EUROPEAN JOURNAL OF BIOMEDICAL AND PHARMACEUTICAL SCIENCES
http://www.ejbps.com

ISSN 2349-8870
Coden USA: EJBPBO
Volume: 12
Issue: 12
Year: 2025

A REVIEW ON PARKINSON DISEASE: DRUGS TREATMENT OR MODIFICATIONS AFTER TREATMENT

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DOI: https://doi.org/10.5281/zenodo.17746674

How to cite this Article: Dr. Challa Srilekha*, Dr. Safi Almas. (2025). A REVIEW ON PARKINSON DISEASE: DRUGS TREATMENT OR MODIFICATIONS AFTER TREATMENT. European Journal of Biomedical and Pharmaceutical Sciences, 12(12), 117–127.

Article Received on 03/11/2025 **Article Revised on 24/11/2025** **Article Published on 01/12/2025**

ABSTRACT

Parkinson's disease (PD) is a gradual neurodegenerative disorder, which is marked by the depletion of dopaminergic neurons in the substantia nigra. This leads to the emergence of the motor and non-motor symptoms that greatly disrupt the patient's quality of life. The primary treatment consists of dopaminergic replacement therapies such as levodopa, the dopamine agonists, MAO-B inhibitors, and also COMT ones. Yet, the long-term therapy usually progresses to complications such as motor fluctuations, dyskinesias, and wearing-off phenomena, which require therapeutic alterations and support measures. Recent innovations involve the use of protracted-release formulations, continuous infusion systems, and the stimulation of deep brain areas to gain the best control over symptoms and to reduce the side effects. The research that is still unfolding is mainly centered around the neuroprotective strategies, gene therapy, and the development of personalized pharmacological interventions. It is the clinical pharmacists who are at the forefront in treatment optimization, patient education, and managing adverse drug reactions. This review provides a comprehensive overview of the current pharmacotherapy, the modifications made after treatment, and the future therapeutic trends that are all aimed at improving the clinical outcomes in Parkinson's disease.

KEYWORDS: Parkinson's disease, Levodopa, Dopamine agonists, MAO-B inhibitors, COMT inhibitors, Dyskinesia, Pharmacotherapy, Treatment modification, Deep brain stimulation, Neuroprotection.

INTRODUCTION

Parkinson's disease (PD) is a progressive neurodegenerative condition that is marked by the specific destruction of the dopamine-producing neurons in the substantia nigra. This neuronal loss results in motor dysfunction and a range of non-motor symptoms. PD is the second most common neurodegenerative disease after Alzheimer's and the most common in older adults. Not only does the disease damage the motor system, but it also affects learning and memory, emotional state and autonomic functions, causing a huge burden on the whole family and health care facilities. The global incidence of PD is on the rise due to the longer life span, and around 10 million people are estimated to be suffering from it worldwide. The economic impact of the disease is enormous, as it includes not only direct medical costs but also the costs related to disability and the decrease of productivity.[1,2,3]

PD is a disease that mostly weighs down those over 60 years of age, however, there are also some cases of early-onset in younger adults. The disease is more common in men than in women, probably because of the protective influence of estrogen and also due to some gender-related genetic or environmental differences. It requires meticulous attention to long-term therapy with a goal of not just preserving but also improving the patient's quality of life and functional independence while at the same time reducing the treatment-associated difficulties such as motor fluctuations and dyskinesias.[4]

The discovery of Parkinson's disease is credited to Dr. James Parkinson who in 1817 introduced it in his classic "An Essay on the Shaking Palsy." The doctor's observations were the beginning of the path that eventually led to the recognition of the motor symptoms as the disease's hallmark. Later on, progress in the field

of neuropathology brought to light the degeneration of the substantia nigra and the ensuing dopamine deficiency as the principal pathological traits.[5]

The levodopa therapy's introduction in the 1960s was a turning point in the management of PD and was a major advance in the treatment of neurologic diseases. The process of time saw the development of dopamine agonists, MAO-B inhibitors, COMT inhibitors, and amantadine which all played their part in reaping the medicine solutions. In the last few years innovations like controlled-release formulations, continuous infusion therapies, and deep brain stimulation (DBS) have been playing the role of overcoming long-term complications and enhancing symptom management.[6]

