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(REVIEW ARTICLE)

A newer approach to Parkinson's disease: Addressing therapeutic features, repurposing drugs and the latest concepts with future goals

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Abstract

The article reviews advances in understanding and managing Parkinson's disease (PD), a progressive neurodegenerative disorder. PD primarily results from neuronal damage in the brain regions controlling movement, causing dopamine deficiency. With over 10 million people affected globally, it poses a significant healthcare challenge. The disease's multifactorial etiology includes genetic, environmental, and epigenetic factors, with aging as a major risk factor.The review discusses the pathophysiology of PD, highlighting α-synuclein aggregation and its role in neurodegeneration, and addresses diagnostic methods like MRI and DAT-SPECT imaging, which enhance diagnostic accuracy. It examines therapeutic avenues, including pharmacological interventions like levodopa, dopamine agonists, and MAO-B inhibitors. Challenges with long-term medication use are also discussed.Emerging therapies such as electroceuticals, gene therapy, and stem cell approaches show promise in disease management. Non-invasive treatments like focused ultrasound and innovative technologies like deep brain stimulation (DBS) aim to modulate brain activity to alleviate symptoms. Complementary approaches, including physical, psychological, and nutritional therapies, offer holistic care, enhancing quality of life.The review underscores the need for personalized medicine and continuous research to address unanswered questions and develop disease-modifying treatments. It concludes by advocating for a multidisciplinary approach and the integration of advanced technologies to improve patient outcomes and address PD's complexity.

Keywords: Parkinson's disease; Neurodegeneration; Dopamine deficiency; α-Synuclein aggregation; Personalized medicine; Emerging therapies

1. Introduction

Parkinson's disease is a progressive neurodegenerative illness that damages and/or destroys the neurones, or nerve cells, in the area of the brain responsible for controlling movement. Even though the brain needs a certain amount of dopamine to regulate movement, weaker neurones produce less dopamine than healthy neurons. Some Parkinson's disease patients have low levels of norepinephrine, a chemical that communicates through nerve endings and controls various bodily functions, such as heart rate and blood pressure. Over 10 million individuals worldwide already suffer from Parkinson's disease, and nearly 1 million instances will occur in the US this year. Over 10 million individuals worldwide suffer from Parkinson's disease (PD), and 60,000 Americans are diagnosed with the disease each year. According to estimates, only 4% of instances of Parkinson's disease are identified before the age of 50, although the condition is increasingly prevalent as people age.[1]

Age is the main risk factor for this disease, hence it is anticipated that as the population ages, so will the prevalence of this disorder. According to some estimates, the number of people with Parkinson's disease may treble to almost 12 million cases by 2040.[2] Males are more likely than females to acquire this disease, accounting for 52.5% of cases vs

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47.5%. Likewise, people from nations with medium-to-high sociodemographic indices represent 85.2% of instances, compared to 14.8% in nations with a low sociodemographic index.[3] The use of pesticides, tobacco, coffee, physical activity, and a history of traumatic brain injury are other lifestyle-related risk factors that have been found.[4] Furthermore, PD has been linked to bacteria like Helicobacter pylori and viral microbes including Ebolavirus, Human Immunodeficiency Virus, and Herpes Simplex Virus-1.[5] Nonetheless, the most significant risk factor is genetic, as there are presently over 90 loci linked to this illness.[6]

Historically, bradykinesia, postural instability, resting tremor, and stiffness have been used to describe Parkinson's disease.[7] Non-motor and motor aspects comprise the clinical presentation; the traditional presentation includes motor symptoms. Anxiety, sleep issues, gastrointestinal issues, sadness, loss of smell, dysautonomia, and cognitive impairment are examples of non-motor symptoms. Individual differences exist in the clinical presentation and the course of the disease. The condition often develops slowly, taking an average of ten years from symptoms beginning to a medical diagnosis.[8] Constipation, hyposmia, sleep difficulties, or sadness are some of the earliest symptoms that are vague, making it difficult to establish an early diagnosis.[9]

The prodromal PD notion emerged as a result of the numerous non-motor symptoms that appear far before motor symptoms.[10] Additionally, the reasons of the disease are specific to each patient, and its aetiology is complicated.[11] Lewy body and Lewy neurite neuronal inclusions, together with cell loss in the substantia nigra and other brain areas, are the hallmark histological hallmarks of Parkinson's disease.[12] Death of dopaminergic neurones in the substantia nigra pars compacta results in the disease's distinctive motor signs.[13] Patients continue to endure increasing weakening despite the availability of surgical, non-pharmacological, and pharmaceutical treatments, such as brain, spinal, and vagus nerve stimulators; no treatment has been proven to be a real disease modulator.[14] Regretfully, despite research efforts, Parkinson's disease (PD) still has many unanswered questions and no treatment or preventative measures.[15]

The **purpose** of this study is to present a thorough analysis of current knowledge on Parkinson's disease (PD), diagnostic methods, therapeutic approaches, and research instruments that show encouraging results for PD patients.Current non-invasive brain stimulation methods and their clinical use in the treatment of Parkinson's disease are examined in detail in this study. The purpose of the therapeutic use of brain stimulation techniques is to either selectively increase adaptive or decrease maladaptive patterns of neuronal activity. The ultimate objective is to restore normal physiology in the afflicted brain networks, which will alleviate the presentation of symptoms. The use of certain biomarkers strengthens this tactic even further. Multiple attempts have been made to improve human brain function by changing the electrical processes in the brain; nevertheless, clinically useful stimulation devices and effective stimulation paradigms have only lately been available.The ultimate goal of this review article is to give a thorough and current summary of electroceuticals as a Parkinson's disease therapy option, assisting both patients and professionals in making informed decisions.

2. Pathophysiology

Parkinson's disease has a complex etiology, which originates from a mix of genomic, epigenetic, and environmental factors.[16] The etiology of Parkinson's disease is complicated and stems from a combination of environmental, epigenetic, and genomic variables. The start and progression of the disease are influenced by several genes.[17] The lrrk2 or park8 gene is where the most prevalent mutations linked to Parkinson's disease occur, especially in people 50 years of age and older.[18] In the microglia, they also regulate the oxidative stress and inflammatory response.[19-20] The genes that protect dopaminergic neurones from rotenone, hydrogen peroxide, and mutant synucleins are DJ-1, also known as PARK7, PARK6, and PARK2.[21-22] Another linked gene is PINK1, a mitochondrial kinase that builds up on damaged mitochondrial membranes and recruits parking to control mitophagy and prevent the accumulation of harmful substances that result in the death of neurones.[23-24-25] Deterioration of the substantia nigra pars compacta and a decrease in dopaminergic neurones are two of the hallmarks of Parkinson's disease. The overproduction of α-synuclein, a 140-amino acid protein found in neurones' presynaptic terminals, has been directly connected to this degradation.Mostly found in the substantia nigra, thalamus, neocortex, and cerebellum, α-synuclein is essential for axonal transport, neurotransmitter release, vesicle fusion and movement, and synaptic connection.[26]The α-synuclein gene is in charge of encoding it. Prompt and rapid α-synuclein misfolding and aggregation are linked to SNCA mutations, primarily missense or multiplication variations.[27] Similar to this, mutations in the GBA gene, which codes for glucocerebrosidase, decrease its enzymatic performance. This decrease results in inadequate α-synuclein breakdown and increased exosomal release, which ultimately contributes to the buildup of Lewy bodies.[28] It has been disputed whether α-synuclein is the primary cause of Parkinson's disease. Recent research with new monoclonal antibodies that prevent α-synuclein from aggregating has demonstrated that even when these aggregates are removed, parkinsonian symptoms endure and the illness worsens. This implies that the goal of research should be to find novel

pathophysiological targets for Parkinson's disease.[29] Using blood samples, Madetko et al.'s study assessed the NLR and PLR in peripheral inflammation in PD and found that PD patients had greater NLR and PLR ratings in relation to the control group. Consequently, this can be a parameter for suspected PD.[30]

