities, senses, coordination, and reflexes.

- Blood and lab tests. These are used to rule out other conditions that may be causing your symptoms.

- Imaging tests, such as an MRI, brain ultrasound and PET scan. These are used to rule out other conditions. They are not very helpful in diagnosing Parkinson's disease.

- A specific single-photon emission computerized tomography (SPECT) scan called a dopamine transporter (DAT) scan. This can help support the suspicion that you have Parkinson's disease and help identify different types of tremor. But it is your symptoms and the results of your neurological exam that determine your diagnosis. Most people do not require a DAT scan.

- Genetic testing. This tests for gene changes if there is a known family history of Parkinson's disease or if you have early-onset disease.

- A short, low-dose treatment of medicines. You may be given medicines used to treat Parkinson's disease to see if you get better. If your symptoms show significant improvement, this may help confirm your diagnosis. You must be given a sufficient dose to show the benefit, as getting low doses for a day or two isn't reliable.

- Follow-up appointments. Regular appointments with neurologists trained in movement disorders may be needed over time to confirm a diagnosis.

- Alpha-synuclein test. This test, also called an alpha-synuclein seed amplification assay, detects Parkinson's disease before symptoms begin. Alpha-synuclein clumps are a hallmark sign of Parkinson's disease. Healthcare professionals can test for this condition in the skin or spinal fluid.

TREATMENT

Parkinson's disease can't be cured, but medicines can help control the symptoms. Medicines often work very well. When medicine is no longer helping, some people may have surgery. Your healthcare team also may recommend aerobic exercise, physical therapy that focuses on balancing and stretching, and speech therapy.

MEDICINES

Medicines may help improve problems with walking, movement and tremor. The medicines work by increasing or substituting for dopamine in the brain.

People with Parkinson's disease have low levels of brain dopamine. But dopamine can't be given directly because it can't enter the brain.

Your symptoms may improve significantly after you start treatment. The benefits may lessen over time, but usually medicines still control symptoms well.

Medicines you may be prescribed include:

- Carbidopa-levodopa (Rytary, Sinemet, others). Levodopa is the most effective Parkinson's disease medicine. It is a natural chemical that passes into the brain and becomes dopamine. Levodopa is combined with carbidopa to help levodopa reach the brain and to prevent or lessens side effects such as nausea.

  Side effects may include nausea and light headedness when you stand, called orthostatic hypotension. Higher doses of levodopa may cause involuntary movements, known as dyskinesia. If this happens, your dose may need to be lessened or adjusted.

  The benefit from levodopa may lessen over time. It also may wax and wane. This is called wearing off.

  Carbidopa-levodopa usually is best taken on an empty stomach if you have advanced Parkinson's disease. Follow your healthcare team's advice on the best time to take it.

- Inhaled levodopa (Inbrija). This medicine helps manage symptoms when oral medicines suddenly stop working during the day.

- Carbidopa-levodopa infusion (Duopa). This medicine is given through a feeding tube in a gel form and goes directly into the small intestine.

  The tube is placed during a minor surgery. There are some risks of having the tube. The tube may fall out or cause an infection at the infusion site.

Carbidopa-levodopa infusion is for patients with advanced Parkinson's who still respond to the medicine but need a more constant level of levodopa. It helps control motor difficulties and other symptoms such as anxiety and depression.

- Dopamine agonists. Unlike levodopa, dopamine agonists don't change into dopamine. Instead, they mimic dopamine effects in the brain.

They aren't as effective as levodopa in treating symptoms. But they last longer and may be used with levodopa to improve how well it works.

Dopamine agonists include:

- Pramipexole (Mirapex ER).
- Rotigotine (Neupro), given as a patch.
- Apomorphine (Apokyn), a short-acting dopamine agonist shot for quick relief.

Side effects of dopamine agonists may include lightheadedness, nausea, hallucinations and sleepiness. The medicine also may cause involuntary movements and compulsive behaviors, such as hypersexuality, gambling, and eating.

If you're taking these medicines and behaving in ways that aren't typical for you, talk with your healthcare team.

- Monoamine oxidase B (MAO B) inhibitors. These medicines include:
  - Selegiline (Zelapar).
  - Rasagiline (Azilect).
  - Safinamide (Xadago).

MAO B inhibitors help block an enzyme called monoamine oxidase B (MAO B) that breaks down brain dopamine. When selegiline is given with levodopa, it may keep levodopa from wearing off.

Side effects of MAO B inhibitors may include headaches, nausea, insomnia and confusion.

MAO B inhibitors also may cause hallucinations. When added to carbidopa-levodopa, these medicines increase the risk of hallucinations.