ETIOLOGY

Category	Causative Factors	Mechanism / Description
Genetic Factors	SNCA (α-synuclein)	Mutation leads to abnormal α-synuclein aggregation forming Lewy bodies
	LRRK2 (Leucine-rich repeat kinase 2)	Alters neuronal signaling and mitochondrial function
	PARK2 (parkin), PINK1, DJ-1	Impaired mitochondrial quality control and oxidative stress response
	VPS35, GBA1	Affects lysosomal and vesicular trafficking
Environmental Factors	Pesticides (e.g., Paraquat, Rotenone)	Mitochondrial complex I inhibition causing oxidative stress
	Heavy metals (Manganese, Lead)	Neurotoxicity and oxidative damage
	Rural living, well-water exposure	Possible contamination with pesticides
Lifestyle Factors	Cigarette smoking	Nicotine may enhance dopaminergic activity
	Caffeine consumption	Adenosine receptor antagonism supports dopamine release
Aging	Natural neuronal degeneration	Mitochondrial dysfunction, oxidative stress, reduced neuronal repair
Inflammatory / Immune Mechanisms	Chronic microglial activation	Release of pro-inflammatory cytokines (TNF-α, IL-6) damaging neurons
Gut–Brain Axis Dysfunction	Altered gut microbiota, α-synuclein propagation	Misfolded proteins may spread from enteric nervous system to brain via vagus nerve
Other Contributing Factors	Head injury, trauma	May accelerate neuronal loss[7,8]

PATHOGENESIS OF PARKINSON'S DISEASE

Parkinson's disease (PD) pathogenesis is a rather complicated process involving a mix of neurodegenerative, genetic, biochemical and inflammatory mechanisms which all in the end result to gradual loss of dopaminergic neurons in substantia nigra pars compacta. The following dopamine deficit causes basal ganglia circuit to be affected thereby producing the motor symptoms of PD like bradykinesia, rigidity and tremor. The neurodegeneration is invoked by several interrelated factors namely loss of dopaminergic neurons, α-synuclein aggregation, disturbed mitochondrial functioning, production of reactive oxygen species, and inflammation in the nervous system.

Degeneration of Dopaminergic Neurons

The primary disease process in PD is the death of neural cells that release dopamine, especially in the substantia nigra pars compacta, and this results in a considerable reduction of dopamine in the striatum. The reduction of dopamine causes a disruption in the basal ganglia motor pathways, in such a way that the direct pathway gets overstimulated while the indirect pathway is not. Such an imbalance leads to poor motor control. The lack of dopamine results in the motor cortex being less activated, which is why, on the one hand, the patient suffers from slowness of movement and increased muscle tone, and on the other hand, tremor occurs as a side effect of overactive acetylcholine due to the dopamine "vacuum." The motor symptoms are detectable when there is already a loss of 70-80% of the dopamine neurons and the striatum has below a minimum amount of dopamine.[9,10]

Lewy Body Formation and α-Synuclein Aggregation

The abnormal α-synuclein aggregates, which are a typical feature of PD, lead to the formation of the so-called Lewy bodies and Lewy neurites within the neurons that are affected. α-Synuclein is a protein that is found at the presynaptic level and is responsible for the transport of vesicles and the regulation of the neurotransmitter; however, in disease conditions, it misfolds and forms aggregates that are fibrillar and insoluble, thus very distressing to the neuronal function. They do so by interfering with synaptic transmission, impairing axonal transport, and causing cellular stress that eventually leads to cell death. The Braak staging hypothesis states that the progression of the α-synuclein

pathology follows a predetermined path that starts in the olfactory bulb and the enteric nervous system and goes up to the midbrain and cerebral cortex. This gradual process of accumulation is associated with the developing of the motor and non-motor symptoms, e.g., cognitive and autonomic dysfunctions.[11,12]

Mitochondrial Dysfunction and Oxidative Stress

The mitochondrial dysfunction is a significant factor in the development of PD. Inhibition of the mitochondrial complex I in dopaminergic neurons causes energy depletion, increased ROS production, and oxidative damage to biomolecules such as lipids, proteins, and DNA. Besides, mutations in PINK1, PARK2 (parkin), and DJ-1 genes further deteriorate the mitochondrial quality control and antioxidant defenses, thereby speeding up degeneration of neurons. Oxidative stress in dopaminergic neurons is at its highest due to dopamine's auto-oxidation, which creates free radicals and toxic quinones as by-products. Eventually, oxidative stress will lead to the fragmentation of mitochondria, loss of ATP production, and death of nigral neurons, which will keep on fostering the neurodegenerative cycle.

