Revealing New Advancements in the Management of Parkinson Disease

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Abstract: Parkinson's disease is a neurodegenerative disorder characterized by progressive motor decline. In Parkinson, decrease in dopamine production disrupts communication between brain and muscles which affects once lifestyle drastically. Factors like age and genetics significantly influence the development of Parkinson. Current Treatments available in the market are expensive and lose efficacy over time, that's why we are looking forward to the new advancements in the treatment of Parkinson disease. Researchers are investigating various therapies to tackle Parkinson. The review has been designed to discover new treatment regimen to improve lifestyle of patient suffering from Parkinson.

Keywords: Parkinson, Dopamine, Lifestyle modification, management

1. INTRODUCTION

Parkinson disease is a progressive, chronic neurodegenerative disease that leads to abnormal motor control due to the selective degeneration of dopaminergic neurons in the substantia nigra, which causes low level of dopamine in striatum [1]. The population over the age of 60 year is affected by this chronic, multicentric, and progressive neurodegenerative disease [2, 3]. The accumulation of α-synuclein (α-SN)-enriched intra-neuronal aggregates is known as lewy bodies [4]. At the onset of PD when motor symptoms start to emerge, the patient lost already 60% of the dopaminergic neurons. Some motor symptoms may include- resting tremor, muscle tone rigidity, akinesia and postural changes. On the other side, non-motor symptoms may include dementia, sensory abnormalities, sleep disorders and autonomic dysfunctions [5].

Parkinson's disease affects roughly 0.1% to 0.2% of the global population. While it can occur at any age, the likelihood of developing PD increases significantly with advancing age. Over 1% of individuals above 60 years old are estimated to have the disease. Although genetic factors play a role in 5-10% of cases, most instances are not directly linked to family history. Men are slightly more susceptible to PD than women and both the number of people diagnosed and the overall prevalence of the disease rise as the population ages.

Levodopa or dopaminergic agonist reimpose neurotransmission and reduce only motor symptoms, long term use may result in severe side effects like wearing off symptoms[6]. This review article will focus on recent updates in Parkinson disease.

2. PATHOGENESIS

There are many mechanisms included in the pathogenesis of Parkinson disease are as follows:-

1. α-synuclein aggregation
2. Mitochondrial dysfunctioning
3. Protein clearance system dysfunctioning
4. Neural inflammation

1. α-synuclein aggregation:-

Parkinson disease may not occur due to the loss of the normal function of the α-Syn but occur because of its toxic function and this toxic function is associated with the accumulation of α-Syn which results in its aggregation. The level of protein in the CNS is maintains by the rate of synthesis and clearance of the α-Syn [7]. α-Syn clearance and degradation takes place by direct proteolysis with the help of chaperons, autophagy and proteasome mediated degradation [8, 9]. The accumulation of α-Syn in cell may occur due to the failure of any of these pathways [10, 11].

Gene duplication, triplication or mutation changes the expression of SNCA gene and result in the accumulation of misfolded α-Syn [12]. Then this phenomenon led researchers to study the in vitro aggregation pathway of α-Syn. These studies showed that α-Syn aggregates generated in vitro shows very much similarity to the amyloid fibrils [13]. The comparison was made between the fibrils directly observed by electron micrographs of LBs in PD brain

tissue section and the measured dimensions like atomic force microscopy and morphologies of the α-syn fibrils formed in vitro. The aggregated α-syn showed some atomic force micrographs which show the species with different morphologies which were termed as oligomeric forms of α-syn [14]. Then these aggregates of α-syn bind with amyloid specific dyes such as Congo red and thioflavin T (ThT) [15]. The ologomeric species have also been detected in the PD patient. The toxic oligomeric forms of disease mutants of α-syn disrupt the chaperone mediated autophagy making it difficult in clearance process [16]. The overexpression of α-syn in primary dopaminergic neurons especially in mutant form results in neuronal death, which shows its major role in pathogenesis [17].