MAO B inhibitors usually are not used along with most antidepressants or some pain medicines because serious but rare reactions may happen. Ask your healthcare professional before taking any other medicines with an MAO B inhibitor.

- Catechol O-methyltransferase, also called COMT, inhibitors. These help levodopa therapy last longer by blocking an enzyme that breaks down dopamine. They include:
  - Entacapone (Comtan).
  - Opicapone (Ongentys).
  - Tolcapone (Tasmar). This medicine is rarely prescribed because of its risk of serious liver damage and liver failure.

Side effects of COMT inhibitors may include increased risk of involuntary movements. Side effects also may include diarrhea, nausea or vomiting.

- Anticholinergics. These medicines were used for many years. They aren't used as often now because of their modest benefits and risk of side effects. They may be helpful in controlling severe tremor for some people with Parkinson's disease. They include:
  - Benztropine.
  - Trihexyphenidyl.

Side effects of anticholinergics may include memory loss, urinary problems, confusion, blurred vision, dry mouth and constipation.

- Amantadine (Gocovri). This medicine may be taken alone for short-term relief of mild, early-stage Parkinson's disease symptoms. It's mainly used with carbidopa-levodopa during advanced Parkinson's disease to help control involuntary muscle movements.

Side effects of amantadine may include mottled skin, thinking and memory problems, ankle swelling, hallucinations, and agitation.

- Adenosine receptor antagonists (A2A receptor antagonists). One of these medicines is istradefylline (Nourianz). This help prevent the wearing off of dopamine and allow more dopamine to be released. Researchers also are looking into whether these medicines may help treat other Parkinson's disease symptoms.
- Pimavanserin (Nuplazid). This medicine treats hallucinations and delusions that can occur with Parkinson's disease.

