WORLD JOURNAL OF PHARMACEUTICAL RESEARCH
Coden USA: WJPRAP Impact Factor 8.63
Volume 15, Issue 9, 296-320. Review Article ISSN 2277–7105

AN OVERVIEW OF PARKINSON'S DISEASE TREATMENT AND IT'S STRATEGIES

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Article Received on 02 April 2026,
Article Revised on 23 April 2026,
Article Published on 01 May 2026,

https://doi.org/10.5281/zenodo.19874917

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How to cite this Article: Soujanya Munegowda[1]*, Alfiya[2], Priyanka Anjinappa[3]. (2026). An Overview of Parkinson's Disease Treatment and It's Strategies. World Journal of Pharmaceutical Research, 15(9), 296–320.

ABSTRACT

Parkinson's disease (PD) is a neurological condition that typically manifests between the age of 55 and 65. The entire quality of life is significantly impacted by the increasing development of both motor and non-motor symptoms. Although there isn't a cure, a number of therapies have been created to assist control Parkinson's disease symptoms. The discipline of Parkinson's disease (PD) management is expanding and focuses on both novel and improved therapeutic approaches. Physicians can now address patient-specific issues as they emerge in addition to the primary motor symptoms of Parkinson's disease (PD) thanks to pharmaceutical, surgical and therapy interventions. But the therapeutic approach to this condition should incorporate both pharmacological and non-pharmacological strategies. Therefore, in order to improve these treatments and consequently, the patient's quality of life, further research into the biology of the condition is required. The established and novel options for treating Parkinson's disease (PD) that can offer patient-specific care and lessen the negative effects of standard therapies are covered in this review.

KEYWORDS: Parkinson's disease, Parkinson's treatment, substantia nigra, basal ganglia, Lewy bodies, a- synuclein, dopamine, levodopa.

INTRODUCTION

The clinical syndrome delineated by James Parkinson in 1817 ‘Essay on the shaking palsy, commonly known as ‘Parkinson’s disease’ (PD), is characterised by the principal features of resting tremor, bradykinesia, rigidity and posturalin stability alongside a range of additional motor and non- motor symptoms.[1-3] Parkinson's disease (PD) is a neurodegenerative condition brought on by the loss of a particular kind of neuron that is essential to the brain's synthesis of dopamine.[1,2] Lewy bodies, which are intracellular protein aggregates and the loss of dopaminergic(DA) neurons in the substantianigra parscompacta (SNpc) are the pathological hallmarks of the illness. Genetic mutations, environmental exposures, mitochondrial dysfunction, oxidative stress, neuro inflammation and compromised protein homeostasis are all part of the complex pathophysiology of Parkinson's disease (PD). Leucine-rich repeat kinase 2 (LRRK2) and glucosyls-amidase (GBA1) mutations are among the genetic risk factors. Parkinson's disease (PD) is the second most common neuro degenerative disease, affecting 0.2% of the world's population, 1% of those over 60 and up to 4% of those over 80. Its frequency is increasing exponentially, particularly in men.[3-6] With a long-term frequency of up to 80%, PD patients have a risk of dementia that is 6–8 times higher than that of aged- matched controls.[7] Although the exact origin of Parkinson's disease (PD) is unknown, environmental and genetic factors are thought to be involved. Age is still the primary risk factor for Parkinson's disease (PD), despite the fact that its etiology is frequently unknown. Although 5% of PD patients are thought to have a hereditary component, the majority of cases have random origins. Parkinson's disease (PD) is most commonly caused by the genetic mutation parkin. 15% of instances of late Parkinson's disease (PD) and 50% of cases of early PD (less than 45 years old) have this autosomal recessive mutation.[8] Furthermore, exposure to pesticides, herbicides, insecticides, solvents, fertilizers and other agricultural-related environmental variables has been linked to the development of Parkinson’s disease.[9] However, some research indicates that drinking alcohol, caffeine or tobacco, staying hydrated and living in a rural area are linked to a decreased risk of Parkinson's disease.[10] The length of time it takes to identify Parkinson's disease (PD) is one of the biggest barriers to stopping its progression. The most noticeable symptom, tremors, might develop years after the disease first manifests. Indeed, it has been suggested that the preclinical stage of Parkinson's disease (PD) may last an average of 15 years.[11] The most well-known sign of the illness, tremors in the limbs, is typically used to make the diagnosis. When 50–70% of nigrostriatal dopaminergic activity is compromised, certain motor symptoms appear. Nevertheless, 30–40% of patients do not exhibit tremor,