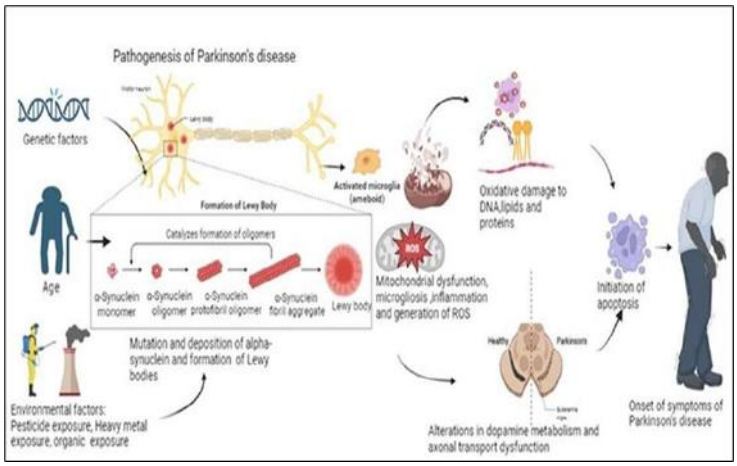

Figure 1 Pathogenesis of PD (Parkinson disease)

3. Diagnostic method

About 10% of patients are misdiagnosed with other illnesses because non-motor symptoms frequently occur before motor manifestations. In order to increase diagnostic precision, the International Parkinson and Movement Disorders Society developed particular standards. Bradykinesia and at least one of the following symptoms—resting tremor (4–6 Hz) or limb rigidity are required for the diagnosis of Parkinson's disease, per their guidelines. Furthermore, it is essential to carefully examine data that can point to possible indications of other illnesses and take into account exclusion criteria in order to rule out PD as a diagnosis.[31-32]

The diagnosis of Parkinson's disease is aided by a number of resources in addition to thorough questioning and accurate physical examination. Due to their specificity, imaging methods including structural magnetic resonance imaging (MRI) and dopamine transporter single-photon emission computed tomography (DAT-SPECT) are frequently used. Neuromelanin imaging (NMI), which identifies alterations in the substantia nigra pars compacta and the locus coeruleus is one of the distinctive features of MRI that help detect atypical parkinsonism.[33] Usually, genetic testing is saved for situations where Parkinson's disease is thought to have a genetic foundation. However, given that the discovery of particular genes linked to severe PD symptoms has been linked to a worse prognosis, it is becoming more widely acknowledged that such studies should be regarded as standard.[34]

4. Recommended medications

4.1. Levodopa (Dopamine precursor)

The amino acid l-3,4-dihydroxyphenylalanine, often known as levodopa or l-dopa, was the first drug to effectively treat Parkinson's disease.Dopamine's precursor, levodopa, has a much lower concentration in parkinsonism. When given orally in large quantities every day, levodopa can enter the brain and bypass the surviving dopamine neurons' metabolism. Dopamine is produced there by decarboxylating the molecule (removing a carboxyl group, COOH). To boost the amount of levodopa that reaches the brain, carbidopa, a levodopa analogue, is added to levodopa prescriptions. Carbidopa prevents levodopa from converting to dopamine before it reaches the blood-brain barrier because dopamine cannot cross the barrier by itself.Levodopa's primary adverse impact is an elevated likelihood of episodes resembling schizophrenia, which is most likely brought on by an excess of dopamine.[35-36]

Parkinson's disease can be effectively treated with carbidogpa-levodopa, a natural chemical that enters your brain and is converted to dopamine. Most often associated with motor issues and most helpful for managing symptoms Dyskinesias are a consequence of prolonged therapy. COMT inhibitors are recommended for improved outcomes.[37-38-39]

4.2. Dopamine agonists

Dopamine-receptor agonists function by attaching to dopamine receptors on dopaminergic neurons, which are the neurons that normally make and use dopamine. Activating the receptors increases dopaminergic activity in the brain, reducing the intensity of parkinsonian symptoms. The group that replicates the effects of dopamine in the brain includes apormorphine, pramipexole, ropinirole, and rotigotine (in patch form). It has a longer half-life than levodopa but is less effective. A few adverse effects include obsessive behaviors, drowsiness, and hallucination.[40]

4.3. MAO-B inhibitors

These drugs gradually break down dopamine in the brain. It is made up of rasagiline, selegiline, and safinamide. They work by stopping the breakdown of the dopamine inhibiting enzyme monoamine oxidase B. This family of medications can cause personality disorders, headaches, nausea, insomnia, and hallucinations.[41]

4.4. Catechol-O-methyltransferase (COMT) inhibitor

The enzyme catechol-O-methyltransferase catalyzes the enzymatic breakdown of dopamine, and COMT inhibitors such as Entacapone and tolcapone prevent this from occurring. Because they prevent levodopa from being broken down by COMT in peripheral tissues, these medications are commonly used in conjunction with levodopa and carbidopa. This lengthens the drug's half-life in the blood and increases the quantity of medication that may pass through the blood-brain barrier. The primary adverse effects include hallucinations, nausea, vomiting, and dyskinesia.[42]

4.5. Antichollinergics

A number of parkinsonian symptoms are caused by the abnormal neurotransmitter activation of acetylcholine. This is mediated by acetylcholine.activity by binding to the brain's muscarinic acetylcholine receptors, which are named for their selectivity for acetylcholine and sensitivity to the substance muscarine. Consequently, medications such as trihexyphenidyl and benztropine mesylate are used to alleviate symptoms, but with few side effects. These medications are also thought to raise dopamine levels in the brain. However, their usage in elderly people is limited because of their sedative effects and adverse effects linked to vision.Negative effects include memory loss, disorientation, constipation, and issues with the micturition reflex.[43]

