Advancement in the Management of Parkinson's Disease

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Abstract*— Parkinson's disease (PD) is neurodegenerative brain disorder defining features of motor parkinsonism and non-motor impairment. Treatment of PD are not much like Levodopa, MAO-B inhibitors, Dopamine receptor antagonist, Anticholinergic drugs, COMT inhibitors. By taking current approaches on a point and modification in these treatment option can ease to treat PD. As considerate PD pathogenesis grows, novel therapeutic boulevards are evolving. However, prevention or slowing down the PD is done by deep brain stimulation, Nigral cell transplantation, immunotherapies and by doing drug purposing. Here is an overview of current pharmacotherapies for managing and treatment of PD. Finding accurate biomarkers for early diagnosis, including prodromal diagnosis and preclinical diagnosis, is critical in order to provide better clinical intervention and treatment at the outset of disease. At the same time, these dependable indicators can be used to track the disease's progression. We will address current breakthroughs in the development of PD biomarkers from several perspectives, including clinical, biochemical, neuroimaging, and genetic aspects, in this review paper. Although several biomarkers for Parkinson's disease have been established to date, their specificity and sensitivity when used singly are not perfect. As a result, combining multimodal biomarkers will considerably increase diagnostic accuracy and make personalised therapy easier to execute.

Indexed Terms*— Dopamine, Parkinson, Levodopa, Deep brain stimulation.

I. INTRODUCTION

Parkinson's disease (PD) is the neurodegenerative brain disorder, which affecting 1% of the population over 55 years of age. Parkinson symptoms are slow movement, stiffness, and loss of balance. It also caused by nerve cell's damage in the part of the brain called the substantia nigra. These nerve cells are in charge for producing chemical which are known as Dopamine [1]. A chemical messenger (Dopamine) transmits signals between 2 regions of the brain to manage activity. In 1817, James Parkinson's firstly define the symptoms of this neurodegenerative disorder or movement disorder are known as Parkinson's disease or Parkinsonism. Firstly, chemicals alterations in the brain of Parkinson's patients were identified in 1960s. The lower level of dopamine and degeneration of nerve cells of brain that is called as Substantia nigra and found by the researchers. When neurons, or nerve cells of the brain which control movements become impaired or die [2]. Normally, the brain neurons produce a chemical which are known as Dopamine. These symptomatic therapeutic breakthroughs may explain that why medicines for the large spectrum of disabling non-motor symptoms (NMSs) that PD patients experience are still being developed. Has been neglected throughout the course of the sickness [3]. In addition, attempts are being made to produce disease-modifying drugs. A massive number of medicines were tested in acute toxin-induced animal models. (6-hydroxy-dopamine, or MPTP) and the research findings failed to translate into clinically effective medications [4].

Pathophysiology of Parkinson's Disease

Physiologically, the symptoms associated with Parkinson's disease are the result of the loss of several neurotransmitters, utmost notably dopamine [5]. Symptoms worsen over time as more and more of the cells exaggerated by the disease are lost. This disease course is highly variable, with some patients displaying very few symptoms while other having symptoms progress rapidly [6,7].

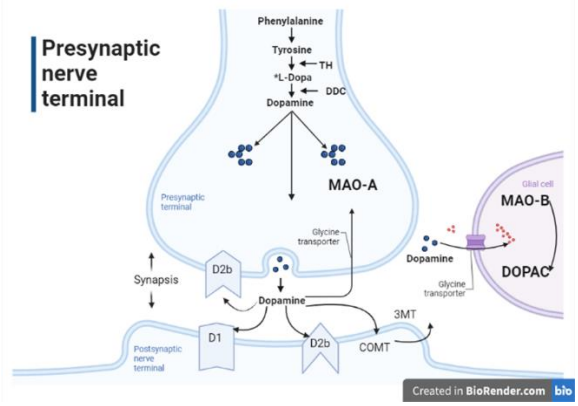
- Basal Ganglia - Controls movement.

- Dopamine - Inhibitory neurotransmitter in the basal ganglia.
- Acetylcholine - Excitatory neurotransmitter in the basal ganglia.
- Without dopamine, inhibitory influences are lost and excitatory mechanisms are unopposed → Neurons of basal ganglia are over stimulated → Excess muscle tone, tremors & rigidity.