which could lead to half of PD cases remaining misdiagnosed.[12] Furthermore, because of the rising frequency in an ageing population, it is predicted that number of affected individuals will double over the next 30 years.[13] In Europe, the annual cost per patient treated is EUR 3910[14], while in the USA, it is USD 4551.[15] The emergence of new deep- stimulation therapies, which have significant upfront costs (32,363euros) but subsequently lower treatment expenses to EUR 1295 per patient, may cause this statistic to shift in the years to come.[14] PD is defined by extremely specific motor symptoms, such as tremor, rigidity, bradykinesia, inability to initiate voluntary movements and postural instability, due to the death of dopaminergic neurons. Other non-motor characteristics of Parkinson's disease (PD) include Autonomic dysfunction, mood disorders, sleep problems, cognitive impairment, gastrointestinal symptoms and pain, even though these symptoms are the most typical.[16,17] The typical age at which Parkinson's disease (PD) symptoms first appear was thought to be in the late 50s, but as the average age has increased, the average age at which symptoms first appear has risen to the sixties.[18–20] There is presently no therapeutic treatment to cure Parkinson's disease (PD) and all current medications are designed to reduce symptoms. The majority of current PD treatments are symptomatic and concentrate on using pharmaceuticals or neurosurgical procedures to restore DA signaling. Although these methods significantly reduce motor symptoms, they neither stop neurodegeneration nor alter the course of the illness. Additionally, side effects and motor changes frequently hamper long-term treatment underscoring the critical need for disease-modifying and restorative approaches. Recent developments in immunology, molecular biology and regenerative medicine have produced intriguing experimental treatments that target key disease mechanisms. These include gene therapies to address or reduce genetic risk factors, immune therapies against a-synuclein (α-syn) and cell replacement techniques utilising DA neurones produced from foetal or pluripotent stemcells (PSC). When combined, these new approaches provide hope for both better symptom management and changing the course of Parkinson's disease. This review emphasises recent advancements in stem cell-based regenerative therapies and disease-modifying interventions while summarizing the present status of clinical therapies for Parkinson's disease. Understanding the physiology of Parkinson's disease (PD) (the neuronal pathways of the SN) essential to comprehending the pathophysiology under pinnings of PD. For a long time, the primary motor symptoms of Parkinson's disease (PD) were thought to be caused by the gradual degradation of dopaminergic nerve cells in the substantia nigra (SN). Recent scientific and clinical findings, however, indicate that this is really a small part of Parkinson's disease. Therefore, the term "Parkinson's disease" currently refers to three stages:

the preclinical phase, when the neurodegenerative process has started but is not yet causing any symptoms; the prodromal phase, when the progression of neurodegeneration in various regions of the peripheral nervous system(PNS) and central nervous system(CNS) is causing noticeable symptoms; and the clinical phase, when the classic motor symptoms are prominent enough to be diagnosed with PD. Therefore, without a significant loss of dopaminergic neurones in the brain, the disease's initial symptoms may appear before the start of typical motor symptoms.[21] Lewy bodies have been seen in the cortex, amygdale, locus ceruleus, vagal nucleus and peripheral autonomic nervous system in addition to the SN. This may be a contributing factor to non-motor symptoms. The brain's five primary routes link the basal ganglia to other cerebral regions. The names of these circuit pathways—motor, oculomotor, associative, limbic and orbitofrontal—indicate the primary projection area of each circuit. In advanced stages of Parkinson's disease, all of these pathways are impacted and the disease's symptoms are explained by their dysfunction.[22] The definition of the motor control circuits of the basal ganglia has made it possible to understand the motor symptomatology of Parkinson's disease. Sensory afferent data from the cerebral cortex and SN pars compacta converge in the striatum (caudate nucleus and put amen). In terms of the efferent, the globus pallidus and the substantia nigra reticularis serve as the basal ganglia's departure route. If the GABAergic neurones of the striatum (the caudate nucleus and putamen) inhibit the neurones of the reticular SN and globus pallidus the cells of the thalamus and superior colliculus avoid tonic inhibition. This happens when the cerebral cortex and SN pars compacta give an order to perform a voluntary movement.[23,24] Degeneration of dopaminergic neurons in the SN pars compacta disrupts the signaling system and deregulates voluntary movement execution, resulting in involuntary movements at rest that precisely characterize Parkinson's disease symptoms.[25]

General risk factors

Studies have connected beliefs about the PD pandemic to both genetic and environmental factors.[26] According to these hypotheses, PD may be linked to neurotoxins, chemical interactions and genetic sensitivity or propensity. Environmental factors that are positively correlated with Parkinson's disease (PD) include head injuries, rural living, pesticides, anxiety and/or depression and consumption of dairy products on the other hand, physical inactivity, smoking, coffee and/or alcohol consumption and serum uric acid concentration are reported to have an inverse relationship with PD.[27] The degree of heredity is hotly contested, despite the fact that familial factors undoubtedly contribute to this illness. As of right now, six

extensive meta-analysis studies have connected 41 distinct genetic loci to the pathophysiology of Parkinson's disease. The first PD-related gene, α-synuclein (SNCA), was discovered in 1997 as a result of early twin research and the identification of many families displaying a Mendelian inheritance pattern (dominant and recessive). Ten year later, an autosomal recessive type of Parkinson's disease (PD) was related to a mutation in Parkin (PRKN).44 We prefer the International Parkinson and Movement Disorders Society's classification using the gene names because the nomenclature of giving these genes a PARK" number has proven confusing.

General Symptoms

Parkinson's disease's primary symptoms have an impact on movement**:** Tremor or shaking, typically starts in the hand or arm and is more likely to happen when the limb is relaxed and at rest. Bradykinesia or slowness of movement, is a condition in which physical movements are significantly slower than usual. This can make daily tasks challenging and result in a characteristic slow, shuffling walk with very small steps. Muscle stiffness, also known as rigidity, is tension and stiffness in the muscles that can cause excruciating cramping (dystonia) and make it difficult to move and produce facial expressions. Doctors occasionally refer to these primary symptoms as Parkinsonism.

Mental and cognitive symptoms are: Anxiety and depression mild cognitive impairment includes mild memory issues and difficulties with tasks requiring organization and planning. Dementia is a collection of symptoms that includes increasingly serious memory issues, personality changes, visual hallucinations (seeing things that are not there) and delusions (believing things that are false).