2. Mitochondrial dysfunctioning:-

Many intracellular reactions are performed in the mitochondria, as it is the powerhouse of the cell and involve the production of energy through the mitochondrial respiratory chain, the regulation of cell death, calcium metabolism, and the production of reactive oxygen species [18]. The increased level of OS is alleviated due to mitochondrial dysfunctioning, and a number of cellular pathways become affected which leads to the damage of intracellular components and to cell death. Among the various pathogenic mechanisms, OS is the one which involves in nigral dopamine cell death in PD. The etiopathogenesis of sporadic PD involves various environmental and genetic factors.

Environmental toxins:

During oxidative phosphorylation process there is production of ROS and mitochondria is exposed to highly oxidative environment [19]. In the pathogenesis of PD, there is crucial role of mitochondrial dis-functioning and defects of mitochondrial compex-1 of the respiratory chain may be the most appropriate cause of the degeneration of neurons in PD by reducing the synthesis of PD by reducing the synthesis of ATP. Various studies states that pesticides and other toxins from the environment are involved in the pathogenesis of sporadic PD which mainly inhibits the complex-I. In the very first step, complex-1 is inhibited by 1-methyl 4-phenyl 1,2,3,6-tetrahydropyridine (MPTP) [20]. Also production of ATP is decreased and generation of ROS is increased [21], mitochondrial complex 3 and 4 are also inhibited [22], which leads to reduction of mitochondrial activity and mitochondrial gene expression [23], due to which alteration of mitochondrial proteins such as chaperons, metabolic enzymes, oxidative phosphorylation related proteins, inner and outer mitochondrial proteins[24], also alters protein associated with mitochondrial dysfunction, dopamine signaling, ubiquitin system, calcium signaling, OS response and apoptosis [25], and cause the symptoms of PD in humans and animal models. Secondly the activity of complex 1 is reduced by Rotenone [26]. And then the accumulation of paraquat occurs in mitochondria [27]. In the end, mitochondrial complex 3 is inhibited by maneb [28].

Genetic factors:-

Genetic factor plays a significant role of the mitochondrial dysfunctioning in the pathogenesis of disease. Different physiological and functional aspects of mitochondria can be affected by the genes associated with the Parkinson disease.

PARK genes are involved in Parkinson disease is stated in table 1:-

Symbol	Genes	Pathological effects of mitochondria
PARK1	SNCA	Abnormalities in mitochondrial morphology
PARK4		Complex 1 activity ↓ UPS & ALP dysfunction
PARK2	Parkin	ETC enzyme activities↓ protein level of several subunits of complex 1&4↓
PARK5	UCHL1	UPS dysfunction
PARK6	PINK1	ETC enzyme activities↓ ATP production↓ Mitochondrial fission↓ Disruption of mitochondrial morphology ALP dysfunction
PARK7	Dj-1	Complex 1&2 activities↓

		ATP production, O(2) consumption, and mitochondrial membrane potential↓ Defect in mitochondrial morphology Defect in the assembly of complex 1
PARK8	LRRK2	ATP production and mitochondrial membrane potential↓ Defects in fission/fusion dynamics ALP dysfunction
PARK9	ATP13A2	ALP dysfunction
PARK13	HTRA2	Abnormalities in mitochondrial morphology ALP dysfunction

Above table is obtained from article containing complete information about myocardial dysfunction (86)

3. Protein clearance system dysfunctioning:-

Mainly two protein clearance system are involved in the removal of dysfunctional protein:

- The ubiquitin-proteosome system (UPS).
- The autophagy-lysosome pathway.

The UPS primarily breakdown the abnormal protein and it does it by tagging them with the ubiquitin and transport for degradation to the proteasome.

Further, the autophagy-lysosome pathway is divided into three constituents:

- Macroautophagy
- Microautophagy
- Chaperone mediated autophagy (CMA)

- Macro-autophagy: The cells wraps up unwanted parts like proteins in a special sac called autophagosome. This sac then merges with a recycling bin called lysosomes where everything gets broken down
- Micro-autophagy: Lysosomes directly destroys unwanted cytoplasmic components.
- Chaperone-mediated autophagy (CMA): Chaperons identify specific proteins for disposal and take then straight to the lysosome for breakdown. This is a more targeted approach [29].

