International Journal of Pharmaceutical Research and Applications
Volume 8, Issue 1 Jan-Feb 2023, pp: 491-497 www.ijprajournal.com ISSN: 2249-7781

Recent advancement in treatment of Parkinson Disease:- A critical review

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Submitted: 05-01-2023 Accepted: 13-01-2023

ABSTRACT
According to experts, one of the most complicated disorders seen in clinical medicine is Parkinson's disease (PD). The mainstay of therapy, long-term dopaminergic medication, calls for ongoing calibration and may also require supplementary pharmacological, behavioural, and surgical treatment. Numerous motor and no motor PD symptoms might make a diagnosis difficult and provide treatment difficulties. There is presently no cure for Parkinson's disease, however a number of medications can help manage the motor symptoms. While these medications can significantly enhance motor function, they can also have unfavourable side effects, especially as the condition worsens. The medications that are currently used to treat PD are the main topic of this chapter, together with a description of their mechanism of action, clinical value, and side effects. We also discuss several intriguing, recently developed methods that are being looked into.

Keywords: Levo-Dopa, Dopamine, inflammasomes, Parkinsonism

I. INTRODUCTION

Parkinson is a chronic neurodegenerative condition that primarily affects the motor system. Typically, symptoms appear gradually, and as the condition progresses, non-motor symptoms increase in frequency. [1] [5] Tremor, stiffness, slowness of movement, and trouble walking are the most noticeable early signs. In addition to behavioural and cognitive issues, many patients with Parkinson's disease experience sadness, anxiety, and apathy. [11] As the condition progresses, dementia caused by Parkinson's disease becomes more prevalent. Parkinson's patients may also experience issues with their sleep and sensory systems. [1] [2] The disease's motor symptoms are caused by a dopamine shortage brought on by cell loss in the substantia nigra, a midbrain area. [1] Unfolded proteins accumulate as Lewy bodies in the neurons, which is thought to be the cause of this cell death. [12] [5] The primary motor symptoms are collectively referred to as parkinsonism or a parkinsonian condition. [5] Although the exact aetiology of Parkinson's disease is unknown, it is thought that a mix of hereditary and environmental factors are responsible. [5] Certain genes are known to be inheritable risk factors for the condition, which increases the risk for those who have a family member with the disease. [13] Pesticide exposure and past head traumas are important environmental risk factors. Smokers, tea drinkers, and coffee drinkers all have a lower risk. [5] Symptoms, particularly motor symptoms, are the primary basis for diagnosis in typical instances. To help rule out other disorders, tests like neuroimaging (such as magnetic resonance imaging or imaging to look at dopamine neuronal dysfunction known as a DaT scan) can be utilised. [15] [1] About 1% of those over the age of 60 who have Parkinson's disease experience it on a regular basis. [1] [4] Males are afflicted more frequently than females, at 3:2. [5] Early-onset PD is the term used to describe it when it affects persons under the age of 50. [16] By 2015, PD has killed roughly 117,400 individuals worldwide and impacted 6.2 million people. [8] [9] by 2030, the number of patients with PD who are over fifty is anticipated to increase. [17] After diagnosis, the typical life expectancy ranges from 7 to 15 years. [2]

Treatment for PD seeks to lessen the consequences of the symptoms as there is no known cure. [1] [18] Levodopa (L-DOPA), MAO-B inhibitors, or dopamine agonists are frequently used as the first line of therapy for Parkinson's disease. These drugs produce a side effect known

International Journal of Pharmaceutical Research and Applications
Volume 8, Issue 1 Jan-Feb 2023, pp: 491-497 www.ijprajournal.com ISSN: 2249-7781

as involuntary muscular movements, but as the condition worsens, they become less effective. [2] At that point, drug combinations and dosage adjustments are both possible. [15] Diet and some rehabilitation techniques have shown some promise in relieving symptoms. In extreme situations where medications are inadequate, surgery to implant microelectrodes for deep brain stimulation has been performed to lessen motor symptoms. [1] Treatments for PD symptoms unrelated to mobility, such sleep issues and mental issues, have less solid scientific support. [5]