Pathophysiology

Neuronal loss in the substantianigra parcompacta, locus ceruleus and other neuronal populations is well known in human postmortem investigations.[28] According to the Braak hypothesis, early pathological alterations take place in the olfactory bulb and medulla oblongata (Braak stages 1and 2) before moving to the substantia nigra and midbrain (Braak stages 3 and 4) at which point clinical symptoms and signs are probably going to be present. In later stages, the cortical regions eventually become affected (Braak stages 5and 6). A detailed description of the several potential pathophysiologic mechanisms is outside the purview of this paper. However, a number of important molecular processes and hallmark have been repeatedly identified in human postmortem tissues, invitro human cell lines,

human brain or ganoids and animal models, regardless of the underlying etiologies (genetic, environmental, or other risk factors)(1A). These include oxidative stress, neuro inflammation, impaired protein clearance (including important ubiquitin-proteasome and autophagy-lysosomal systems), mitochondrial dysfunction and α-synuclein misfolding and aggregation. Numerous other interconnected events, such as disruption of vesicular transport, loss of microtubular integrity, neuronal excitotoxicity, disruption of trophic factors, dysregulation of the iron metabolic pathway, impairment of the endoplasmic reticulum, poly (ADP- ribose) polymerase and other enzymatic activation, are frequently linked to these major molecular and cellular hallmarks. Some have proposed that distal axons in the striatum may be the first site of neurodegeneration in Parkinson's disease (PD). Axonal mitochondria are especially sensitive and their malfunction can lead to decreased axonal transport.[29] In essence, each of these processes may encourage necrosis or programmed cell death (apoptosis). It is impossible to say with certainty whether these routes operate independently or converge to a single route to neuronal death because cellular processes are dynamic, neurodegeneration happens over an extended period of insults/stresses and several compensatory mechanisms are at action. A viscous cascade of insults and ultimately irreversible cellular damage are more likely to result from the intersection of the various pathophysiologic processes Parkinsonism. Mental and cognitive symptoms are: Anxiety and depression Mild cognitive impairment includes mild memory issues and difficulties with tasks requiring organisation and planning. Dementia is a collection of symptoms that includes increasingly serious memory issues, personality changes, visual hallucinations (seeing things that are not there), and delusions (believing things that are false).

We highlight some of the most important pathophysiologic mechanistic discoveries from research that could have therapeutic significance

1. When specific biochemical interactions occur, α-synuclein, which is naturally unfolded, takes on a tertiary structure. It has been discovered that aberrant protein aggregation is harmful to dopaminergic neurones causing neuro degeneration linked to Parkinson's disease. The structural alterations and aggregation of α-synuclein can be influenced by oxidative stress, PD gene mutations and over expression. The relative toxicity of the oligomeric and fibrillar species of α-synuclein has been disputed and it also appears in various forms and species based on experimental settings.[30] More significantly, some of these species have the ability to "seed" and disseminate α-synuclein disease from cell to cell, as well as trigger a there is increasing evidence that the gut-brain connection plays a

role in the pathophysiology of Parkinson's disease (PD), with the vagus nerves serving as a "highway" for aggregated α- synuclein to go from the gastrointestinal tract to the lower brainstem.[31]

A work demonstrating that isolates from Parkinson's disease patients caused motor abnormalities when transplanted into transgenic α-synuclein mice, with antibiotic therapy rescuing part of the problems and microbial decolonization aggravating the pathology, supports the gut-brain link. Additionally, a number of studies have demonstrated that appendectomy and vagotomy may lower the incidence of Parkinson's disease. To further understand how the gut microbiota, dysbiosis, infection and inflammation cause α-synuclein aggregation and spread to the central nervous system as a pathogenic pathway for Parkinson's disease, more research is required response. These findings serve as the foundation for treatment options, some of which have been incorporated into ongoing clinical trials. These tactics range from lowering the formation of oligomeric species and cellular transmission to limiting its expression.

2. Patients with Parkinson's disease (PD) have been shown to have reduced activity of mitochondrial complex 1, and using its inhibitor, such as rotenone, has been shown to cause mitochondrial damage in experimental PD models, including decreased mitochondrial potential, cytochrome c release, activation of the caspase cascade and eventual cell death. Similarly, the detrimental effects of several PD-related genes, such as Parkin, PINK1, and DJ1, have been linked to characteristics of mitochondrial dysfunction, including reduced mitophagy.[28,32,33] Additionally, researchers have demonstrated that mitochondrial damage increases oxidised dopamine accumulation and decreased glucocerebrosidase, indicating that dopamine is the common link between lysosomal dysfunction and α-synuclein accumulation.[29] Future mitochondrial focused and antioxidant treatment techniques will benefit from these investigations.

3. PD patients have been shown to exhibit both innate and adaptive immune response abnormalities, such as elevated pro-inflammatory cytokines and changed immune cell populations (such as monocytes and their progenitors). Sixty Clinical association studies that show a connection between autoimmune disorders and Parkinson's disease (PD), molecular imaging evidence of inflammatory cell activation (such as microglia), and characteristics of neuro inflammation in experimental PD models all corroborate this.

4. There is increasing evidence that the gut-brain connection plays a role in the pathophysiology of Parkinson's disease (PD), with the vagus nerves serving as a "highway" for aggregated α-synuclein to go from the gastrointestinal tract to the lower brainstem.[31] A work demonstrating that isolates from Parkinson's disease patients caused motor abnormalities when transplanted into transgenic α- synuclein mice, with antibiotic therapy rescuing part of the problems and microbial decolonization aggravating the pathology, supports the gut-brain link. Additionally, a number of studies have demonstrated that appendectomy and vagotomy may lower the incidence of Parkinson's disease. To further understand how the gut microbiota, dysbiosis, infection and inflammation cause α-synuclein aggregation and spread to the central nervous system as a pathogenic pathway for Parkinson's disease, more research is required.

TREATMENT

There's currently no cure for Parkinson's disease, but treatments are available to help relieve the symptoms and maintain your quality of life. The current pharmacological treatment is mainly based on the restoration of dopamine levels, with Levodopa considered the principle option. This dopamine precursor was breakthrough in the treatment of PD for reducing motor symptoms and improving quality of life of patients. Nevertheless, the administration of levodopa has limitations due to the occurrence of adverse reaction, with dyskinesia being one of the complications. Therefore current formulations of levodopa contain decarboxylase inhibitors, better known as carbidopa.