Monomeric, or single forms of alpha-synuclein are typically cleared through two cellular disposal systems: the ubiquitin-proteasome system (UPS) and the autophagy-lyosomal pathway [30]

Ubiquitin-proteosome system-

Proteosomal abnormalities are a shared feature among many proteinopathies, that is, neurodegenerative diseases characterized by abnormal protein accumulation [31]. Evidence of such abnormalities in PD was first provided by postmortem studies in the SNpc, where the catalytic activity of the UPS was found substantially reduced compared to healthy brains [32]. The same findings were later reported in peripheral blood mononuclear cells of PD but not in healthy individuals [33]. Along with diminished activity, lesser expression of different proteasomal components has also been discovered in the SNpc of PD brains. Specifically, the 20S proteasome α-subunit [34] and other molecules involved in the normal function of the UPS, like PA700 and PA28 (proteasome activators), are reduced [35]. Genetic studies and discovery validated that two of the PARK genes linked to monogenic PD encode proteins involved in UPS function, namely, parkin (PARK2; E3 ubiquitin ligase) [36]. and UCH-L1 (PARK5; Ubiquitin C-terminal hydrolase) [37].

Furthur findings in human PD, altered proteasome activity was observed in different disease models. Marmosets injected with the toxin MPTP had diminished enzyme activity in the UPS, in addition to decreased levels of the 26S subunit components [38]. In a second set of experiments, the same group showed that pharmacological inhibition of the proteasome in wild-type rats leads to dopaminergic cell death [39]. Similarly, Bedford and colleagues using transgenic mice with proteasomal defects (knockout for 26S proteasome regulatory subunit 4) showed dopaminergic cell degeneration and observed LB-like inclusions in the brain, which however lacked the dense core of classical human LBs, and it is unclear whether they contained aggregated α-synuclein [40]. Nevertheless, all these studies show that dysfunction of protein turnover can result in neuronal cell death, thus providing a potential pathogenic mechanism for PD.

Autophagy-lysosome system-

In nigral neurons of PD brains, the levels of the autophagosome marker LC3-II were increased, suggesting an accumulation of autophagic

vacuoles [41]. In contrast, vital proteins of lysosomal membranes (LAMP1 and LAMP2A), and several molecular chaperones from the heat-shock protein family (such as hsc70 and hsp35) were found to be decreased at postmortem examination [42]. Furthermore, of particular note is the discovery of a point mutation in the gene of the lysosomal protein ATP13A2 (PARK9), leading to an autosomal recessive atypical Parkinsonian syndrome, referred to as Kufor–Rakeb syndrome [43]. Point mutations in two more PARK genes impair the function of either parkin (PARK2) or PINK1 (PARK6), both of which are involved in the autophagic turnover of mitochondria [44]. Additionally, the emergence of *GBA1* mutations, which result in dysfunction of the lysosome-autophagy system, as a strong genetic risk factor for PD adds weight to the idea that this system is important in the development of PD.

5. Neuro-inflammatioin:-

Postmortem brain studies have spotted microglial and complement activation, T-lymphocyte infiltration, and increased concentration of pro-inflammatory cytokines in the SNpc and striatum of PD patients compared to healthy individuals [45]. Furthermore, positron emission tomography (PET) neuroimaging with the [^{11}C]-PK11195 radioligand has demonstrated increased microglial activation early on in PD in the brainstem, basal ganglia, and front temporal cortices, with added involvement of the parietal and occipital cortices in patients with PD dementia, compared to healthy subjects [46].

Evidence stated that inflammatory responses can themselves contribute to disease pathogenesis. Demonstration in early studies with rodent models of PD (6-hydroxydopamine and MPTP) shows that inhibition of microglial activation with minocycline pre- and post-neurotoxic insult led to a significant attenuation of DA cell death in the SNpc, suggesting that microglia-induced inflammatory processes may be contributing to the degeneration of these cells [47]. Plethora of evidence suggests that α-synuclein can directly trigger microglial activation and initiate inflammatory processes. For instance, in primary cultures, α-synuclein mediates a dose-dependent activation of microglia [48].

Receptors:-

Dopamine is a 7 transmembrane G protein-coupled receptor and a monoamine neurotransmitter, which regulates motor and non-motor functions like motivation, emotion, cognition and neuroendocrine secretion [49].