Etiologic factors- The most common cause i.e, idiopathy of Parkinson's disease includes certain factors such as environmental toxins (1- methyl-4-phenyl-1,2,3,6-tetrahydropyridine) MPTP, occasionally pesticides), Viral infections (encephalitis lethargica), no strong genetic factors, but genetic impact may be more than earlier thought have been observed.

II. EXISTING TREATMENT OF PARKINSON'S DISEASE

Extensive number of valuable advancements done in understanding the main cause of PD and several treatments are there which can be useful for the long-term management of PD [8]. The importance of existing and a novel drug-delivery system in PD has been observed to give basic regimens, motor control, reduction in motor activity complication. Dopamine deficiency, caused by degradation of nigrostriatal dopaminergic neuron, this is the origin of major clinical motor symptoms of PD [9]. These types of symptoms be easily treated through a extensive range of drugs which includes levodopa, an inhibitor of enzymatic breakdown of levodopa and dopamine agonist. This can be delivered by oral, subcutaneous, IV(Intravenous). Patient with advanced PD generally suffer disabling motor complication which cannot be controlled by medical therapy [10]. Deep train stimulation is used for treating advanced PD. In this procedure an electrode is rooted in the brain target and linked to a pacemaker. Anticholinergic drug was given to the patient before the introduction of levodopa [11].



III. MECHANISM OF ACTION OF DIFFERENT DRUGS

(1) Levodopa is immediate metabolic precursor of dopamine, dopamine enters brain and bind with dopamine receptors, hence the level of dopamine gets increase so, parkinsonism will quite effect by this [12].
(2) MAO-B inhibitors (selegiline) it increases the duration of action of dopamine by blocking the major pathway in dopamine metabolism.
(3) Dopamine receptor agonists (bromocriptine, pramipexole) it directly activates the dopamine receptors on postsynaptic neurons [13].
(4) Anticholinergic drugs it blocks the acetylcholine receptors on the nerve cells. This help to reduce the effect of acetylcholine and also reduce the dopamine level.
(5) COMT inhibitors block an alternate metabolism of dopamine so, it can easily cross the blood brain barrier [14].

- Progress in the Treatment of Parkinson's Disease

Notwithstanding the way that 200 years passed since the disclosure of PD, it wasn't until some other time in the twentieth century that advancement in the treatment of PD was accomplished, overwhelmingly because of the restricted comprehension of PD pathophysiology [15]. Given Carlsson's disclosures of DA's association during the 1950s, it turned out to be evident that PD advancement included dopaminergic cell passing and a diminishing of DA in the striatum and different constructions of the forebrain. The initial moves towards treatment were made via Carlsson (2001), who proposed focusing on this DA inadequacy to work with side effect decrease [16].

1. Deep Brain Stimulation:

In late 1990_s, the dual organization theory of the striatum led to neuro-surgical procedures for the treatment of PD [15]. Based on this theory, deep brain stimulation (DBS) has been shown to help people with Parkinson's disease who have dopamine-mediated motor symptoms because of levodopa treatment. Electrodes are surgically placed into subcortical areas to control brain activity. In individuals with severe PD, DBS has been shown to improve motor symptoms and reduce fluctuations, as well as relieve depression and improve sleep quality, urinary and gastrointestinal problems, among other things, although it has had minimal effect on gait freezing and postural instability. Its effect in tremor prevention and improvement in early PD is being investigated. It has, however, been related to cognitive and neuropsychiatric disorders, as well as speech issues. A new surgical treatment to reduce the symptoms of PD called deep brain stimulation (DBS) was established. The working of DBS isn't totally seen; in any case, the real proof recommends that vascular changes might be associated with its remedial impacts. The overexpression of the vascular endothelial development factor (VEGF) and the downregulation of neuroinflammatory factors are viewed as key atomic components engaged with DBS-instigated microvascular changes. L-DOPA and DBS medicines are often applied together to potentiate their advantageous impacts. To improve the clinical benefits of DBS, additional targets and better imaging of electrode placement are being developed. Adaptive DBS is another area of investigation, whereas non-invasive DBS remains a promising topic. External devices would administer electric fields to deep brain areas in this case, obviating the necessity for surgical treatments and their associated complications. The gamma knife and MRI-guided focused ultrasound could also be utilised to prevent craniotomy and allow deep brain ablation [17].