These treatments include

1) Medication

★Dopaminergic therapies such as Levodopa

Dopamine agonists

(e.g.: Rotigotine, Pramiprexole)

MAO-Binhibitors

(e.g.:Selegiline, Rasagiline) **COMT inhibitors**:

(e.g.:Entacapone, Opicapone)

★Non dopaminergic symptomatic therapies such as Anticholinergics

(eg: Amantadine, Benztropine, Trihexyphenidyl) Adenosine A2A receptor antagonist.

2) Surgical interventions

Deep brain stimulation

Lesion therapies

3) Supportive therapies such as

Physiotherapy Occupational therapy

Speech and language therapy

TREATMENT APPROACHES

Even though the precise origin of Parkinson's disease is still unknown, advances in treatment have been made. Since the disease has no known cure, treatments aim to control symptoms rather than stop or reduce the disease's course. Treatments can include medication, surgery, counseling or a mix of these. Additionally, they need to be modified as the illness progresses because several standard treatments, such L-DOPA, become less effective with time.[34] There is no disease- modifying or neuroprotective therapeutics available to delay the course of Parkinson's disease (PD), despite the fact that treatments with currently available medications have beneficial clinical benefits.[35] Therefore, when symptoms start to interfere with functioning or cause social humiliation, the patient and doctor decide when to start treatment. For first treatment, no medication is more effective than another; instead, the severity and beginning time of the condition must be considered.[36] Multiple neuronal pathways in the brain are impacted by Parkinson's disease (PD). L-DOPA may help with motor issues brought on by low dopamine levels, but it won't help with issues brought on by low acetylcholine in other routes. Every subtype also reacts to medications in a unique way. The doctor has the authority to select a treatment plan that is effective for each patient based on their symptoms and level of responsiveness.

1) DRUG TREATMENT

The three main categories of current therapeutic techniques include surgical operations, non dopaminergic (ND) symptomatic treatments and DA therapies.

Dopaminergic medications

The most effective anti-parkinsonian pharmaceutical now on the market, L-DOPA, continues to be the "gold standard" for PD therapy. Dopaminergic drugs are typically used to treat motor symptoms in Parkinson's disease. Dopaminergic drugs are used to assist raise or mimic dopamine levels since many Parkinson's disease symptoms, particularly movement-based

ones, are caused by a shortage of dopamine accessible for transmission in the nigrostratial pathway. The blood-brain barrier is difficult for dopamine to cross, although L-DOPA, its precursor, may.[37] Aromatic-L-amino-acid decarboxylase(AADC) and catechol-O-methyl transferase (COMT) metabolise it in the small intestine and transform it into dopamine, which can then be stored in the nigrostratial terminals. Dopamine agonists, on the other hand, directly affect post synaptic receptors, reducing the requirement for dopamine synthesis.[37] Eighty percent of people with idiopathic Parkinson's disease are responsive to L-DOPA, which lessens stiffness and bradykinesia. However, it is inadequate or useless in treating a number of common Parkinson's disease symptoms, including autonomic dysfunction, freezing, speech issues, posture and gait issues, cognitive abnormalities, emotional disorders, and sleep issues.[34] L-DOPA-related dyskinesia is a problem, as was previously highlighted about early-onset Parkinson's disease. Although the use of L-DOPA is associated with dyskinesia, the development of dyskinesia depends on both the disease (PD) and a pulsatile drug delivery. L- DOPA doesn't usually induce dyskinesia in Parkinsonism with post synaptic involvement and Pre-existing dyskinesia has been demonstrated to be lessened by intestinal gel administration. Therefore, rather than considering dyskinesia as an inherent impact of levodopa, it could be more fair to consider it as a consequence of the way levodopa is administered.[38] L-DOPA is preferred as an initial treatment for late-onset Parkinson's disease (PD) due to the increased risk of negative neuropsychiatric effects from dopamine agonists. Both forms of Parkinson's disease necessitate pharmaceutical modifications as the condition worsens. Patients who initially take dopamine agonists frequently need to switch to L-DOPA after two to five years, and L-DOPA also loses its efficacy over time.[34] Dopamine agonists can be used to treat non-motor symptoms like depression in addition to the motor symptoms of Parkinson's disease. For people with Parkinson's disease (PD), medications like pramiprexole are clinically beneficial and successful in treating depression and its symptoms. But not all dopamine agonists work; rotigotine, for instance, is in effectual and only being tested in real- world settings.[39] Other neurotransmitters beyond dopamine are used by the majority of medications that treat non-motor symptoms.[40] Dopamine agonist treatment for depression should be tailored to the patient's needs and the medicine itself.[39] L-DOPA is the "gold standard" for treating Parkinson's disease, although it has a number of drawbacks. Whether levodopa's symptomatic advantages are linked to neurotoxic consequences and long-term decline is uncertain. However, it has long-term issues, the most troublesome of which are wearing-off, dyskinesias, freezing episodes, and unpredictable "on- off" swings.[41] Forty to fifty percent of patients will experience dyskinesias and motor fluctuations after five years

of long-term L- DOPA therapy. That figure rises to 70%–80% of patients after ten years.[34] Due to varying dosage schedules and levodopa's brief half-life, L-efficacy also decreases in advanced Parkinson's disease.[34] Patients are frequently asked to take larger doses and more frequently; for instance, they may be asked to take a dose every two to three hours.[40] Dyskinesia presentation rises in tandem with the consequent increase in medication dosage. L - DOPA- induced alleviation of Parkinson's disease symptoms can also make it challenging to accurately assess the patient's true condition, making it harder to monitor the disease's progression. L-DOPA administration must be stopped for at least two weeks in order to assess the disease's development or decline. This option is impractical, particularly when Parkinson's disease is advanced. Positron emission tomography (PET) and single-photon emission computed tomography (SPECT) techniques have demonstrated strong associations with the overall severity of Parkinson's disease (PD), and the search for biological surrogate markers is on going.[41] Apart from discovering novel biological alternative, surrogate indicators, and improved L-DOPA use management are being researched. People with advanced Parkinson's disease (PD) require continuous dopaminergic stimulation, which can be supplied via deep brain stimulation as an alternative to oral L-DOPA and levodopa-carbidopa intestinal gel.[34]