1.1 Pathophysiology

The primary pathogenic features of PD include cell death in the basal ganglia of the brain, which towards the end of life can impact up to 70% of the dopamine-secreting neurons in the substantia nigra pars compacta. [19] Alpha-synuclein clumps together with other alpha-synuclein when it develops a misfolded state in Parkinson's disease. Because the clumps can't be broken up by the cells, the alpha-synuclein becomes cytotoxic and harms the cells. [20] Lewy bodies are the aggregates that may be observed in neurons under a microscope. The death of astrocytes, which are star-shaped glial cells, and a marked rise in the density of microglia, another kind of glial cell, occur simultaneously with the loss of neurons in the substantia nigra. [21] The evolution of the PD-affected brain regions is explained by Braak staging.

The basal ganglia are connected to other brain regions through five main routes. They go under the names motor, oculomotor, associative, limbic, and orbit frontal circuits, with each term denoting the circuit's primary projection region. Since these circuits are involved in a range of processes, including movement, attention, and learning, they are all damaged in PD, and their disruption explains many of the symptoms of the condition. The motor circuit has undergone the most thorough scientific analysis. [22]

Since 1980, a specific conceptual model of the motor circuit and how it changes with Parkinson's disease (PD) has had a significant impact, despite numerous drawbacks that have forced changes. According to this theory, the basal ganglia generally have an inhibitory effect that prevents a variety of motor systems from being active when they should not be. When a choice is made to carry out a certain action, the needed motor system's inhibition is lowered, freeing it up for activation. High levels of dopamine function tend to stimulate motor activity, whereas low levels of dopamine function, as those found in PD, need higher effort for each movement. Dopamine serves to aid this release of inhibition. Dopamine depletion thus ultimately results in hypokinesia, a general decrease in motor output. Contrarily, medications used to treat PD may result in excessive dopamine activation, allowing motor systems to fire at the wrong times and leading to dyskinesias. [22]

1.2.1 Brain cell death

Several hypothesised processes might cause the loss of brain cells. [88] Alpha-synuclein that is linked to ubiquitin abnormally accumulates in the injured cells as one way. Lewy bodies, which are accumulations of this insoluble protein within neurons, are formed. [23] Lewy bodies first occur in the olfactory bulb, medulla oblongata, and pontine tegmentum, according to the Heiko Braak staging, a categorization of the illness based on pathological findings. Individuals at this stage may be asymptomatic or may have early nonmotor symptoms (such as loss of sense of smell, or some sleep or automatic dysfunction). Lewy bodies form in the substantia nigra, various regions of the midbrain and basal forebrain, and eventually the neocortex as the condition worsens.

These areas of the brain are the primary sources of neuronal degeneration in PD, yet Lewy bodies might not really kill cells and instead serve a protective function (with the abnormal protein sequestered or walled off). The hazardous forms of alpha-synuclein may really exist in other forms of the protein, such as oligomers, which do not assemble into Lewy bodies and Lewy neuritis. Lewy bodies are often seen throughout cortical regions in dementia patients. The hallmarks of Alzheimer's disease, neurofibrillary tangles and senile plaques, are uncommon unless the patient is severely demented. Dysfunction of the proteasomal and lysosomal systems and decreased mitochondrial activity are two additional cell-death pathways. Protein inclusions are frequently seen in association with iron buildup in the substantia nigra. The processes are unclear, however they might be connected to neuronal death, protein aggregation, and oxidative stress.

1.2.2 The neuroimmune connection

The pathogenesis of PD is significantly influenced by the neuroimmune interaction. Numerous biological mechanisms and genetic variants are shared by PD and autoimmune diseases. According to one study, certain