D1-like dopamine receptor expression and its functions:- There are two types of dopamine receptors called D1 and D5. These receptors are like tiny antennas on brain cells that pick up signals from dopamine, a messenger molecule. They're concentrated in areas that control movement, reward, and smell, such as the striatum, nucleus accumbens, and olfactory bulb [50,51]

D2-like dopamine receptor expression and its function:- There are 3 types of D2-like dopamine receptors (D2, D3, D4). The main D2 receptor comes in two versions (short and long). These receptors are found in many brain areas like movement control (striatum), emotion (amygdala), and memory (hippocampus) [52]. D2 dopamine receptor messages (messenger RNA) are found in areas of the brain linked to thinking (prefrontal cortex), memory (temporal cortex), and navigation (entorhinal cortex). They're also present in regions that control emotions (septal region) and movement (VTA and SN) [53]. D2 receptor activate cell proliferation-related pathways:-

Receptors	D1	D5	D2	D3	D4
Location	Striatum, nucleus accumbens. olfactory bulb, amygdala hippocampus, substantia nigra Hypothalamus, frontal cortex	Cortex, substantia nigra, hypothalamus	Striatum, VTA olfactory bulb, cerebral cortex	Striatum, islands of Calleja, cortex	Frontal cortex, amygdala, hypothalamus, nucleus accumbens
Type	Gs-coupled	Gs-coupled	Gi-coupled	Gi-coupled	Gi-coupled
Mechanism	Increased intracellular level of cAMP by activated adenylate cyclase	Adenylate cyclase↑	Increased intracellular level of cAMP by activate adenylate cyclase	Adenylate cyclase↓	Adenylate cyclase↓

Function	Locomotion, learning and memory, attention, impulse control, sleep, regulation of renal function	Cognition, attention, decision making, motor learning, renin secretion	Locomotion, learning and memory, attention, sleep, reproductive behaviour	Locomotion, cognition, attention, impulse control, sleep, regulation of food intake	Cognition, impulse control, attention, sleep, reproductive behavior
Selective agonist	SKF-38393 SKF-81297 Fenoldopam (SKF-82526)	–	Bromocriptine Pergolide Cabergoline Ropinirole	7-oH-DPAT Pramipexole Rotigotine PD-128907	A-412997 ABT-670 PD-168077
Selective antagonist	SCH-23390 SCH-39166 SKF-83566	–	Haloperidol Raclopride Sulpiride Spiperone Risperidone	Nafadotride GR 103691 GR-218231 SB-277011A NGB-2904 PG-01037 ABT-127	A-381393 FAUC213 L-745870 L-750667

Advances in the management of Parkinson disease

1. Stem cell therapy:-

Stem cell restores the response of diseased and damaged tissues and also called as regenerative therapy. The main goal of stem cell therapy is to focus on either cellular replacement or giving environment improvement. [54]. The difference between the stem cells and their comparison is as follows;-

Stem cell types	Origin	Advantages	Disadvantages
ESCs (pluripotent)	Embryo (blastocyst)	Unlimited proliferation	Ethical problems. Risk of immune rejection. Unpredictable differentiation. High risk of tumor formation.
IPSCs (pluripotent)	Reprogrammed adult cells: fibroblasts, hepatocytes, circulating T cells, and keratinocytes	No ethical problems Low risk of immune rejection High accessibility	High risk of tumor formation Risk of susceptibility to the original pathology of the patient Genetic and epigenetic abnormalities
MSCs (multipotent)	Adult tissues (bone marrow, skin, blood, umbilical cord, etc.)	No ethical problems High accessibility Easy isolation methods Autologous cells generation Self-renewal capacity Low risk of immune rejection	Risk of tumor formation
NSCs (Multipotent)	Embryo, human fetal brain and brain tissue of adults (SVZ and SGZ of hippocampus)	Low risk of tumor formation	Ethical problems Risk of immune rejection Limited differentiation Low self-renewal capacity Limited proliferation and expansion Limited availability Difficult isolating methods

- Embryonic stem cells:-

Embryonic stem cells show good results due to their ability to self-renew and differentiate into all cell types. Researchers are currently focusing heavily on the therapeutic potential of ESCs. Although ESCs offer new means of treatment, it still raises some thorny ethical and religious restrictions since it involves destroying human embryos [55].