For people with advanced Parkinson's disease (PD), levodopa-carbidopa intestinal gel, commonly known as Duodopa, is an alternative. Compared to oral L-DOPA, the intestinalgel exhibits less motor fluctuations and dyskinesias, while they are not entirely eliminated. A continuous dose of levodopa- carbidopa equal to the oral L-DOPA dose is administered by injecting the gel into the jejunum. Without worrying about decreased absorption, there is faster absorption.[34] "Off" periods are decreased and "on" periods are increased due to the medicines' continual release.[42] Ninety percent of patients experienced better quality of life in one research.[43] All patients who transitioned to levodopa-carbidopa gel injections saw improvements in their nocturnal sleep patterns, including improvements in motor symptoms, Parkinson’s disease symptoms, and sleep disturbances. Drowsiness during the day also decreased.[44] Other non-motor problems, such as attention, memory, gastrointestinal, urological and pain, have shown improvements.[45] When compared to other options for advanced Parkinson's disease, levodopa-carbidopa intestinal gel has the advantage of having no age restriction. The majority of adverse effects are caused by technical issues like duodenal catheter displacement, kinking, blockage and breakage.[42] Patients with Parkinson's disease (PD) who experience motor fluctuations may benefit from apomorphine, a non-

selective dopamine agonist that stimulates both D1 and D2 receptors. In terms of its ability to manage motor symptoms, it is the only antiparkinsonian medication that is similar to L-DOPA.[46] The requirement for verified levodopa-responsive Parkinson's disease (PD) limits the use of apomorphine; however it is not usually age-limited. For patients who experience "off" times, such as delay sin the effects of oral drugs like L-DOPA or "off" periods when waking up, apomorphine is an alternative. The most efficient and tolerable administration methods have been found to be intermittent or continuous infusion given subcutaneously.[46] For quick treatment from "off" variations and end-of- dose biphasic dyskinesia, intermittent infusion is injected by pen. A modified insulin pump is used to supply continuous infusion, which is often dispensed in a 12 to 16 hour schedule. However, it can be administered throughout the 24-hour period and does not need to be stopped at night. The "off" periods at night may be decreased as a result.[42] Nodules at the injection site, which can occur in as many as 70% of individuals, bruising, itching or soreness is examples of adverse side effects.

Compared to deep brain stimulation or levodopa-carbidopa intestinal gel, apomorphine is less intrusive, which is advantageous for people with severe Parkinson's disease.[46]

Patients with Parkinson's disease are thought to frequently suffer pain, which may be partially caused by central alteration of nociception. Dellapina et al.'s randomised, controlled, double-blind research of 25 PD patients[47] examined the effects of apomorphine against placebo on pain thresholds and pain-induced brain activity. When compared to a placebo, apomorphine did not significantly alter either subjective or objective pain thresholds or pain activation profiles. In conclusion, apomorphine has no effect on how PD patients process pain, which raises the possibility that additional monoamine systems are at play.[47]

Monoamine oxidase inhibitors, Catechol O-methyl transferase inhibitors and N-methyl D-aspartate receptor antagonist

In order to extend their effects, COMT inhibitors like entacapone and monoamine oxidase inhibitors (MAOIs) like rasagiline or selegiline block the breakdown of dopamine and L-DOPA. MAOIs lessen the amount of dopamine that is degraded at the synapse. COMT inhibitors stop COMT from turning L- DOPA into dopamine too soon. Before L-DOPA reaches the brain, it lessens peripheral loss.[34,37] Because MAOIs have less adverse effects, need fewer dosages, and might postpone the use of dopaminergic medications, patients with moderate symptoms may be treated with them first. They may also use in later stages to reduce specific symptoms such as tremors or dyskinesia unlike L-DOPA, MAOIs do not

require dosage increases over time; instead, they are administered 1-3 times daily for the duration of the illness.[40] Cognitive decline or hallucinations/ delusions linked to advanced or later stages of Parkinson's disease (PD) may be alleviated by treatment with cholinesterase inhibitors, such as rivastigmine.[41] Amantadine and memantine are examples of putative N-methyl-D-aspartate (NMDA) receptor antagonists that are used as supplements to other treatments.[34] They block NMDA and acetylcholine receptors, which has two effects: first, they work in concert with dopaminergic drugs to increase dopamine release and turn over instriatal neurones; second, Parkinson's disease (PD) interferes with glutamatergic transmissions, leading to an over activation of NMDA receptors, which can worsen dyskinesias.[48] Agonists lower the subthalamic nucleus's aberrant glutamate signaling levels.[48] When combined with regular doses of L-DOPA, amantadine was shown in one research to lower the severity of dyskinesia in advanced stage Parkinson's disease by 60%.[49] The sole FDA-approved drug for treating levodopa-related dyskinesia is amantadine extended release, which shortens the "off" period and increases the sustainability of L-DOPA therapy.[50] There are currently no medications that significantly improve symptoms including postural instability, dysphagia, dysphonia, dyskinesias and constipation that arise in the later stages of this illness.[41] An NMDA receptor agonist may have neuroprotective properties. By preventing glutamatergic - mediated excitotoxicity and promoting synaptogenesis and neurotrophic release, they can stop the course of illness.[48]