International Journal of Pharmaceutical Research and Applications
Volume 8, Issue 1 Jan-Feb 2023, pp: 491-497 www.ijprajournal.com ISSN: 2249-7781

autoimmune conditions can potentially raise a person's chance of having PD by up to 33%. PD is connected to autoimmune disorders that have been related to the protein expression patterns of monocytes and CD4+ T cells. There is some proof that Herpes virus infections can cause autoimmune responses to alpha-synuclein, possibly due to viral protein mimicry. Microglia can attach to alpha-synuclein and Lewy bodies, which are formed when it aggregates. When alpha-synuclein binds to the MHC receptors on inflammasomes, it can cause the overactivation and proliferation of microglia and the production of proinflammatory cytokines such IL-1, IFN, and TNF. Additionally, activated microglia have an impact on astrocyte activation, changing their neuroprotective phenotype to a neurotoxic one. In a healthy brain, astrocytes function to safeguard neural connections. In those with Parkinson's disease, astrocytes are unable to shield the striatal dopaminergic synapses. T cells are also given antigens by microglia via MHC-I and MHC-II. As a result of this process, CD4+ T cells become activated and can pass across the blood-brain barrier (BBB) to produce additional proinflammatory cytokines including interferon-(IFN), TNF, and IL-1. BBB collapse in PD is also associated with mast cell degranulation and consequent proinflammatory cytokine release. Peripheral monocytes, another immune cell linked to PD, have been discovered in PD patients' substantia nigra. More deterioration of dopaminergic connections may result from these monocytes. Furthermore, high levels of pro-inflammatory cytokines, such IL-6, can cause the liver to produce C-reactive protein, a protein that is frequently seen in PD patients and which can enhance peripheral inflammation. The gut-brain axis, a region of the body heavily linked to Parkinson's disease, can also be impacted by peripheral inflammation. Years before motor impairments appear, PD patients frequently have changed gut flora and gastrointestinal disorders. The gut produces alpha-synuclein, which may go through the vagus nerve to the brainstem and subsequently to the substantia nigra. Furthermore, greater levels of alpha-synuclein and an increase in motor symptoms in PD patients have been linked to the bacterium Proteus mirabilis. [24]

Furthermore, greater levels of alpha-synuclein and an increase in motor symptoms in PD patients have been linked to the bacterium Proteus mirabilis. To comprehend the catastrophic progression of PD, it is necessary to further clarify the causative roles of alpha-synuclein, inflammation, the gut-brain axis, and individual variability in immunological stress responses.

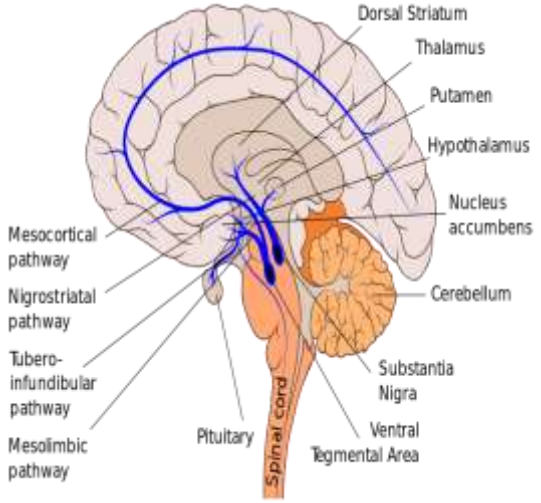

Fig 1 An illustration of the dopamine pathways throughout the brain

1.2.3 Management

Parkinson's illness currently has no recognised cure. When compared to therapies for other neurological conditions including Alzheimer's disease, motor neuron disease, and Parkinson-plus syndromes, medications, surgery, and physical therapy are significantly more likely to relieve symptoms, enhance a person's quality of life, and help. [25] Levodopa is always paired with a dopa decarboxylase inhibitor, and on occasion, a COMT inhibitor, as well as dopamine agonists and MAO-B inhibitors. These medication families are the most effective for treating motor symptoms. Whichever group is most beneficial depends on the illness stage and the age at which the sickness first manifests. Early, medium, and late phases of PD can be distinguished using the six stages of Braak staging. Later stages associated with the emergence of complications related to levodopa usage are followed by a third stage where symptoms unrelated to dopamine deficiency or levodopa treatment may predominate after the initial stage, in which some disability has already developed and requires pharmacological treatment. [26] The initial stage of treatment looks for the best possible trade-off between symptom management and adverse effects. Levodopa treatment can be delayed by first utilising other drugs, such as MAO-B inhibitors and dopamine agonists, in an effort to delay the onset of side effects brought on by levodopa use. [27] However, levodopa continues to be the best therapy for the motor symptoms of PD and should

International Journal of Pharmaceutical Research and Applications
Volume 8, Issue 1 Jan-Feb 2023, pp: 491-497 www.ijprajournal.com ISSN: 2249-7781

not be postponed in patients whose quality of life is compromised. Levodopa-related dyskinesias are more strongly correlated with the duration and severity of the illness than with the length of the levodopa treatment, therefore postponing this medication could not result in much more time without dyskinesias than starting it early.