Parkinson's disease patients may experience less tremor and bradykinesia (slow movements) if they take amantadine, an antiviral medication used to treat influenza A infections. symptoms of movement. It has been discovered to cause dopamine to be released from brain cells, albeit it is unclear exactly how it works in this capacity. It also inhibits movement-related neuronal overactivity and excitatory transmission. Amantadine is used to temporarily alleviate the symptoms of mild, early-stage Parkinson's disease when combined with carbidopa-levodopa therapy in the later stages of the disease to lessen dyskinesia, or involuntary movements, caused by carbidopa-levodopa. Among the adverse effects are nausea, vomiting, wooziness, confusion, hallucinations, or swelling of the ankles.[44]

4.6. Intranasal Insulin

Insulin receptors are found throughout the basal ganglia, indicating that it plays a role in regulating neuronal growth, synaptic maintenance, and neurotransmission [69]. Intranasal insulin (INI) administration can slow the loss of dopaminergic neurons in Parkinson's disease, improving motor function [69]. It has also been shown to reduce dopamine-dependent cognitive impairment by restoring insulin signaling pathways without the use of medications.[45]

4.7. DPP-4 Inhibitors and GLP-1 Agonist

The central nervous system (CNS) has receptors for the hormone glucagon-like peptide 1 (GLP-1), which has been shown to enhance cell survival and prevent apoptosis. GLP-1 is metabolized and removed from the bloodstream by the enzyme dipeptidyl peptidase 4 (DPP-4).[46] Drugs that target these pathways include DPP-4 inhibitors, which prevent the breakdown of GLP-1, and GLP-1 receptor agonists, which mimic the actions of GLP-1. Due to their incretin activity, these medications induce satiety, reduce glucagon production, delay stomach emptying, and increase glucose-dependent insulin release.[47] Foltyine et al.'s study demonstrated the possible benefits of GLP-1 receptor agonists and DPP-4 inhibitors in the treatment of neurodegenerative illnesses. Their anti-inflammatory and antiapoptotic qualities enable them to exercise their neuroprotective impact in Parkinson's disease (PD), hence enhancing motor and cognitive function. These substances have also been demonstrated to influence mitochondrial biogenesis, encourage neurogenesis, and reestablish insulin signaling in the central nervous system.[48] According to a cohort research by Brauer et al., those treated with DPP-4 inhibitors and GLP-1 agonists had a 36–60% reduced incidence of Parkinson's disease (PD) than people treated with other antidiabetic drugs [75]. Exenatide, a GLP-1 receptor agonist, was linked to improved motor symptoms, decreased non-motor symptoms, improved cognitive function, and an overall improvement

in quality of life, according to a 2020 meta-analysis by Wang et al.[49-50] Around the world, metformin, an oral hypoglycemic medication belonging to the biguanide family, is frequently used to treat type 2 diabetes. This drug lowers blood sugar levels by acting on several different locations. It increases the presence of GLP-1, decreases intestinal glucose absorption, increases muscular glucose uptake, and limits hepatic glucose synthesis by decreasing gluconeogenesis and glycogenolysis.[51]

The use of metformin in neurodegenerative illnesses is up for controversy because of contradicting literature. It has been linked to cobalamin (vitamin B12) deficiency, which may raise the risk of neurodegenerative illnesses and cognitive impairment, according to certain research. As a cofactor for enzymes involved in the synthesis of genetic material, fatty acid metabolism, and amino acid synthesis, as well as for its neuroprotective function and participation in bone marrow cell maturation and myelin production, vitamin B12 is essential. Sluggett et al.'s study, however, found that long-term metformin use does not increase the risk of Parkinson's disease (PD) and may even lower its occurrence. It is consistent with recent studies showing that metformin has anti-inflammatory and neuroprotective properties.[52]

5. Surgical therapy

Parkinson's disease patients may experience less tremor and bradykinesia (slow movements) if they take amantadine, an antiviral medication used to treat influenza. It has been discovered to cause dopamine to be released from brain cells, albeit it is unclear exactly how it works in this capacity. It also inhibits movement-related neuronal overactivity and excitatory transmission. Amantadine is used to temporarily alleviate the symptoms of mild, early-stage Parkinson's disease when combined with carbidopa-levodopa therapy in the later stages of the disease to lessen dyskinesia, or involuntary movements, caused by carbidopa-levodopa. Among the adverse effects are nausea, vomiting, wooziness, confusion, hallucinations, or swelling of the ankles. Numerous surgical methods can help PD patients when drugs don't seem to be working, depending on the disease's stage and progression. Parkinson's disease can be treated with deep brain stimulation, or DBS, a non-invasive surgical technique. It involves putting in place a battery-operated neurostimulator that uses electrical impulses to target particular areas of the brain. For the motor symptoms of Parkinson's disease, this is the most common surgical treatment. Furthermore, in more advanced stages of PD that are being treated medically, it reduces the frequency of "off" episodes, which often occur throughout the day.

The two areas of the brain that receive DBS the most are the globus pallidus pars interna and the subthalamic nucleus (STN) (GPi). Similar benefits for motors have been observed in extensive, controlled, randomized studies between these two targets. It is believed that the abnormal brain signalling patterns that cause problems with motor control are blocked by the electrical signals generated by DBS. There is no known cure for Parkinson's disease; its symptoms can only be managed.

5.1. Ablative or Lesioning Procedure Leison surgery

Techniques for burning tissue include thalamotomy, sub-thalamotomy, and pallidotomy. A thalamotomy, which entails lesioning or destroying the thalamus, can only affect one side of the brain, whereas a pallidotomy, which involves destroying a small area in the globus pallidus interna, can affect both sides.One novel treatment that offers a less invasive alternative to traditional surgical techniques is focused ultrasound. Targets located deep within the body are the focus of multiple ultrasound beams, and the process is tracked and guided in real time by an MRI. Targeted sonic energy can be used to destroy unwanted tissue or interfere with ineffective brain circuits Pharmacological treatment effectively controls PD symptoms and improves quality of life. However, long-term use at high doses can lead to refractory symptoms and drug-induced side effects in some patients. In cases where pharmacological treatment fails to achieve its objectives, surgical options become a viable alternative. Surgical approaches are tailored to individual needs and may include unilateral procedures like thalamotomy, pallidotomy, or subthalamotomy, along with deep brain stimulator (DBS) placement, aiming to enhance the relief of motor symptoms.[53-54] Since the clinical characteristics of Parkinson's disease can be mimicked by other disorders, it is imperative to confirm a diagnosis before contemplating surgical intervention. Postural instability and significant gait abnormalities are relative contraindications for fetal cell transplantation in Parkinson's disease. The main indication for neurosurgical treatment is for individuals with moderate to severe disease who respond to levodopa medication but have fluctuating motor symptoms that interfere with their ability to live independently on a daily basis.[55]

An improvement of at least 30% on the Movement Disorder Society Unified Parkinson's Disease Rating Scale (MDS-UPDRS III) or Unified Parkinson's Disease Rating Scale (UPDRS III) typically indicates a response to levodopa medication, which is a predictor of surgical results. Surgery usually does not help people who do not respond well to levodopa, with the exception of cases involving tremor relief. For people who benefit somewhat from low-dose levodopa but cannot tolerate higher dosages due to drug-induced side effects such nausea, dystonia, or dyskinesias, surgery may

be a good choice. Fetal cell transplantation may help functional persons in the early stages of Parkinson's disease preserve their everyday routines and standard of living S. Pallavaram et al. Neurologist consistency in interpreting information provided by an interactive visualization software for deep brain stimulation postoperative programming assistance.[56]