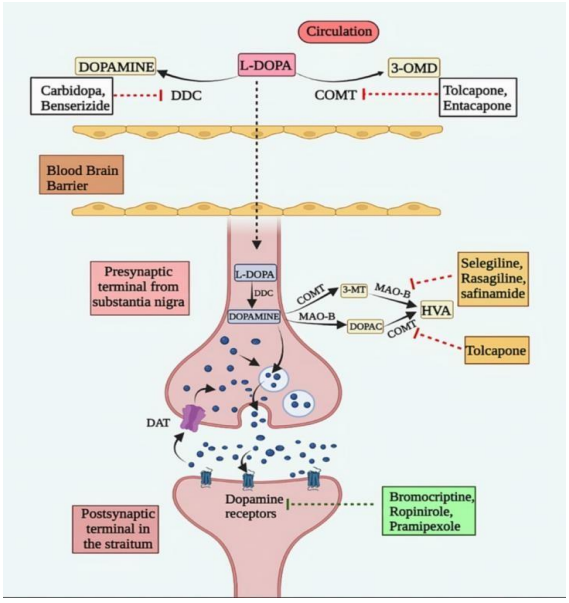
Non dopaminergic symptomatic therapy; Anticholinergics early on

Anticholinergics medications were the first pharmacological medicines employed in PD treatment.[51] By functioning as antagonists at choline receptors, they lower acetylcholine activity in an effort to restore the dopamine and acetylcholine balance that was upset by Parkinson's disease.[52] Although L-DOPA and other centrally acting dopaminergic agonists have essentially supplanted these medications, they are still used to treat Parkinson's disease.

This therapeutic class of medications includes benztropine, biperiden, diphenhydramine, ethopropazine, orphenadrine, procyclidine, and trihexyphenidyl however, due to their low plasma drug concentrations, limited pharmacokinetic data is known on them.[51,53] Anticholinergics medications can be used alone in the early stages of tremor-predominant Parkinson's disease (PD), but they are typically used in conjunction with L-DOPA or other prescription therapies.[52] This family of drugs is quickly absorbed by humans when taken orally. The oral bioavailability of the many medications in this class varies, ranging from

30% to 70%. These medications are widely distributed in both people and animals and their tissue dispersion happens quickly. These medications comparatively low clearance in relation to hepatic blood flow is one of their characteristics. These medications seem to be widely metabolised, primarily to hydroxylated and N-dealkylated metabolites.[51] Compared to younger people, older adults have lower tolerance to certain medications. Additionally, due to a higher risk of disorientation, these medications may be avoided in older people.[52] There is a death of pharmacokinetic data about these medications in the elderly because most studies have been limited to young, healthy volunteers who receive single doses. Additionally, the lack of knowledge regarding the administration of numerous doses and administration in the elderly may discourage PD patients from using these medications in a safe and competent manner.[51] It should be mentioned that although Anticholinergics are still an effective medication treatment, research on the pedunculopontine nucleus later dorsal tegmental complex (PPN) suggests that cholinergic therapy may be able to help manage mobility issues in Parkinson's disease.

Maintaining balance is a crucial function of the PPN, and PD patients may have decreased postural control and gait as a result of PPN dysfunction.[54] Anticholinergics medications may make falls more common in older people. Additionally, balance may deteriorate if CNS cholinergic neurones are lost. According to preliminary findings from a short, controlled investigation, PD patients who received the central cholinesterase inhibitor donepezil fell half as frequently as the control group.[55]



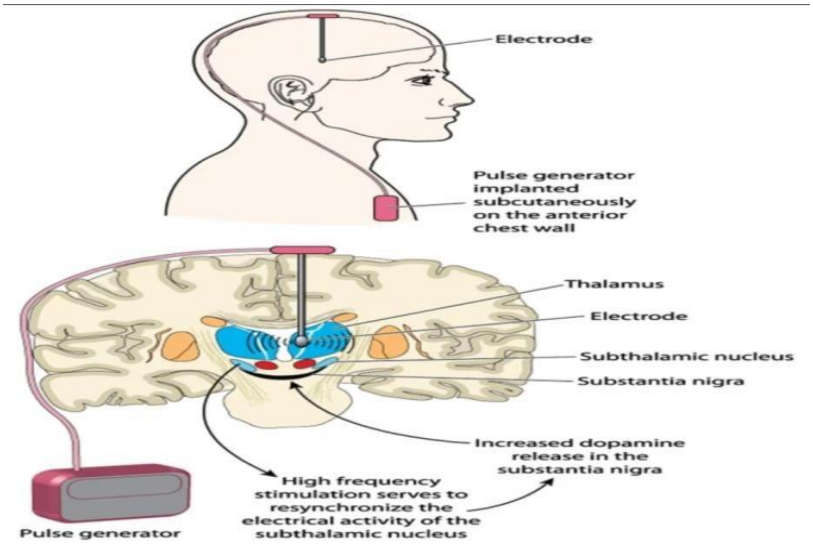
Mechanisms of action of drugs which are used in Parkinson's disease

2) SURGICAL INTERVENTIONS

The majority of patients with Parkinson's disease are treated with medicine, yet in certain instances, deep brain stimulation surgery is utilised. Although it's not appropriate for everyone, this procedure is also offered in specialized neuroscience facilities throughout the United Kingdom. Your specialist will go over the potential risks and advantages with you if surgery is being considered.