2. Nigral Cell Transplantation:

Additional capable therapeutic approach for PD is cell replacement therapy to restore dopaminergic neuron [18]. The classical motor symptoms of PD are triggered through the loss of dopaminergic neurons in the substantia nigra pars compacta, foremost to a decrement in the release of dopamine in the striatum. This therapy consists of grafting dopamine-producing cells directly into the brain to reestablish dopamine levels. Different cell sources have been shown to induce functional benefits on both animal models of PD and humans. Unfortunately, this approach resulted in high mortality and morbidity rate in elderly patient patients.

3. Immunotherapies:

The presence of aberrant aggregates of -synuclein is a pathological characteristic of PD. Although the role of -synuclein in PD is unknown, it is thought to play a central pathogenic role, as evidenced by the fact that mutations or duplications/triplications of the gene (SNCA) cause rare familial forms of PD, as well as numerous independent studies showing the negative effects of manipulating -synuclein in cell and animal models. For example, vesicular transport disruption, changes in the lysosome–autophagy system, mitochondrial malfunction, and oxidative stress are all potential pathogenic pathways of -synuclein. Pathological forms of -synuclein have also been postulated to work in a prion-like manner, allowing pathology to spread from cell to cell, and the "strains" underpinning this are currently being found [19]. A humanized monoclonal antibody directing the C-terminus of aggregated α-synuclein (prasinezumab or PRX002, Prothena) has been shown to reduce free serum α-synuclein by approximately 97%. The use of immunotherapies to reduce the spread of PD disease is an intriguing option for additional research, but major concerns remain, including how much of PD in the clinic is caused by protein spread. Furthermore, these antibodies' capacity to traverse the blood–brain barrier and impact -synuclein homeostasis in the brain could be a hurdle to their clinical usage. Furthermore, the neuroprotective effects of these immunotherapies appear to be owing in part to intracellular actions, and their capacity to enter cells may affect their efficacy. Engineered fragments (intrabodies and nanobodies) may allow for more central nervous system penetration and cell entrance, although clinical trials have yet to begin [20].

4. Drug repurposing:

An alternative approach to limit PD pathology and progression of disease is using drugs that reduce α-synuclein pathology or have beneficial effects on other processes caught up in PD. One class which is under

consideration, but to enter clinical trials, is the β-adrenergic receptor agonists.

The glucagon-like peptide-1 (GLP-1) analogue exenatide, which is used for the treatment of type two diabetes mellitus, has advanced the most. Another repurposed drug that has been trialed for PD is nilotinib. This is an ABL tyrosine kinase inhibitor used to treat chronic myelogenous leukaemia, it enhances autophagy activity, potentially reducing the accumulation of α-synuclein aggregates. Inhibition of apoptosis, reduced microglial activation and neuroinflammation, reduced oxidative stress, and stimulation of neurogenesis are some of the mechanisms reported to mediate this impact via GLP-1 receptor activation.

In human trials, just a few of these have shown to be effective. Exenatide, which is based on the neuroprotective drug exendin-4 and is currently being used to treat type 2 diabetes, is an exception. This has demonstrated the ability to improve motor function in treated patients over time.

5. Targeting non-dopaminergic neurotransmitter systems:

Though many of the motor features of PD are dopamine responsive, which might not be true in all cases.

It is nowadays understood that deficiencies in other neurotransmitter systems underlie some of these features. As such, there is interest in modulating their function to treat specific dopamine-resistant aspects of PD.