Lesioning treatments involve the intentional destruction of certain brain areas to disrupt affected neuronal networks [104]. Examples include unilateral thalamotomy, subthalamotomy, and pallidotomy. While unilateral thalamotomy does not improve bradykinesia, dyskinesia, or motor fluctuations, it may benefit some PD patients with tremors that are resistant to therapy. Unilateral pallidotomy is a safe and efficient treatment for severe dyskinesia and motor fluctuations, with the added advantage of long-term suppression of contralateral dyskinesia. However, because unilateral subthalamotomy has a greater risk of adverse neurological effects, including chronic dyskinesia, it is considered an experimental treatment for advanced Parkinson's disease.[57] An inventive technique for treating tremors in Parkinson's disease is unilateral thalamotomy with MRI-guided focused ultrasonography. An MRI-compatible ultrasonic transducer is used to position the patient in a stereotactic frame during this treatment. The transducer is oriented according to real-time MRI imaging, and successive doses of ultrasonic energy are applied until the target region reaches the therapeutic temperatures needed for lesioning. Clinical evaluations of tremors, while the patient is awake, are used to measure the procedure's efficacy intraoperatively.[57] Radiosurgery is another non-invasive therapy option that targets and damages specific nervous system regions using high doses of ionizing radiation. This approach aims to lessen symptoms by focusing on regions such the ventral intermediate nucleus (VIN), subthalamic nucleus, and internal globus pallidus (GPi). On the other hand, radiosurgical pallidotomy has shown less success than other targets.[58-59]

Neural grafting

Although nigral transplants are obviously effective in certain PD cases, the method must be refined before it can be applied effectively in a large a number of patients due to the adverse effects it has on them.Dopaminergic neurons from the human embryonic brain were transplanted into the striatum of PD patients in clinical trials conducted in the 1990s, demonstrating the possibility of long-lasting therapeutic benefits.

Focused Ultrasound Stimulation (FUS)

FUS is a minimally invasive procedure that modifies deep tissues chemically, thermally, or mechanically for therapeutic purposes using focused ultrasonic waves. FUS, which operates at higher frequencies and intensities, focuses energy on certain regions, allowing for targeted treatment with less harm to other tissues. A safer and more accurate substitute for invasive surgical treatments is offered by this cutting-edge technology.[60-61]

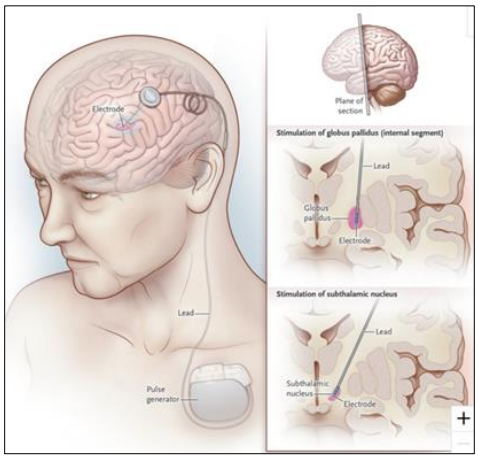

Figure 2 FUS (Focused Ultrasound Stimulation)

FUS has shown great promise in the treatment of Parkinson's disease (PD), especially when combined with high-intensity focused ultrasound (HIFU). Unlike conventional diagnostic ultrasonography, HIFU uses high-energy pulses to target tissues accurately while reducing collateral damage. This non-invasive approach successfully accomplishes improved neuro- modulation, thermal ablation, and pharmaceutical administration. Because FUS alters deep brain regions in a non-ionizing and reversible manner, it may help PD patients live better lives and experience less motor

symptoms. To establish FUS as a feasible, less invasive substitute for traditional treatments like deep brain stimulation, ongoing research and clinical trials are being conducted to show its safety and effectiveness. Focused Ultrasound Foundation. Clinical Trial to Disrupt the Blood-brain Barrier for Brain Tumor Treatment Launched at University of Maryland.[62-63]

5.2. Gamma Knife Thalamotomy (GKT)

Refractory tremors, particularly those linked to Parkinson's disease, can be treated with GKT, a minimally invasive neurosurgical technique. It disrupts abnormal neuronal circuits that cause tremors by precisely delivering gamma radiation to the ventral intermediate nucleus of the thalamus. GKT has benefits such being less intrusive, avoiding the hazards associated with open surgery, and being appropriate for people who are not candidates for DBS. GKT is safe, according to clinical data, and no notable long-term cognitive, gait, or speech problems have been documented. Risks include the possibility of radiation-induced brain alterations and temporary side effects such headache and nausea, which emphasise the necessity of cautious patient selection and ongoing monitoring.[64-65]

6. Nutritional therapy

In conjunction with standard medication therapy, food supplements are widely utilised to treat a variety of chronic illnesses by addressing nutritional deficiencies or promoting particular physiological processes. Over the past few decades, there has been a notable growth in the use of functional foods and food supplements, particularly to make up for improved health and the modern lifestyle.[66-67]

6.1. What ought to be included in your meal?

Broccoli, berries, soy nuts, pears, celery, carrots, beetroot, and many more foods contain phytochemical.Foods that contain omega-3 DHA include fish, seafood, and plant oil. Caffeine has neuro- protective properties. Soy (genistein) is beneficial for menopausal women with Parkinson's disease.Foods high in magnesium include spinach, pumpkin seeds, almonds, seeds, and more.Coenzyme Q10, lipoic acid, N-acetyl cysteine, carvacrol, turmeric, creatine, melatonin, niacin, and lycopene are examples of biological substances. Vitamins such as vitamins D3 and C. Plants such as 6-shogaol and gingko biloba extract.Foods high in antioxidants include beans and berries.Foods that include iron and zinc.

6.2. What foods should you stay away from?

Steer clear of or substantially reduce foods high in sugar. Foods that have been processed overconsumption of fat, oil, and carbs. Dairy goods too much meat. Foods that are difficult to chew and swallow. Important tips for managing your food intake include: Eating a range of lightly prepared meals throughout the day. Eat foods that control your blood sugar, heart rate, and blood pressure. Assesses the nutritional condition of the body. Get enough vitamin D by being in the sun. Enhance your digestion get tested for dietary intolerances and allergies. Eat meals at regular intervals. Avoid skipping meals.