★ Deep brain stimulation

As a substitute for dangerous bilateral ablative operations, deep brain stimulation (DBS) was created. It is used in the thalamus, sub thalamic nucleus, and internal globuspallidus.[56] The mechanism and symptoms that DBS aims to alleviate are comparable to those of ablative procedures. The implants in conventional DBS deliver electrical impulses constantly and without feedback, making it an open-loop system.[57] It is an established treatment for advance stage PD, improving motor symptoms both in long and short term. DBS is useful in reducing "off" episodes, which are more common during the day in individuals with more advanced stages of medically treated Parkinson's disease. Both motor and non-motor symptoms, including problems with posture and gait, cognitive decline, sleep, swallowing and speech or micturition are affected in different ways.[58] Two of the most common DBS targets, the subthalamic nucleus (STN) and the globus pallidus pars interna (GPi), have shown similar motor improvements in controlled studies using large, randomised groups. However, after STN DBS, DA replacement medications can be reduced, while GPi DBS has fewer adverse effects on mood and cognition.[59] Additionally, research indicates that focusing on the pedunculopontine may help with freezing and gait instability.[60,61]



DBS improves levodopa - responsive symptoms of tremor, bradykinesia and rigidity in a manner comparable to the best responses of L-DOPA. Speech, balance and gait are unlikely to get better.[34] In actuality, dysarthria, imbalance and dyskinesia are adverse effects brought on by stimulation. A short battery life is another drawback.[62] DBS can be beneficial for at least ten years in certain cases, although there is no set amount of time that it is effective.[34] Deep brain stimulation side effects could include: cerebral haemorrhage. Tissue damage or death, skin fractures. The muscles twitch depression. Issues with speech or eyesight.

Lesion therapy

In order to disrupt maladaptive neural networks, lesioning or ablative operations (LS) selectively destroy a particular volume of brain tissue. Although LS has been used for many years in certain PD patients, its use declined in the 1960s following the advent of levodopa and again in the 1990s due to DBS. Since then, the field of LS has expanded and current methods include laser interstitial thermal therapy (LITT), MRI-guided high-intensity focused ultrasound (HIFU) thermal ablation (also known as MR-guided focused ultrasound, MRg FUS), radio frequency (RF) thermo ablation, and stereotactic radio surgery (SRS). The first three are frequently used in movement disorders.[63] Since SRS and HIFU do not require an intracranial probe or a burr hole, they are seen as less invasive than radiofrequency lesioning.

3) SUPPORTIVE THERAPIES

There are a number of therapies that can help you manage your symptoms on a daily basis and make life with Parkinson's disease simpler. There are initiatives in place to try and make these supportive therapies more accessible to Parkinson's patient on the NHS. You may be able to get guidance and assistance from your local government. Request a care and support needs assessment.

Physical therapy

PT is the most effective treatment for persons with Parkinson's disease (PD), aside from medication. It is essential to Parkinson's patients care and well-being. Single-pulse transcranial magnetic stimulation (TMS) studies have shown abnormalities in cortical silent period (CSP duration) and other corticomotor excitability measurements in Parkinson's disease (PD) patients. Voluntary exercise increases brain-derived neurotrophic factor (BDNF), which may improve neuronal function by promoting synaptogenesis and neurogenesis. Physical activity (PA) has been shown to be beneficial for people with Parkinson's disease (PD) in the majority of published reviews. Aerobic exercise can greatly

enhance motor action, balance, and gait parameters such as walking ability, stride length, and gait velocity in Parkinson's disease patients.[64,65] PT exercises that have been researched in relation to Parkinson's disease include yoga, dance, treadmill training, and the use of PT external cues.[66] Through exercise and movement (manipulation), a physiotherapist can help you relieve joint discomfort and stiff muscles. The physiotherapist's goals are to facilitate mobility and enhance your flexibility and gait. They also aim to raise your level of fitness and self-management skills.

Occupational therapy

Despite the availability of excellent medication and surgical therapy, patients with Parkinson's disease (PD) have a progressive development of both motor and non-motor impairments. The goal of occupational therapy is to support patients in continuing their employment, leisure, and self-care activities for as long as feasible. Occupational therapists may use scheduling, activity planning and physical environment adaptation as techniques.[67] Self-perceived performance improvement in everyday chores can result from home- based individual occupational therapy sessions.[68] An occupational therapist can pin point areas of your daily life where you struggle, such clothing yourself or going to the neighbourhood stores. They can assist you in coming up with workable solutions and make sure your house is secure and ready for you. This will enable you to continue being independent as long as possible.

Speech and language therapy

Upto 89% of PD patients have speech problems, although only 3%–4% of them undergo speech therapy.[69] Both one's quality of life and communication abilities may suffer as a result. The Lee Silverman Voice Treatment (LSVT) LOUD has been used to enhance communication abilities and vocal loudness. Research indicates that it may enhance not just loudness but also speech rate, intelligibility, quality, monotony, vocal fold adduction, swallowing, facial emotion, and brain activation.[70] Training improves the afore mentioned symptoms while concentrating on a particular parameter—in this example, loudness and self-perception of vocal loudness. LSVT/LOUD offers the possibility of single-target treatments, promoting cross-system enhancement and delivery methods consistent with brain plasticity principles.[71] Although research has been done on several forms of speech and language therapy, LSVT/LOUD is still the most common type. Novel variants have also been explored, but because to the small number of trials and patients, there is insufficient data to determine

whether these new versions are any more beneficial than LSVT/LOUD.[72] Modified versions that concentrate on factors like articulation have also been studied.