In later phases, reducing PD symptoms is the goal, and drug effect fluctuations are managed. It's important to control pharmaceutical usage or abrupt withdrawals. Surgery, deep brain stimulation or more recently high-intensity focused ultrasound, subcutaneous waking-day apomorphine infusion, and enteral dopa pumps may be helpful when oral drugs are unable to treat symptoms. The issues presented by late-stage Parkinson's disease (PD) necessitate a range of therapies, including those for psychological symptoms, in particular depression, orthostatic hypotension, bladder dysfunction, and erectile dysfunction. [28] Palliative care is given to patients in the latter stages of their illness to enhance their quality of life.

1.2.4 Medications

Levodopa

Reduced dopamine synthesis in the basal ganglia of the brain is what causes the movement symptoms of Parkinson's disease (PD). Dopamine cannot be administered as a medication to replenish the brain's low levels of dopamine because it cannot penetrate the blood-brain barrier, but levodopa may. Levodopa can cross the blood-brain barrier and enter the brain, where it is easily converted to dopamine. For more than 40 years, levodopa has been the most frequently used medication for PD. [29]

Levodopa only penetrates the blood-brain barrier in 5–10% of cases. The majority of the remaining substance gets converted to dopamine somewhere else in the body, which has a number of negative consequences like nausea, vomiting, and orthostatic hypotension.

Levodopa only penetrates the blood-brain barrier in 5–10% of cases. The majority of the remaining substance gets converted to dopamine somewhere else in the body, which has a number of negative consequences like nausea, vomiting, and orthostatic hypotension. [30] Dopa decarboxylase inhibitors such as carbidopa and benserazide, which do not cross the blood-brain barrier, prevent levodopa from being converted to dopamine outside the brain. This lessens adverse effects and increases the amount of levodopa that is available for entry into the brain. Levodopa and one of these medications are frequently given together in the same tablet.

COMT inhibitors

Affected individuals with PD may experience a wearing-off phenomena, in which their symptoms return after taking a dosage of levodopa but just before taking their subsequent dose. Levodopa is broken down by the protein catechol-O-methyltransferase (COMT) before it can pass the blood-brain barrier, but these inhibitors allow more levodopa to do so. [31] They can be used in conjunction with levodopa or carbidopa when a person is experiencing the wearing-off phenomena along with their motor symptoms, although they are often not utilised in the therapy of early symptoms.

Opicapone, entacapone, and tolcapone are three COMT inhibitors that can be used to treat people with PD and end-of-dose motor irregularities. Tolcapone has been around for a while, but due to potential problems that might cause liver damage, its usefulness is constrained, necessitating liver function monitoring. It has not been demonstrated that entacapone or opicapone significantly impair liver function. Entacapone can be found alone or in combination with carbidopa and levodopa in authorised formulations. A once-daily COMT inhibitor is opicapone.

Dopamine agonists

Levodopa-like effects are shared by a number of dopamine agonists that bind to dopamine receptors in the brain. These are now primarily used on their own as the first therapy for the motor symptoms of PD with the goal of delaying the initiation of levodopa therapy, thereby delaying the onset of levodopa's complications. Initially, these were used as a complementary therapy to levodopa for people experiencing levodopa complications (on-off fluctuations and dyskinesias); they are now primarily used on their own as the first therapy for the motor Bromocriptine, pergolide, pramipexole, ropinirole, piribedil, cabergoline, apomorphine, and lisuride are examples of dopamine agonists.