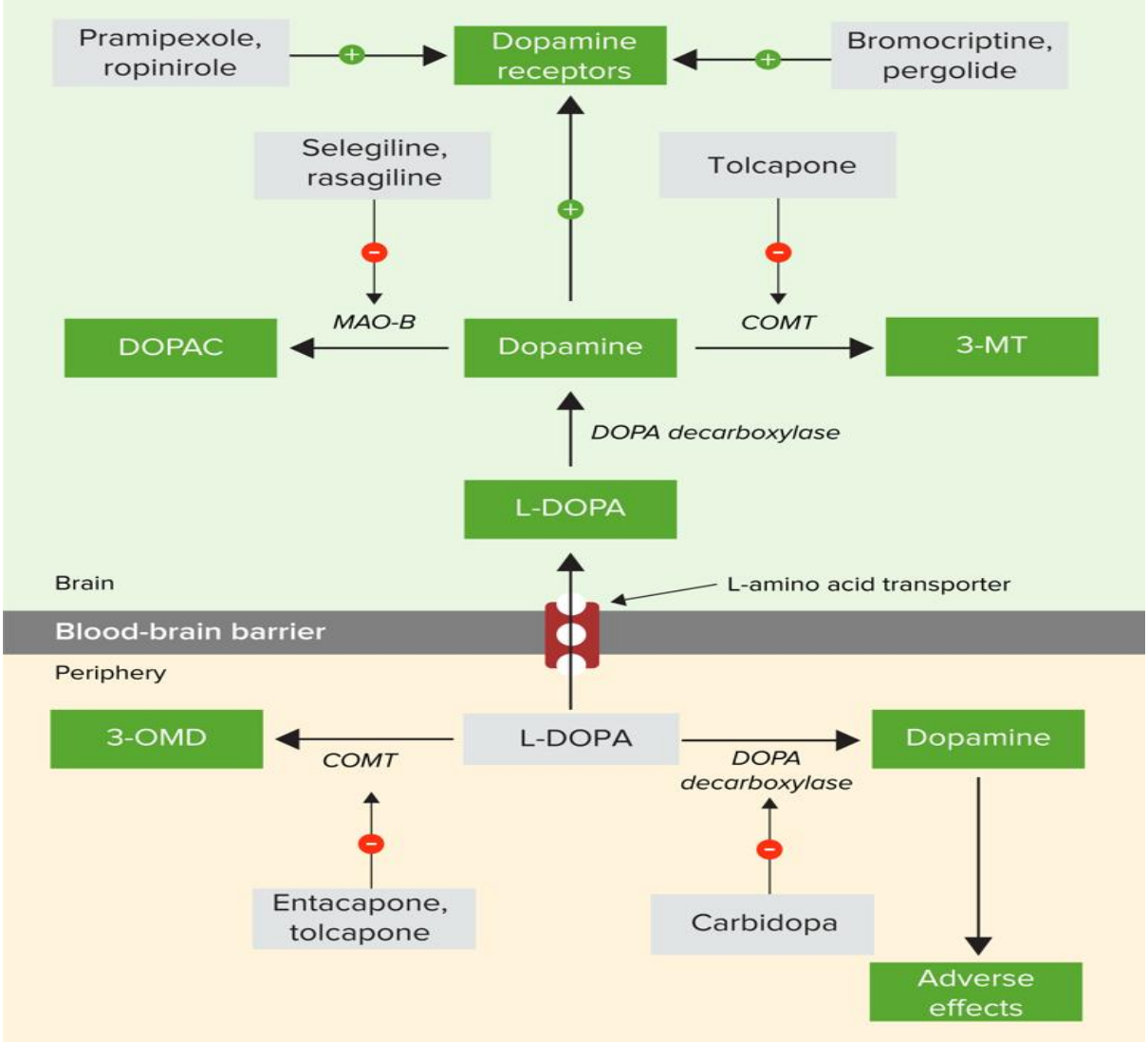


Fig: Pharmacologic strategies for the management of Parkinson's disease

COMT: catechol O-methyltransferase
3-MT: 3-Methoxytyramine
3-OMD: 3-O-methyldopa
DOPAC: 3,4-dihydroxy-phenylacetic acid
L-DOPA: levodopa
MAO-B: monoamine oxidase type B

Advanced therapy for PD:

Surgery for Parkinson's disease includes deep brain stimulation.

1. Deep brain stimulation:

Deep brain stimulation, also called DBS, involves putting electrodes within the brain. The electrodes

are connected to a pacemaker-like device that is inserted under the skin on the chest. The electrodes are connected to a generator placed in the chest near the collarbone. The generator sends electrical pulses to the brain and may reduce Parkinson's disease symptoms.

You may need follow-up appointments to adjust the settings for best results. Some people experience problems with the DBS system or have complications due to stimulation. A member of your healthcare team may need to adjust or replace some parts of the system.

DBS can be very helpful for improving severe tremor and controlling involuntary muscle movements, called dyskinesia. It is effective for controlling changing responses to levodopa or for controlling dyskinesia that doesn't improve with medicine changes.

Deep brain stimulation is most effective for people who respond to levodopa therapy. Although DBS may have long-term benefits for helping with symptoms, it does not keep Parkinson's disease from getting worse. Researchers are looking into ways to improve how well DBS works.

Side effects of deep brain stimulation may include:

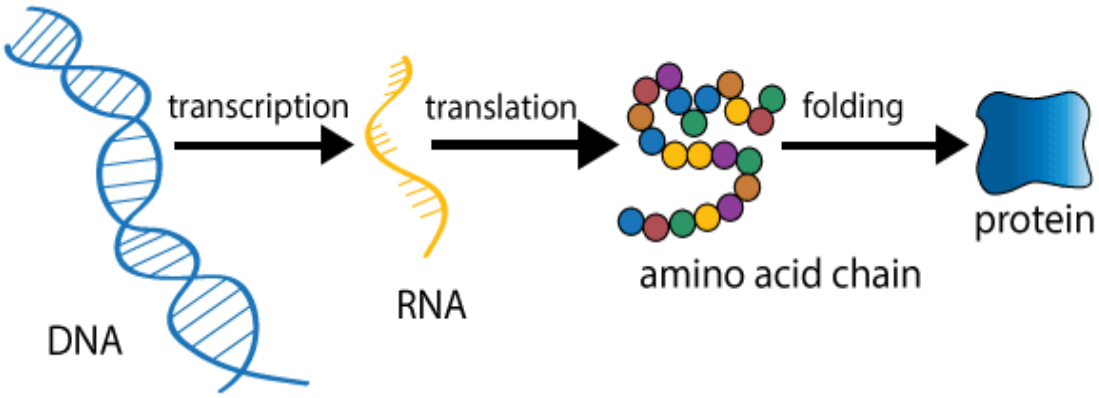
- Bleeding in the brain.
- Injury or death of tissue.
- Infection.
- Skin breakage.
- Muscle twitches.
- Depression.
- Speech or vision problems.

2. Gene therapy:

Gene therapy is a category of treatments that involve introducing DNA into cells in an effort to alter which proteins are created and thereby improve symptoms or even cure disease.

For decades, researchers have been trying to perfect gene therapy treatments for a variety of conditions. There have been successes for certain rare genetic disorders which are characterized by a single, well-described mutation in a particular gene. In this situation, a healthy gene is introduced into the cells of these patients. The cell's machinery then uses the healthy gene to create a healthy protein, which can effectively cure the patient. Diseases that have been helped in this manner include severe combined immune deficiency, adenosine deaminase deficiency, and hemophilia.