- Induced pluripotent stem cells:-

These stem cells are artificially derived from non-pluripotent cells. These reprogrammed cells now provide promising strategy for producing unlimited neurons in patients. iPSCs can be converted into mature functional neural lineages using an optimized differentiation method [56].

- Mesenchymal stem cells:-Adult stem cells, called MSCs, live in your bone marrow, umbilical cord, fat, and spleen. These special cells can become many different cell types, like bone, cartilage, muscle, and fat [57]. MSCs are promising for treating neurodegenerative diseases. They can renew themselves and turn into many cell types, making them a good source for cell transplants [58].
- Neural stem cells:- Neural stem cells (NSCs), found within brain tissue, are more limited in their developmental potential compared to embryonic stem cells (ESCs). NSCs can divide and replenish themselves, but to a lesser extent. This specialization restricts them to becoming only certain cell types in the brain, such as neurons, oligodendrocytes, and astrocytes [59]

Stem cell therapy for Parkinson disease:-

For the past 20 years, scientists have explored using stem cells to replace dopamine-producing brain cells lost in Parkinson's disease. They're focusing on three types of stem cells: embryonic, neural, and induced pluripotent [60]. Early studies transplanting fetal brain cells into Parkinson's patients showed some promise. This approach aimed to replace lost dopamine-producing cells in the brain (striata) with healthy ones from human fetuses [61].

In animal studies, embryonic stem cells (ESCs) seemed particularly effective at creating dopamine-producing cells for Parkinson's treatment. This wasn't the case with adult neural stem cells. ESCs also showed promise for spinal cord injuries in rats, migrating to the injured area and improving movement. However, due to ethical concerns, religious objections, and the risk of tumors, this approach wasn't pursued further [62].

Adult neural stem cells (NSCs) also show promise for Parkinson's treatment. These cells can naturally release dopamine, a key brain chemical lacking in PD patients. This helped improve movement problems in rats with the disease, according to research by Deleidi et al [63].

Studies using a different type of stem cell, called mesenchymal stem cells (MSCs), have shown promise in animal models of Parkinson's. These cells may help the brain by reducing dopamine loss and repairing the network of nerves that use dopamine in a key area (striatum) [64].
Cells created from adult patients' own skin cells (iPSCs) show promise for treating Parkinson's disease. Studies using these cells in animal models of PD have found they can be converted into dopamine-producing brain cells. These new cells survive and connect with existing brain tissue, improving movement in the animals [65].

2. Gene therapy:-

Gene therapy involves introducing genetic material into cells to treat a disease. In the context of PD, this could involve delivering genes that:

Increase dopamine production:- Genes encoding enzymes involved in dopamine synthesis, like tyrosine hydroxylase (TH) and aromatic L-amino acid decarboxylase (AADC), could be delivered to surviving brain cells to boost dopamine levels [66].

Protect dopamine neurons:- Genes encoding neuroprotective factors like glial cell line-derived neurotrophic factor (GDNF) could be introduced to promote the survival and function of dopamine neurons [67].

Modulate brain circuits:- By altering the activity of specific brain circuits with genes like glutamic acid decarboxylase (GAD) which is the rate limiting enzyme in the synthesis of GABA, researchers aim to restore balance and improve movement control [68].

How gene therapy works:-

Gene therapy aims to modify faulty genes or introduce functional ones into cells [69]. In the context of PD, researchers are exploring two main strategies:

Non-Disease modifying:- Levodopa (L-DOPA) is converted into dopamine by the enzyme aromatic L-amino acid decarboxylase (AADC). While AADC therapy can enhance the effects of L-DOPA, it wouldn't be sufficient on its own due to the ongoing need for L-DOPA from external sources (exogenous L-DOPA). However, encouragingly, clinical trials have shown that AADC therapy improves patients' response to L-DOPA. Scientists are exploring another approach to manage Parkinson's symptoms: gene therapy to rebuild the body's natural dopamine production system. This would involve introducing genes that code for three key enzymes: tyrosine hydroxylase (TH), aromatic L-amino acid decarboxylase (AADC), and GTP cyclohydrolase 1 (GCH). These enzymes work together to convert a molecule called tyrosine into dopamine, eliminating the need for patients to take L-DOPA medication. This could potentially lead to more stable dopamine levels