MAO-B inhibitors

The basal ganglia contain more dopamine because monoamine oxidase B, an enzyme that breaks down dopamine, is inhibited by MAO-B inhibitors including safinamide, selegiline, and rasagiline. When administered as monotherapy (all

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Volume 8, Issue 1 Jan-Feb 2023, pp: 491-497 www.ijprajournal.com ISSN: 2249-7781

by themselves), they have been shown to aid in the relief of motor symptoms; when combined with levodopa, they shorten the duration of the off phase. Levodopa start-up time has been demonstrated to be delayed by selegiline, indicating that it may be neuroprotective and reduce the course of the illness (but this has not been proven). Initial research claimed that using selegiline with levodopa doubled the chance of mortality, however this has now been debunked.

II. METHOD

Gene therapy

Gene therapy often uses a viral vector, such as the adeno-associated virus, to deliver genetic material into a specific area of the brain. There have been several methods tested. These methods include the production of growth factors (including neuroturin, a member of the GDNF family), as well as enzymes like glutamic acid decarboxylase (GAD), tyrosine hydroxylase (the enzyme that creates L-DOPA), and catechol-O-methyl transferase (COMT – the enzyme that converts L-DOPA to dopamine). The techniques have mainly failed in phase 2 clinical studies, although there have been no documented safety problems. [32] In phase 2 studies in 2011, the administration of GAD had promise, however it lagged behind DBS in terms of enhancing motor function.

Neuroprotective treatments

Affiris, an Austrian business, produced PD01A, a vaccine that stimulates the human immune system to eliminate alpha-synuclein. It started clinical trials, and a phase 1 report in 2020 indicated safety and tolerability. In stage I studies in 2018, an antibody called PRX002/RG7935 provided early safety data that supported the continuation of stage II trials. [33]

Cell-based therapies

Since the early 1980s, dissociated cells from foetal, porcine, carotid, or retinal tissues have been injected into the substantia nigra in the hopes that they may integrate into the brain in a way that will replace the lost dopamine-producing cells. Dopaminergic neurons produced from induced pluripotent stem cells have essentially taken the place of these tissue sources as a more practical supply of tissue. Transplants of mesencephalic dopamine-producing cells appeared to be advantageous at first, but double-blind studies have not yet established a sustained effect. [34] Another noteworthy concern was the transplanted tissue's excessive dopamine release, which resulted in dyskinesia.

Pharmaceutical

There have been efforts to investigate adenosine receptor antagonists, especially A2A antagonists, as potential new Parkinson's treatment options. 2019 saw the approval of istradefylline for medical usage in the United States, making it the most effective of these drugs. [35] As a supplement to the levodopa/carbidopa regimen, it is authorised.

III. DISCUSSION

In order to treat Parkinson's disease (PD), there are currently three main surgical options: (1) ablative surgery (such as pallidotomy and thalamotomy); (2) deep brain stimulation (DBS) of the thalamus, internal globus pallidus (GPi), and subthalamic nucleus (STN); and (3) grafting foetal mesencephalic cells into the striatum. Surgery has regained top priority in the treatment of PD as a result of improved knowledge of the biology of the basal ganglia and the discovery that it may relieve experimental parkinsonism. There is presently no cure for Parkinson's disease, however a number of medications can help manage the motor symptoms. While these medications can significantly enhance motor function, they can also have unfavourable side effects, especially as the condition worsens. The medications that are currently used to treat PD are the main topic of this chapter, together with a description of their mechanism of action, clinical value, and side effects. We also discuss several intriguing, recently developed methods that are being looked into.

IV. CONCLUSION

Clinical examinations are used to diagnose PD; there is no evidence that particular tests increase diagnostic precision. There is no proof that the therapeutic benefits of various dopamine agonists (DAs) vary. In early PD, treatment with DAs with levodopa (L-dopa) may be able to better control PD symptoms than treatment with L-dopa alone, according to meta-analysis, albeit this was not always the case. The combination treatment consisting of L-dopa + selegiline did not consistently improve symptom management compared to L-dopa taken alone. Although long-term (greater than 7 months) results are lacking, and hepatotoxicity is a rare but potentially fatal side effect associated with tolcapone, treatment with catechol O-methyl transferase (COMT) inhibitors

International Journal of Pharmaceutical Research and Applications
Volume 8, Issue 1 Jan-Feb 2023, pp: 491-497 www.ijprajournal.com ISSN: 2249-7781

combined with L-dopa provides significantly greater PD symptom control than treatment with L-dopa alone and is associated with lower L-dopa doses.

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