It is much more difficult to attempt gene therapy for diseases that involve more complicated DNA changes, such as Parkinson's disease. Nevertheless, there has been much effort and some success in using gene therapy techniques to treat cancer, for example, a very complex disease which typically involves many genetic changes.



How gene therapy works,

A virus is a tiny bundle of nucleic acid that is able to penetrate a cell and hijack the cell's machinery to replicate its own nucleic acid as well as produce viral proteins, often causing disease in the process. Certain viruses are even able to incorporate their own genetic material into the genetic material of the cell that they infect. Scientists cleverly take

advantage of these processes to drive gene therapy. The harmful pieces of DNA are removed from the virus and the gene of choice is incorporated into the viral structure. Then the modified virus is injected into a specific part of the body, thereby allowing it to "infect" cells. If all goes according to plan, the piece of DNA that was introduced into the modified virus is used by the cell's machinery to make the protein of choice. Adeno-associated virus or AAV is a common virus to use for gene therapy as it typically does not cause symptoms in and of itself when it is introduced into the cell.

Increasing dopamine production

- Aromatic amino acid decarboxylase (AADC) is an enzyme important in the conversion of levodopa to dopamine and the decline of AADC in the PD brain may be responsible for the changes in efficacy of long-term levodopa treatment. A gene for AADC was introduced into the putamen in the brains of patients with PD. The goal was to increase the amount of AADC present, thereby making levodopa treatment more effective.

- Tyrosine hydroxylase, Guanosine triphosphate cyclohydrolase, and Aromatic amino acid decarboxylase (TH-GCH-AADC) are three enzymes important in the synthesis of dopamine. Genes for all three enzymes were introduced into the putamen of patients with PD, with the goal of increasing dopamine production.

Supporting the survival of dopamine neurons

- Neurturin (NTN) and Glial derived neurotrophic factor (GDNF) – Neurturin is a protein that is a member of the GDNF family of nerve growth factors. A gene for Neurturin was introduced in different brain regions in patients with PD, with the goal of supporting the survival of neurons.

GAD gene therapy: Resetting abnormal brain circuitry

- Glutamic acid decarboxylase (GAD) is an enzyme that increases the production of a brain chemical called gamma-aminobutyric acid or GABA. A gene for GAD was introduced into the subthalamic nucleus in the brains of patients with PD. The goal was to increase the presence of GABA in that brain area, thereby helping to reset the abnormal circuitry of the Parkinson's brain.

Counteracting genetic mutations that contribute to PD risk

- Glucocerebrosidase (GBA) – A subset of people with PD carry a mutation in the GBA gene, which when working correctly, helps to break down cellular products that can be harmful to the cell. Gene therapy introduced the normal GBA gene into the brain.

- Leucine-rich repeat kinase 2 (LRRK2) – A subset of people with PD carry a mutation in the LRRK2 gene, which when working properly, adds phosphate groups onto other proteins. Mutations in LRRK2 that cause PD *increase* the activity of LRRK2. Therefore, one approach to treatment was to introduce a molecule that binds the messenger ribonucleic acid (mRNA) of LRRK2 to inhibit its translation into a protein.

3. Infusion therapy:

Infusion therapy for Parkinson's disease offers continuous delivery of medications like levodopa and apomorphine to help manage motor fluctuations and dyskinesias in advanced stages when oral medications are no longer sufficient. These therapies, including subcutaneous and intestinal infusions, aim to reduce "off" time and improve overall quality of life.

Types of Infusion Therapies:

Subcutaneous Infusion:

This less invasive method involves a portable pump delivering medication (like apomorphine or levodopa/carbidopa) through a thin needle inserted under the skin.

Intestinal Infusion (LCIG):

This involves a tube placed directly into the small intestine (through a percutaneous endoscopic gastrostomy) to deliver levodopa/carbidopa intestinal gel (LCIG).

Foslevodopa/Foscarbidopa Infusion:

A newer approach using a prodrug formulation (foslevodopa/foscarbidopa) for subcutaneous delivery, aiming for better absorption and tolerability.

How Infusion Therapy Works:

Continuous Dopaminergic Stimulation:

Infusion therapies provide a constant supply of dopamine or drugs that help the body produce dopamine, which is lacking in Parkinson's disease.

Reduced Motor Fluctuations:

By maintaining a steady level of medication, these therapies aim to minimize "off" periods (when medications wear off and symptoms return) and reduce dyskinesias (involuntary movements).

Improved Symptom Control:

Infusion therapies can help patients experience more consistent symptom control throughout the day and improve their ability to perform daily activities.

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