and reduce problems like "off" periods when medication wears off [70]. Getting these three enzymes (TH, AADC, and GCH) into the brain is a challenge because they're too big to fit together in one delivery vehicle (called an AAV). The solution is Using three separate delivery vehicles to carry each enzyme. Early attempts combined all the genes into one vehicle, but this caused problems. Researchers found a better way using a single vehicle called a lentiviral vector (LV) that efficiently delivered all three genes in rats. This approach was safe and well-tolerated in monkeys with Parkinson's symptoms, and it even helped restore half of their normal dopamine levels! A drug called Prosavin, which uses this LV approach, is currently undergoing early testing in humans (phase 1 clinical trial) [71].

In parkinson's disease, a brain area called the striatum loses dopamine, a chemical that helps control movement. This disrupts communication within the brain circuits. As a results, another area called the subthalamic nucleus become overactive, leading to tremors, rigidity, and slowness of movement. Researchers explored a gene therapy approach targeting an enzyme called glutamic acid decarboxylase (GAD). In rat studies, increasing GAD levels helped control the overactive subthalamic nucleus, improving Parkinson's symptoms. A company funded an early clinical trial (phase 1) that showed positive results with no side effects. Unfortunately, the longer pursuing this gene therapy approach for Parkinson's [72].

Disease modifying targets:-

Delivering a growth factor called GDNF directly to the brain shows promise in treating Parkinson's symptoms in lab models. This approach helps damaged nerve cells sprout new connections, potentially improving movement control. However, there are challenges:

- Limited spread: Current methods may not deliver enough GDNF or target the right areas of the brain due to faulty "pumps" or a lack of healthy nerve cells.

Researchers are exploring new delivery methods:

- Neurotensin-polyplex: This method uses nanoparticles carrying GDNF instructions that attach to specific receptors on dopamine-producing cells. A switch controlled by an external drug (tetracycline) allows for controlled GDNF production.
- Nanoparticles with lysine polymer: Another method uses nanoparticles made of specific materials to deliver GDNF genes.

Safety concerns and progress:

- Early studies using viral vectors to deliver GDNF raised safety concerns due to side effects.
- However, the FDA has approved a phase 1 clinical trial in the US to test a GDNF gene therapy approach in Parkinson's patients [73].

3. Deep brain stimulations:-

Deep Brain Stimulation (DBS) has undergone significant advancements in recent years, enhancing its effectiveness and safety in managing Parkinson's disease (PD). Here, we highlight some of the latest advancements in DBS technology and techniques that are shaping the field:

1. Closed-loop adaptive stimulations:- Closed-loop DBS systems, also known as adaptive DBS, represent a groundbreaking advancement in neuromodulation technology. These systems continuously monitor neural activity or physiological markers in real-time and adjust stimulation parameters accordingly. By dynamically adapting to changes in disease state and symptom severity, closed-loop DBS offers personalized and optimized therapy, minimizing side effects and conserving battery life [74].
2. Directional Stimulation Leads:-Recent innovations in electrode design have led to the development of directional stimulation leads. Unlike conventional omnidirectional leads, which deliver stimulation in all directions, directional leads allow for more precise steering of electrical currents towards targeted brain regions. This directional stimulation approach enables clinicians to selectively modulate neural circuits involved in motor control while minimizing stimulation of adjacent structures, thereby improving therapeutic outcomes and reducing side effects [75].
3. High-frequency focused ultrasound (HIFU): High-frequency focused ultrasound (HIFU) is an emerging non-invasive alternative to traditional surgical DBS. This innovative technique utilizes focused ultrasound waves to precisely target and

ablate dysfunctional brain tissue implicated in PD pathophysiology. HIFU offers the advantages of being incisionless, reversible, and potentially safer than traditional DBS surgery. Clinical studies investigating the efficacy and safety of HIFU for PD are ongoing, with promising early results [76].