Neuroinflammation

One of the main factors behind PD is chronic neuroinflammation. The neuroinflammatory processes are mainly characterized by the activation of microglia and astrocytes in the substantia nigra that lead to the release of pro-inflammatory cytokines, among which are tumor necrosis factor-alpha (TNF-α), interleukin-1 beta (IL-1β), and interleukin-6 (IL-6) that cause oxidative stress and neuronal death. The inflammatory response continues to cause even more destruction of the dopaminergic cells and interference of the protective mechanisms against the toxicity. Besides, misfolded α-synuclein substitutes for a pro-inflammatory stimulus by activating microglial receptors and thus carrying the process of neuroinflammation and neurodegeneration in a self-sustaining cycle. The surrounding inflammation not only has a negative impact on the motor pathways but also plays a role in the development of non-motor symptoms such as fatigue, depression, and cognitive decline.[13,14]

Involvement of Non-Dopaminergic Systems

The underlying cause of PD is the loss of dopaminergic neurons, but also the other systems of neurotransmitter, e.g., serotonergic, noradrenergic, glutamatergic, and cholinergic pathways, are involved. The demise of the locus coeruleus, raphe nuclei, and cholinergic neurons results in the wide range of non-motor symptoms such as mood disorders, sleep disturbances, autonomic dysfunction, and cognitive impairment. This scenario of changes in different systems reflects the complex and wide-spread neurodegenerative nature of PD, thus emphasizing that it is not only a dopaminergic disorder but a multineurotransmitter disease with systemic manifestations.[15]

SYMPTOMS

Category	Clinical Features
Motor Symptoms	- Bradykinesia (slowness of movement) - Resting tremor (typically “pill-rolling”) - Muscular rigidity - Postural instability - Gait disturbances (shuffling, reduced arm swing) - Masked facial expression (hypomimia) - Micrographia (small handwriting)
Non-Motor Symptoms	- Cognitive impairment and dementia - Depression, anxiety, apathy - Sleep disturbances (REM behavior disorder, insomnia) - Autonomic dysfunction (constipation, orthostatic hypotension, urinary issues) - Fatigue and pain - Sensory symptoms (loss of smell, paresthesia) - Hallucinations and psychosis in advanced stages[16,17]

STAGES

Stage	Description
Stage 1	Unilateral involvement only, usually with minimal or no functional disability.
Stage 1.5	Unilateral and axial involvement affecting the neck or trunk muscles.
Stage 2	Bilateral or midline involvement without impairment of balance.
Stage 2.5	Mild bilateral disease with early postural instability but recovery on pull test.
Stage 3	Bilateral disease with mild to moderate postural instability; physically independent.
Stage 4	Severe disability; patient able to walk or stand unassisted but needs help with daily activities.
Stage 5	Wheelchair-bound or bedridden unless aided; complete dependence on caregivers.[18,19]

PHARMACOLOGICAL MANAGEMENT

Drugs Enhancing Dopaminergic Activity

The main aim of these agents is to either restore dopamine levels or improve the transmission of dopamine in the brain. They comprise of levodopa (which is a precursor to dopamine), dopamine agonists, MAO-B inhibitors, COMT inhibitors, and amantadine. All together these drugs alleviate the motor symptoms of the disease which include bradykinesia, rigidity and tremor, and they are thus considered as the mainstay of the medicinal treatment for Parkinson's disease.[20]