7. Herbal therapy

Withania somnifera (Solanaceae family)WS, sometimes referred to as poison gooseberry or winter cherry, is a plant that has been isolated to produce a number of bioactive compounds. These compounds, which are used to treat a range of neurological deficiencies, including poor memory, depression, epilepsy, and neurodegeneration, include triterpene lactones, alkaloids, tropine, steroidal lactones, and withanolides. Additionally, it was found that the ethanol extract of WS roots significantly boosts dopamine synthesis in the substantia nigra and the locomotor activity of PD mice. Furthermore, their study demonstrated that the ethanol extract of WS roots significantly decreased the concentrations of iNOS (oxidative stress) and GFAP protein, a pro-inflammatory indicator of astrocyte activation, in the brain regions of PD mice. The ethanolic extract of Gastrodiaelata Blume (Family: Orchidaceae) at varying concentrations (10, 100, and 200 g/mL) decreased the Bax/Bcl-2 ratio elevation caused by MPP+ in SH-SY5Y cells, attenuated capase-3 activation and PARP cleavage in a dose-dependent manner, and demonstrated an antioxidant effect with notable radical scavenging activity for DPPH and alkyl radicals, suppressed.[68-69]

The aqueous extract of *Centella asiatica* (Family: Umbelliferae) can be used to treat MPTP-induced parkinsonism for 14 days at a dose of 300 mg/kg. It functions by exhibiting its antioxidant activity in the hippocampus and corpus striatum of the brain. Superoxide dimutase, glutathione peroxidase, catalase, total antioxidants, and xanthine oxidase are all increased by the extract, although protein carbonyl content and lipid peroxidation are decreased.[70]

When 6-OHDA promotes aptosis in differentiated PC12 cells, the bioactive components of Pueraria thomsonii (Family:Fabaceae), daidzein and genistein, have neurocytoprotective qualities. At 50 μM and 100 μM, respectively, daizein and genistein decreased caspase-8 and partially inhibited caspase-3 activation, providing a defense mechanism against 6-OHDA-induced cytotoxicity in PC12 cells with NGF differentiation. In order to prevent parkinsonism, Plumbago scandens (Family: Plumbaginaceae) reduces palpebral ptosis, catalepsy, and locomotor activity.

- Chrysanthemum: Chrysanthemum L extract protects against lipopolysaccharide-induced cytotoxicity in the SH-SY5Y cell model, BV-2 Parkinson's disease microglial cells, and 1-methyl-4-phenylpridinium ion. suppresses the mitochondrial apoptotic pathway, decreases ROS aggregation, increases the ratio of Bax to Bcl-2 in SH-SY5Y cells, and lowers SH-SY5Y cell mortality.

The fruit tree, Clausenalansium, is indigenous to southern China. Bu-7, a flavonoid obtained from Clausenalansium leaves, is being used as a treatment; it boosted protein phosphorylation and decreased rotenone-induced apoptosis these models.

Ocimum sanctum (Lamiaceae family). Leaf extract from Ocimum sanctum has a neuroprotective effect on haloperidol-induced catalepsy in albino mice. Mice with rotenone-induced parkinsonism, catalepsy caused by haloperidol, and muscle stiffness showed neuroprotective effects from O. sanctum extract. Cassia: Tora's Cassiae Semenis Clarissa L. (Tora C.) is the ripe, dried seed of Cassia obtusifolia L. Parkinson's disease (PD) is believed to be caused by alaternin, a substance found in C. tora that has strong peroxynitrite scavenging properties. Additionally, it shields mice from the transient neuronal cell death brought on by cervical hypoperfusion. Cassiae semen extract shows therapeutic properties in mouse hippocampus cultures, 6-OHDA-induced neurotoxicity in PC12 cells, MPTP-induced neuronal degeneration in the animal's PD form, and seed extract in these models.[70]

8. Physical therapy

Although no particular treatment is advised for Parkinson's disease, there is enough research and data to demonstrate that exercise improves movement Recent experimental studies have demonstrated the benefits of exercise in preventing and delaying the progression of Parkinson disease. Exercise raisessleep, mood, quality of life, and self-sufficient mobility, Among the short-term effects of this treatment are treadmill gait training, Nordic walking, brisk walking, balance training, virtual reality interventions, dancing, aerobics, and resistance training; all of these activities aid in symptom relief and improve neurophysiological function.[71-72] Massage therapy has two benefits: relaxation and reduced muscle tension. Massage therapy typically promotes relaxation.Urinary stress hormones are involved in the subsequent biological processes. Research shows that therapeutic massage can improve quality of life. Anma and Yin Tui Na have more advantages.[73]

Tai-chi is a traditional Chinese practice that involves slow, flowing movements to improve muscle strength, flexibility, and balance. Tai chi may help lower the chance of falling. Tai chi is suitable for people of all ages and physical conditions. A study suggests that tai chi may improve balance more effectively than stretching or weight training in those with mild to moderate balance issues. Parkinson’s disease.[74] The Alexander technique, which focuses on muscle posture and balance, can reduce muscle discomfort and stiffness. Yoga and mild stretching exercises can also improve flexibility and balance. Meditation, which involves reflecting in silence and focusing on a concept or picture, can improve well-being and reduce pain and stress.[75-76]

8.1. Practice fall prevent method

Older adults can prevent falls by exercising alone. Intense exercise regimens with good balance yield better results. Parkinson's disease patients benefit from rhythmic stimulation and dance, which improve gait and cognitive skills such as spatial memory and motor control.[76-77]

9. Psychological therapy in parkinson

Living with Parkinson's disease can be tough as it can be frustrating to adjust to bodily movements and do daily tasks. Walking, conversing, and eating are all time-consuming activities. Most Parkinson's patients face psychological challenges, such as: Depression and anxiety,Mental breakdowns and frustration, Insecurities and low self-esteem -,Lack of emotional expression and motivation,High social anxiety during encounters.[74]

9.1. Pharmacological approach

Serotonin reuptake inhibitors, tricyclic antidepressants, dopamine agonists, and trazodone are examples of antidepressants that have been shown to be effective in treating or reducing depression in Parkinson's disease.Cognitive behavioural therapy (CBT)à PD-tested to be extremely effective helpful in lowering tension andimproving patient calm and flexibility. Mindfulness behavioural therapy (MBT)à displays similar benefits and has been shown to be beneficial, especially when CBT and MBT are used to improveoutcomes, lower anxiety, and lessen depressive features. Acceptance and commitment therapy (ACT)PD technique that was useful but less popular than other ways. Family support can improve PD patients' mindset and reduce frustration and anxiety in social situations. Social acceptance is crucial for those with Parkinson's disease and other illnesses as it reduces the possibility of negative psychological side effects, calms patients, and increases their likelihood of taking medication.

9.2. Non-Pharmacological Treatments

9.2.1. Personalized Medicine

Pluripotent Stem Cells

Pluripotent stem cells are a promising substitute for cellular therapy in localized neurodegeneration, like Parkinson's disease (PD), and recent developments in genetics and regenerative medicine have sparked the search for novel treatments targeted at stopping or slowing the progression of particular neurodegenerative disorders. The widely varying reactions seen in individuals undergoing L-dopa medication show the presence of diverse biochemical degeneration pathways, even though Parkinson's disease (PD) involves malfunction in multiple systems and neurotransmitters that result in identical symptoms. This emphasizes the necessity of alternate therapeutic approaches. Personalized medicine has the potential to provide more efficient therapies that are customized for each patient.[78-79]

The variability of the response to medications used in PD may be related to certain hereditary variables.The possible involvement of single-nucleotide polymorphisms in PD patients and their reaction to pharmacological treatments has been investigated in a number of studies.