4. Closed-Loop interleaved stimulation: Building upon the concept of interleaved stimulation, closed-loop interleaved stimulation combines high-frequency and low-frequency stimulation pulses within the same electrode contact, guided by real-time feedback from neural signals. This closed-loop approach dynamically adjusts the ratio and timing of high-frequency and low-frequency stimulation based on disease state and symptom fluctuations, optimizing therapeutic efficacy while minimizing energy consumption and side effects [77].
5. Biomarker-Guided Targeting: Advancements in neuroimaging, electrophysiology, and molecular biology have facilitated the identification of biomarkers associated with PD pathophysiology. Biomarker-guided targeting approaches for DBS leverage these markers to precisely localize dysfunctional brain circuits and tailor stimulation targets to individual patient characteristics. By optimizing target selection and electrode placement, biomarker-guided DBS holds promise for enhancing treatment response, reducing side effects, and advancing personalized medicine in PD management [78].
6. Non-Motor Symptom Targets: While traditional DBS targets primarily address motor symptoms, recent research has focused on identifying brain regions involved in non-motor symptoms of PD, such as cognitive impairment, mood disorders, and autonomic dysfunction. Targeting these non-motor symptom circuits with DBS may offer therapeutic benefits beyond motor symptom control, improving overall quality of life for PD patients. Clinical trials investigating the efficacy of non-motor symptom targets for DBS are underway, with encouraging preliminary results [79].

7. Levodopa therapy:-

Levodopa, a precursor to dopamine, remains the gold standard in PD treatment, alleviating symptoms and improving quality of life for patients. However, over time, levodopa therapy can be associated with motor complications such as dyskinesia and 7for PD, focusing on strategies to optimize its efficacy and minimize adverse effects.

Optimizing Levodopa Delivery:

Extended-Release Formulation: Recent advancements in levodopa formulations aim to prolong its therapeutic effects and reduce motor fluctuations. Extended-release formulations deliver levodopa gradually over an extended period, providing more stable plasma concentrations and reducing the frequency of dosing. These formulations offer convenience and improved symptom control, particularly in patients experiencing wearing-off phenomena {80}.

Inhaled Levodopa: Inhaled levodopa offers an alternative route of administration, bypassing the gastrointestinal tract and potentially enhancing drug absorption. This delivery method provides rapid relief of motor symptoms, making it particularly useful in managing "off" episodes. Clinical trials have demonstrated the efficacy and safety of inhaled levodopa, offering a promising option for PD patients with unpredictable motor fluctuations [81].

Enhancing Levodopa Pharmacokinetics:

Peripheral Dopamine decarboxylase Inhibitors: Peripheral metabolism of levodopa by dopa decarboxylase (DDC) outside the central nervous system limits its bioavailability and contributes to motor fluctuations. Recent advancements include novel DDC inhibitors that selectively target peripheral DDC enzymes, reducing the conversion of levodopa to dopamine peripherally and enhancing its central availability. These adjunctive therapies improve levodopa's efficacy, prolong its duration of action, and mitigate motor fluctuations [82].

Continous Subcutaneous Infusion: Continuous subcutaneous infusion of levodopa-carbidopa gel provides continuous dopaminergic stimulation, minimizing motor fluctuations and dyskinesia. This delivery method bypasses the gastrointestinal tract and hepatic first-pass metabolism, maintaining stable plasma levodopa concentrations and improving motor symptom control. Clinical studies have demonstrated the efficacy and safety of continuous levodopa infusion as an adjunctive therapy in advanced PD, offering sustained benefits and improving patients' quality of life [83].

Addressing Levodopa-Induced Complications:

Novel Adjunctive Therapies: Combining levodopa with adjunctive therapies targeting different neurotransmitter systems offers a multifaceted approach to PD management. Recent advancements include adenosine A2A receptor antagonists, glutamate modulators, and serotonergic agents, which complement levodopa's effects and mitigate motor complications such as dyskinesia. These combination therapies optimize dopaminergic signaling while minimizing adverse effects, improving overall treatment outcomes [84].

Precision Medicine Approaches: Individualized treatment strategies based on patients' genetic profiles, disease characteristics, and treatment response offer a personalized approach to levodopa therapy. Advances in pharmacogenomics enable the identification of genetic variants associated with levodopa response and adverse effects, guiding treatment decisions and optimizing therapeutic outcomes. Precision medicine approaches hold promise in tailoring levodopa therapy to individual patient needs, maximizing efficacy while minimizing complications [85].

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