Diet advice

For some people with Parkinson's disease, making dietary changes can help improve some symptoms. These changes can include:

Increasing the amount of fiber in your diet and making sure you're drinking enough fluid to reduce constipation. Increasing the amount of salt in your diet and eating small, frequent meals to avoid problems with low blood pressure, such as dizziness when you stand up quickly.

DISCUSSION

In addition to a variety of non-motor symptoms, bradykinesia, stiffness, resting tremor, and postural instability are the primary motor symptoms of Parkinson's disease (PD), a chronic, progressive neurodegenerative illness. The main goals of treatment options for Parkinson's disease are symptomatic relief, decreasing functional deterioration, enhancing quality of life, and reducing treatment-related problems because there is presently no known cure. Long-term care necessitates a customised, inter disciplinary strategy that changes as the illness progresses. Pharmacological therapy, especially medications that increase dopaminergic activity in the brain, is the main stay of treatment for Parkinson's disease. Degeneration of dopaminergic neurones in the substantia nigra, which results in dopamine deficit in the striatum, is the pathological characteristic of Parkinson's disease. The best drug for managing motor symptoms, particularly bradykinesia and stiffness, is still levodopa, a precursor to dopamine. It is typically used in conjunction with a peripheral dopa-decarboxylase inhibitor, such as benderizine or carbidopa, which inhibits levodopa's peripheral metabolism and lessens adverse effects like nausea and hypotension. Long-term treatment of levodopa is linked to motor problems like wearing-off phenomena and levodopa-induced dyskinesias, which necessitate cautious dose changes and adjunct therapies even if it offers excellent symptomatic improvement. Dopamine agonists, such as rotigotine, ropinirole and pramiprexole are frequently used in the early stages of Parkinson's disease or as supplemental therapy in later stages because they directly stimulate dopamine receptors. When used in conjunction with levodopa, these medications can help lessen motor fluctuations and postpone the start of levodopa therapy in younger individuals. However, adverse problems include hallucinations, excessive daytime sleepiness, oedema and impulse control difficulties

restrict their use, especially in older individuals. By preventing dopamine breakdown in the brain, monoamine oxidase-B (MAO- B) inhibitors such safinamide, rasagiline and selegiline offer a slight improvement in symptoms. They can be combined with levodopa to lessen wearing –off effects, or they can be administered alone in the early stages of the disease. Levodopa's duration of action is extended by catechol-O-methyl transferase (COMT) inhibitors, such as entacapone and tolcapone, which decrease peripheral metabolism. In severe Parkinson's disease, these medications are especially helpful in controlling motor irregularities. Due to its negative cognitive and antimuscarinic effects, Anticholinergics medications like benztropine and trihexyphenidyl are typically saved for younger patients and are mostly useful for controlling tremors. The NMDA receptor antagonist amantadine reduces levodopa-induced dyskinesias and provides modest symptomatic relief. On-pharmacological treatments should be started as soon as possible because they are essential to the overall management of Parkinson's disease. Physiotherapy lowers the risk of falls and impairment by enhancing mobility, balance, posture, and gait. By using adaptive techniques and assistive technology, occupational therapy helps patients preserve their independence in everyday living activities. The management of dysarthria, hypophonia, and swallowing issues—all of which have a substantial influence on communication and nutrition—requires speech and language therapy. Since melancholy, anxiety and cognitive impairment are prominent non-motor symptoms of Parkinson's disease, psychological support and counseling are crucial. For certain individuals with advanced Parkinson's disease who have severe motor fluctuations or medication-resistant tremor, surgical treatment—in particular, deep brain stimulation or DBS—are a significant option. DBS improves motor control and lowers the need for medication by implanting electrodes in particular brain regions, such as the globus pallidus intern us or subthalamic nucleus. Although DBS can greatly enhance quality of life, people with severe dementia or untreated mental illnesses should not use it. An essential part of treating Parkinson's disease is managing non-motor symptoms. Pharmacological and behavioural therapy are among the focused interventions needed for autonomic dysfunction, sleep problems, pain, mood disorders, and cognitive decline. Although they are still mostly experimental, research has recently concentrated on gene therapy, neuroprotective drugs, disease-modifying tactics and stem cell-based methods. In order to achieve the best possible symptom control and improve the patient's quality of life throughout the course of the disease, treatment strategies for Parkinson's disease are complex and progressive, combining pharmaceutical therapy, rehabilitation, psychosocial support, and surgical interventions. In addition to medication and surgical treatments, supportive therapies are essential in the

management of Parkinson's disease. One of the most crucial supportive treatments for Parkinson's disease is physiotherapy. It aids in improving posture, balance, gait, muscle strength, and mobility—all of which are frequently impacted in patients. Frequent exercise and physical therapy improve walking patterns, lessen bradykinesia and rigidity, and lower the risk of falls. To improve motor function and sustain physical health, methods like stretching, balancing training, cueing techniques, and aerobic workouts are frequently employed also occupational, speech and language therapy and diet advice also helps in treatment of PD.

CONCLUSION

Since L-DOPA replaces dopamine in this neurodegenerative condition, it is still the most widely used medication for Parkinson's disease. L-DOPA is the most effective treatment for improving quality of life (QoL), especially as symptoms grow more in tolerable with other anti-parkinsonian drugs, even though other dopamine agonists are successful in reducing PD symptoms early in the disease's beginning. Although there isn't a known cure for Parkinson's disease (PD), it can be treated with different medications, surgeries, and supportive therapies. Additionally, new treatments are being developed to lessen the symptoms and adverse effects of this degenerative illness. For people who prefer more natural methods, physical, occupational, and speech therapies offer non-pharmacological substitutes that can be utilised independently or in addition to drugs. They can assist in treating certain symptoms as they appear. Greatly enhance quality of life, people with severe dementia or untreated mental.

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