One such gene of interest is the dopamine active transporter 1 (DAT1) gene, which is crucial for dopamine reuptake in synapses and has a higher chance of making patients experience hallucinations when exposed to dopaminergic medications and developing dyskinesias when treated with L-dopa. Pluripotent stem cells have shown promise as targets for innovative cell therapy developments in regenerative medicine and human disease models. directed differentiation technologies, which are vital for creating these vital cells, to the mesencephalon.[80-81-82]

Fetal ventral mesencephalic cell transplantation has been studied for many years as a potential treatment for Parkinson's disease. Dopaminergic, oculomotor, and retinal neurons are included in this cell population. In a research by Li et al., post-mortem brains from recipients of fetal cell transplantation showed that the transplanted cells had significantly grown and innervated the striatum. Additionally, they showed that these neurons can endure in the human brain for more than 20 years. Graft-induced dyskinesia did, however, occur in several transplant recipients [90,92]. Since then, attempts have continued to create standardised procedures for cellular transplants, which are presently being researched.[83-84]

Gene Therapy

ATP13A2, dardin, DJ-1, alpha-synuclein, leucine-rich repeat kinase 2 (LRRK2), and PINK1 are among the genes linked to Parkinson's disease (PD), even though it is classified as an idiopathic condition. There are more mutations in the GBA1 gene, which codes for the enzyme glucosecerebrosidase. The age of start, intensity of symptoms, and course of cognitive impairment are all impacted by these alterations, which cause neurotoxicity and neuro inflammation.[85-86-87] Despite encouraging outcomes in animal research, the clinical translation of gene therapy for Parkinson's disease is fraught with difficulties. The results of human research have fallen short of expectations, mostly because of problems with gene distribution. As a result, although gene therapy is a major advancement in the treatment of Parkinson's disease, it is still not a viable alternative until more clinical research verifies its effectiveness and safety.[88-89-90-91]

9.2.2. Life Changes

Exercise

In order to improve motor skills, halt the progression of the disease, and increase functional capacity in people with Parkinson's disease, non-pharmacological treatments including physical activity are advised. Physiotherapy and

rehabilitation are essential for treating both motor and non-motor symptoms, as well as for possibly delaying the course of the illness. Resistance and aerobic workouts involving hand movements are commonly included in fitness regimens.

Regular physical exercise is associated with a better clinical course of Parkinson's disease, according to a retrospective observational cohort research by Tsukita et al.Ernst et al. conducted a meta-analysis that examined the effects of different forms of physical exercise on persons with Parkinson's disease. According to this study, dancing and other moderate-intensity workouts were among the primary activities that reduced motor symptoms and had positive health consequences. According to research, improvements in general wellbeing and motor symptoms can be shown after 12 weeks of exercise.[92-93-94-95]

In a similar vein, dancing regularly helps PD sufferers' balance and mobility. It increases blood flow to the frontal, temporal, parietal, and hippocampus cortices and stimulates neurons that support motor control. It also controls autonomic dysfunction, which helps PD patients better control their sympathetic heart. Yoga helps the upper and lower limbs become more flexible, strong, and balanced. By enhancing the functional connection between the anterior putamen and the sensorimotor brain, Johansson et al. showed that aerobic exercise enhances cognitive control.[96-97]

Nutrition

Because they are more likely to develop osteoporosis and sarcopenia, patients with Parkinson's disease (PD) should make sure they get adequate calcium and vitamin D from their diet or supplements. In order to combat constipation, it's also critical to be properly hydrated. The production of ketone molecules (acetoacetate, acetone, and β-hydroxybutyrate) that induce a state of ketosis in our bodies is a hallmark of the ketogenic diet. This is accomplished by consuming fewer carbohydrates and more fat for energy. A low-calorie diet or fasting can also help achieve it. Numerous studies have shown how the ketogenic diet can help people with Parkinson's disease (PD), suggesting that it has an anti-inflammatory effect that lowers the inflammatory process linked to neurodegenerative illnesses.[98-99]

Nutrition has a major role in the development of a disease, as it does for the majority of illnesses. A Western diet high in calories, including processed foods, fried foods, red meats, and saturated fats, is associated with a poorer prognosis in neurodegenerative diseases. In contrast, it has been demonstrated that the Mediterranean diet increases longevity and overall health. Using olive oil and eating a lot of whole grains, fruits, vegetables, seeds, nuts, and legumes are key components of this diet plan. Red meats, fish, eggs, yogurt, cheese, poultry, milk, and saturated fats are also covered in moderation. The Mediterranean diet, which is high in antioxidants, vitamins, minerals, and anti-inflammatory substances, decreases the progression of Parkinson's disease.[100]

10. Electroceutical approaches in parkinson's disease management

Electroceuticals, or neurostimulation devices, are medical devices that use electrical stimulation to treat neurological diseases, such as Parkinson's disease. These devices use mild electrical impulses to target specific parts of the brain or peripheral nervous system, resulting in improved symptoms, motor performance, and quality of life. Electroceuticals are classified into three types: deep brain stimulation (DBS), spinal cord stimulation (SCS), and vagus nerve stimulation (VNS). Each has a distinct mechanism of action and indications. This review article aims to provide a detailed overview of using electroceuticals to treat Parkinson's disease. This page will explain the many forms of electroceuticals, their mechanisms, and potential benefits and restrictions.

The study will analyze the evidence for using electroceuticals in Parkinson's disease and suggest future research directions. This review article aims to provide a current overview of electroceuticals as a therapeutic option for Parkinson's disease, guiding physicians and patients to make informed decisions. Electrochemicals are medical devices that treat a variety of neurological disorders, such as Parkinson's disease, by stimulating the nerves with electricity. These gadgets control neural activity and reduce symptoms by sending electrical impulses to particular parts of the brain or peripheral nervous system.[101-102-103-104-105]

10.1. Types of Electroceuticals

10.1.1. Electroceuticals come in a variety of forms, such as:

Electrodes are inserted into particular brain regions to transmit electrical impulses that control the activity of the impacted neurons in Deep Brain Stimulation (DBS) devices.

10.1.2. Vagus Nerve Stimulation (VNS) Devices

These devices provide electrical stimulation to the neck near the vagus nerve, which helps alleviate the symptoms of epilepsy, depression, and Parkinson's disease. Electrodes that are implanted on the skin are used by transcutaneous nerve stimulation (TNS) devices to stimulate the nerves via the skin. TNS controls the flow of neurotransmitters in the brain to alleviate symptoms of Parkinson's disease.[106-107]

10.1.3. Working Mechanism of Electroceuticals

Although the precise mechanism of action of electroceuticals is not entirely understood, it is thought that the electrical stimulation that these devices provide helps to relieve symptoms by modulating the activity of afflicted neurons.