Opicapone is a COMT (catecholamine-O-methyltransferase) inhibitor that causes less hepatotoxicity and requires fewer daily doses. It was recently approved for people with intermittent symptoms. Cholinesterase inhibitors rivastigmine and donepezil, norepinephrine reuptake inhibitors methylphenidate and atomoxetine, and serotonin regulators are among the other options in this group. Rivastigmine is used to treat both PD and Alzheimer's disease dementia. Amantadine is an NMDAR (N-methyl-d-aspartate receptor) antagonist that has been shown to help with Parkinson's disease and other symptoms. Istradefylline is an A2A antagonist that was recently approved for usage in combination with L-dopa and carbidopa to minimise on-off swings. It's used in the early stages of Parkinson's disease, before motor difficulties develop, because it can worsen dyskinesia in some patients. Safinamide is a novel drug that has recently received approval, it is proposed to have multi-modal actions. It is a potent reversible monoamine oxidase B inhibitor, conveying a benefit for the treatment of dopaminergic aspects of PD. It also modulates glutamate transmission, which may be implicated in some of the non-motor symptoms of PD [21].

6. Regenerative treatments:

There is considerable interest in the use of cell-based and several of gene therapies to replace the function of the lost dopaminergic neurons. The aim of these treatments is to restore dopaminergic tone in a more targeted and physiological manner than can be achieved with current dopaminergic therapies. Gene therapies may be used to increase dopamine levels in the striatum through the introduction of genes that mediate dopamine synthesis.

Cell-based therapies offer another emerging approach for the targeted replacement of dopamine to treat the dopamine-dependent aspects of PD [22].

Stem cell offers a renewable source of dopaminergic neuron progenitor cells that can be grafted into patients, and clinical trials of such products are now underway.

7. Protective approaches:

Focusing on the reasons for Parkinson's sickness: There is an arrangement that PD is incited by a combination of old enough, sexual orientation, hereditary foundation, and ecological components. In any case, neither of these has, alone, been distinguished as a foremost source of PD. While neurochemical instruments and the cell, basic PD have remained not entirely comprehended.

While the cellular and neurochemical mechanisms underlying PD have remained incompletely understood, data has shown that mitochondrial dysfunction, oxidative stress, inflammation, and excitotoxicity play a impactful role in the pathogenesis of both familial and sporadic cases of PD. Hence,

working on these targets might prove to be beneficial too.

- Initial therapy-

The foremost therapeutic choices for the motor symptoms of PD consist of dopaminergic medications, such as levodopa, dopamine agonists, and MAO-B inhibitors, which all have enough supportive clinical data. There are certain key issues to keep in mind when using these and planning the optimal long-term strategy for a patient with Parkinson's disease [23–25].

Motor complications include both wearing off and dyskinesias. These develop at a rate of approximately 10% per annum in later-onset PD but at a much faster rate in young-onset PD such that 70% are affected after 3 years [26]. The source of motor difficulties is unknown, but it appears to be linked to the consequences of short-duration pulsatile stimulation of a denervated striatum, among other things. As a result, there has been a push to create therapeutic options that include more continuous dopaminergic stimulation, bringing dopamine receptor stimulation back to a more consistent (physiological) level [27].

When taken early in the course of PD, the MAO-B inhibitor selegiline has been demonstrated to provide long-term benefit, with improvements in motor and activities of daily living scores lasting 6 to 7 years or more [28,29]. Rasagiline is an MAO-B inhibitor that was recently approved for the treatment of both early and severe Parkinson's disease [28,29]. Selegiline and rasagiline are both once-daily oral treatments, with selegiline also being accessible as an oral wafer. Inhibitors of monoamine oxidase B are generally well tolerated. Rasagiline, unlike selegiline, contains no amphetamine metabolites, which could explain why it has such a minimal risk of cognitive side effects [29,30].

IV. CONCLUSION

The improvement of powerful preventive or therapeutic treatments for PD has been amazingly difficult. The causes may include added substance or blocking factors, including a restricted comprehension of the systems of neurodegeneration in PD, the heterogeneity of the pathology, and the absence of satisfactory creature models. Additionally, the clinical adequacy of precaution treatments has been trying to evaluate because of the restrictions in preliminary plans and considering the shortfall of solid biomarkers to analyze the pathology at beginning phases before irreversible neuronal harm happens. Regardless of the current limitations, achievement in forestalling or ending the improvement of PD ought to be conceivable because of the consistent appearance of new demonstrative strategies and the current huge advances in quality treatment and other remedial methodologies in the field of nervous system science and neuroscience.

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