For instance, it is thought that DBS devices in Parkinson's disease improve motor function and lessen tremors by controlling the activity of neurons that govern movement. Eight Benefits of Electroceuticals There are various benefits to using electrochemicals to treat Parkinson's disease, such as: Better Symptoms: It has been demonstrated that electro ceuticals can successfully alleviate Parkinson's disease symptoms, such as stiffness, tremors, and trouble moving and coordinating.

10.1.4. Improved Quality of Life

By reducing the symptoms of Parkinson's disease, electroceuticals can help patients feel better and become more independent. 10 Non-invasive: Unlike other surgical procedures, electroceuticals are minimally invasive and don't require a large incision. 11 Customizable Electro ceuticals can be made to fit the unique requirements of each patient, enabling a customized treatment plan other areas that may be targeted include the globuspallidus or the thalamus.[108-109-110-111-112]

10.2. Parkinson's disease electroceuticals

10.2.1. Deep Brain Stimulation (DBS)

Deep Brain Stimulation, or DBS, is a surgical technique used to reduce Parkinson's disease symptoms by placing electrodes in particular brain regions to provide electrical stimulation. Bradykinesia, stiffness, tremors, and other motor complaints have all been demonstrated to be lessened by DBS 17. DBS has been shown in clinical trials to significantly enhance people with Parkinson's disease's functional independence and quality of life 18. Depending on the patient and the intensity of their symptoms, different parts of the brain are addressed by DBS. DBS is considered a safe and effective therapy option for Parkinson's disease, and has been approved by regulatory agencies such as the FDA and the European Union 19. However, DBS carries risks like infection, hemorrhage, and other problems, much like any other surgical surgery. Patients may also encounter adverse effects like mood swings, cognitive decline, or speech abnormalities.[113-114]

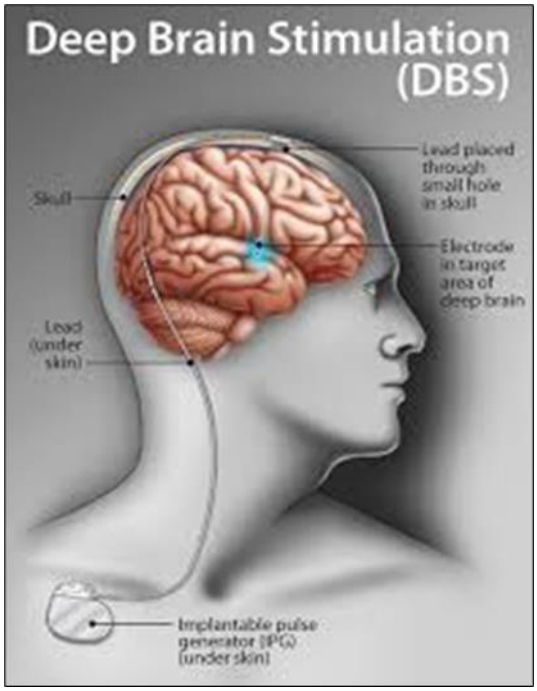

Figure 3 DBS (Deep Brain Stimulation)

VNS (Vagus Nerve Stimulation) is an electroceutical therapy that stimulates the vagus nerve, which connects the brainstem to many organs in the body. VNS can relieve Parkinson's disease symptoms by modulating neurotransmitter flow in the brain. VNS is administered using a tiny implanted device that transmits electrical impulses to the vagus nerve. These impulses are believed to trigger the release of neurotransmitters like dopamine, which can ameliorate motor symptoms in Parkinson's disease. Clinical research indicates that VNS can significantly improve the quality of life and functional independence of Parkinson's disease patients.[106-107] VNS is a safe and effective treatment for Parkinson's disease, approved by regulatory authorities including the FDA and the EU. VNS, like any other medical device, carries risks such as infection, failure, and consequences. Side effects may include changes in voice quality, coughing, or neck ache.[115-116-117-118]

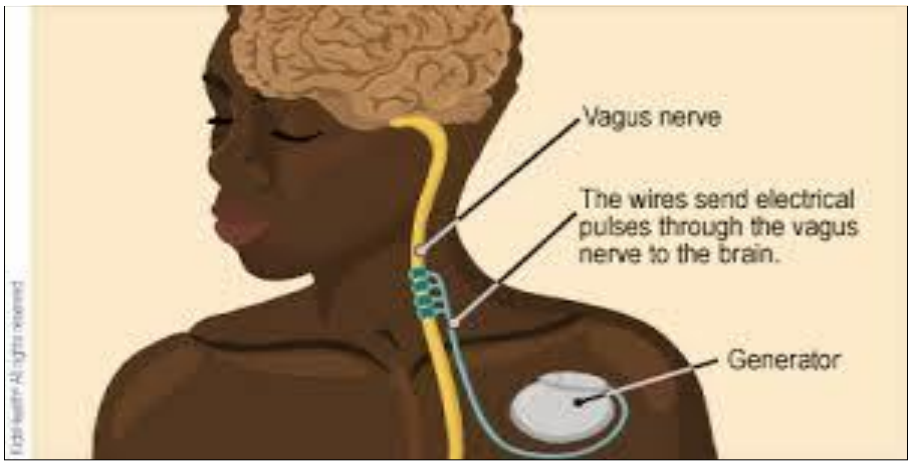

Figure 4 VNS (Vagus Nerve Stimulation)

Transcutaneous Nerve Stimulation (TNS) is an electroceutical therapy that stimulates nerves via the skin. TNS can ameliorate Parkinson's disease symptoms by modulating neurotransmitter flow in the brain. TNS is normally administered using a tiny, wearable device that delivers electrical impulses to the skin. These impulses may trigger the production of neurotransmitters like dopamine, which can ameliorate motor symptoms in Parkinson's disease. Clinical investigations indicate that TNS significantly improves the quality of life and functional independence for Parkinson's patients. TNS is a safe and effective therapy option for Parkinson's disease, approved by regulatory organisations like

the FDA and the EU. TNS, like any medical device, carries hazards such skin irritation, device failure, and consequences. Patients may develop adverse symptoms include skin sensitivity, muscle twitching, or discomfort.[119-120-121]

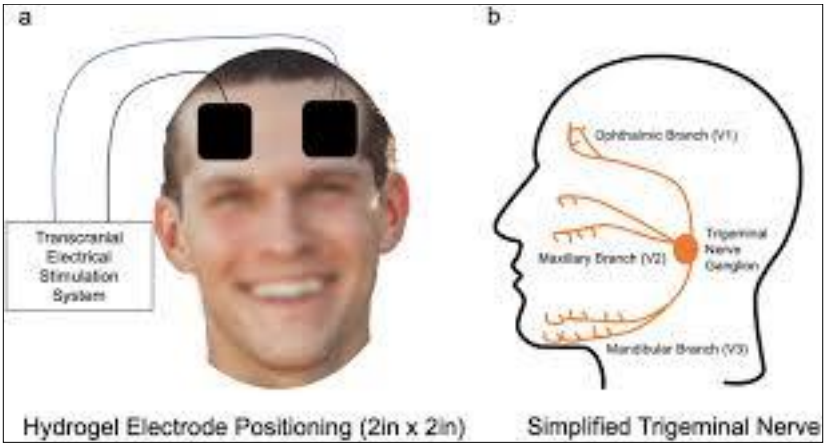

Figure 5 TNS. (Transcutaneous Nerve Stimulation)

Electroceuticals are not the only therapeutic option for Parkinson's disease. Other options include pharmaceutical treatments like levodopa and physical therapies like exercise and rehabilitation.Pharmacological treatments increase dopamine levels in the brain, alleviating motor symptoms. However, these medicines can cause considerable adverse effects, including nausea, dizziness, and motor difficulties. Treatments may become less effective with time, necessitating higher doses or switching to alternative medications. Physical therapy including exercise and rehabilitation can enhance muscle strength, flexibility, and coordination, leading to improved symptoms.[122-123]

Electroceuticals offer a unique form of therapy that can effectively alleviate symptoms without the side effects and limitations associated with other treatments. However, these therapies may not be feasible for all patients, especially those in advanced stages of Parkinson's disease. DBS, VNS, and TNS have been shown to significantly improve quality of life.[124]

Despite their effectiveness, electroceuticals have drawbacks and side effects. Like any medical procedure or device, there is a chance of complications like infection, bleeding, and device failure. Patients may also experience side effects like changes in speech, mood, or cognition, as well as skin irritation, muscle twitching, or discomfort.It is crucial to discuss these possible risks and side effects with a healthcare provider prior to receiving electroceutical treatment for Parkinson's disease. This will help ensure that patients are fully informed and capable of making an informed choice regarding their course of care.[125-126]

10.2.2. Future direction

Emerging Electroceuticals: New treatments are being developed in the rapidly changing field of electroceuticals, which could transform the perception of Parkinson's disease controlled. For instance, scientists are investigating utilizing implanted gadgets that provide electrical stimulation of particular areas within the subthalamic nucleus and the entire brain, including Globus pallidus.[127-128-129]

These tools have the potential to enhance stimulation control and accuracy, which would benefit patients. Another new treatment involves non-invasive methods. transcranial magnetic stimulation (TMS).[130-131] Stimulation with transcranial direct current (tDCS) and these methods entail the utilization of electrical or magnetic stimulation of the scalp, which then affects underlying brain regions. These therapies are non-invasive and have the possibility to be given in a way that is more patient-friendly, increasing their accessibility to a greater variety of patients.[132-133]

There are many chances for additional developments in the field of electroceuticals as long as technology keeps improving. As an illustration, the creation of remote controls and wearable technology.[134-135] There is potential for monitoring systems to enhance treatment accessibility and patient convenience. Furthermore, combining machine learning techniques with artificial intelligence may allow for the customization of electroceuticals to the specific requirements of every patient, resulting in better results.[136-137]

10.3. Research Needed

Although electrochemicals have shown encouraging results in treating Parkinson's disease, further study is required to completely comprehend the underlying mechanisms of these treatments and to maximise their application. [124] For instance, more research is required to assess the long-term safety and effectiveness of these treatments as well as to identify the optimal stimulation parameters for various individuals. Furthermore, more research is required to examine the possible interactions between electrochemicals and other forms of treatment, including physical and pharmaceutical therapies. Developing multidisciplinary strategies that maximise patient outcomes will require an understanding of these connections.[138-139-140]

In short,We looked at the application of electroceuticals to Parkinson's disease treatment in this conversation.We looked at a number of electroceutical forms, such as transcutaneous nerve stimulation (TNS), vagus nerve stimulation (VNS), and deep brain stimulation (DBS). We also talked about the drawbacks and adverse effects of electroceuticals and contrasted them with other therapies.Effects on Patients and Medical Professionals: Electrochemicals have the potential to enhance quality of life and provide greater control over Parkinson's disease symptoms for patients.

It has been demonstrated that these therapies significantly enhance patients' motor function, lessen tremors, and lessen dyskinesia. When thinking about these treatments, patients and healthcare professionals should balance the possible advantages against the risks and be aware of the restrictions and adverse effects related to electrochemicals.In certain situations, electroceuticals might not be the greatest choice for a patient. To decide on the best course of action, it's crucial to go over the possibilities with a healthcare professional.

To sum up, electroceuticals have a lot of potential for Parkinson's disease treatment in the future. Before choosing one of these treatments, it is crucial to exercise caution and thoroughly weigh the dangers and potential advantages.Keeping abreast of the most recent advancements in the pharmaceutical industry and offering patients complete, tailored care that considers their unique requirements and objectives are crucial for healthcare professionals. Lastly, in order to completely comprehend the underlying mechanisms of electroceuticals and maximize their application in the treatment of Parkinson's disease, we advise that more research be done.With sustained technological advancements and a dedication to bettering patient outcomes, electroceuticals in Parkinson's disease have a promising future and might significantly enhance the quality of life for people afflicted by this crippling condition.

11. Conclusion

The review emphasises the growing potential of electroceuticals, such as deep brain stimulation (DBS), vagus nerve stimulation (VNS), and transcutaneous nerve stimulation (TNS), as transformative therapies for Parkinson’s disease (PD). These technologies provide therapeutic benefits through targeted electrical stimulation, addressing motor and non-motor symptoms, and enhancing patients' quality of life.

DBS, the most established modality, has shown significant improvements in motor functions and symptom management. Similarly, VNS and TNS offer promising non-invasive alternatives, modulating neural activity to improve motor and cognitive symptoms. While these interventions have yielded positive outcomes, challenges persist, including procedural risks, device limitations, and variability in patient response.

The review underscores the necessity of personalized approaches in electroceutical therapies to optimise efficacy and mitigate risks. It advocates for advancing research into the mechanisms of action, refining stimulation parameters, and integrating electroceuticals with complementary therapies, such as pharmacological and physical rehabilitation strategies.

Conclusively, the paper highlights the transformative potential of electroceuticals in redefining PD treatment, advocating for sustained innovation and clinical exploration. Despite current limitations, these modalities represent a significant step toward improving patient outcomes and addressing the complexities of Parkinson’s disease. Continued interdisciplinary research and technological advancements are essential for establishing electroceuticals as a cornerstone in PD management, offering hope for enhanced therapeutic options in the future.

Future objectives in the treatment of Parkinson's disease centre on creating disease-modifying treatments that prevent or reverse neurodegeneration in addition to symptom relief. It will be crucial to keep funding studies looking into gene therapy, stem cell treatment, and new pharmaceutical medicines.Furthermore, improving patient involvement with digital health technology might help PD patients adopt better self-management techniques. Healthcare professionals can get real-time data from wearable devices that track symptoms, enabling prompt modifications to treatment

regimens. In conclusion, the most recent methods for treating Parkinson's disease include an integrated model that combines personalised therapy elements with creative tactics like medication repurposing and state-of-the-art research ideas meant to revolutionise future paradigms of care.

Compliance with ethical standards

Disclosure of conflict of interest

The authors declares no conflict of interest.

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