Drugs Enhancing Dopaminergic Activity	Sub-Class / Examples	Mechanism of Action
a. **Dopamine Precursor**	Levodopa (with Carbidopa or Benserazide)	Converts to dopamine in brain; Carbidopa prevents peripheral metabolism
b. **Dopamine Agonists**	Bromocriptine, Pramipexole, Ropinirole, Rotigotine, Apomorphine	Directly stimulate dopamine receptors (mainly D2)
c. **MAO-B Inhibitors**	Selegiline, Rasagiline, Safinamide	Inhibit dopamine breakdown by blocking monoamine oxidase-B
d. **COMT Inhibitors**	Entacapone, Tolcapone, Opicapone	Inhibit peripheral COMT enzyme, prolonging levodopa half-life
e. **Dopamine Releasers / NMDA Antagonists**	Amantadine	Increases dopamine release and inhibits reuptake; NMDA antagonist[21,22]

Drugs Reducing Cholinergic Activity

Anticholinergic medicines are employed to neutralize the situation where there is an increase in the cholinergic activity due to the deficiency of dopamine in the basal ganglia. They do this by obstructing the central muscarinic receptors that leads to the re-establishment of the dopamine-acetylcholine balance. These medicines are mostly recommended for the younger ones who have Parkinson's disease characterized by tremors, and the old ones are usually not allowed to take them because they might impair cognitive function.[23]

2. Drugs Reducing Cholinergic Activity	Examples	Mechanism of Action
Anticholinergics	Trihexyphenidyl, Benztropine, Biperiden, Procyclidine	Block central muscarinic receptors, restoring dopamine–acetylcholine balance[24]

Drugs Acting on Non-Dopaminergic Systems / Adjunctive Agents

They affect the non-dopaminergic pathways positively in terms of motor control and the reduction of" off" periods in patients suffering from advanced disease. It is to be noted that some agents like amantadine not only inhibit NMDA receptor but also ultimately alleviate levodopa-induced dyskinesias and, most importantly, possibly contribute to the neuroprotection.[25]

3. Drugs Acting on Non-Dopaminergic Systems / Adjunctive Agents	Examples	Mechanism / Target
Adenosine A2A Receptor Antagonist	Istradefylline	Blocks adenosine A2A receptors in basal ganglia, enhancing dopaminergic activity
Glutamate Antagonists	Amantadine (dual action)	NMDA receptor blockade
Neuroprotective Agents (under research)	Coenzyme Q10, Creatine, Rasagiline (possible role)	Reduce oxidative stress and mitochondrial dysfunction[26]

MODIFICATIONS AFTER TREATMENT / POST-TREATMENT ADJUSTMENTS IN PARKINSON'S DISEASE

1. Management of Levodopa-Induced Dyskinesia

a. Dose Fractionation

Dose fractionation is a method that refers to splitting the total daily dosage of levodopa into lesser, more frequently administered doses in order to achieve steady-state plasma levels and subsequently prevent peak dose dopamine overstimulation. By doing so, this technique not only controls the patient's motor functions more smoothly but also reduces the occurrence of dyskinesias that are associated with the fluctuating dopamine levels. On the other hand, it does demand very precise adherence to the schedule and, if the intervals between doses are too long, it might lead to an increased incidence of "wearing-off" symptoms. Moreover, if applied together with pharmacokinetic enhancers such as COMT or MAO-B inhibitors, the effect of levodopa can be further prolonged. This line of treatment is still

considered as a practical first step to modification before going into advanced or infusion-based therapies in patients suffering from dose-dependent motor complications.[27]

b. Addition of Amantadine

Amantadine, which blocks NMDA receptors, is among the very few medications that can diminish levodopa-related dyskinesia. It alters the balance of glutamate neurotransmission, thus lessening the abnormalities in receptor sensitivity and excitotoxicity of neurons in the basal ganglia circuits due to dopamine. Moreover, amantadine not only reduces dyskinesia but also acts as a mild antiparkinsonian agent and possibly helps in relieving bradykinesia and stiffness. The drug is ordinarily prescribed when the dyskinesia becomes so severe that it impairs daily activity even with the maximum levodopa dosage. Amantadine has been made available in extended-release formulations with the advantage of steady plasma levels and better tolerance. On the downside, elderly individuals and patients with renal dysfunction require special considerations due to the potential adverse effects of hallucinations, orthostatic hypotension, and livedo reticularis.[28]

c. COMT and MAO-B Inhibitors

COMT (catechol-O-methyltransferase) inhibitors such as entacapone and opicapone, and monoamine oxidase-B (MAO-B) inhibitors, selegiline and rasagiline among them, are adjuvants that thev have their respective effect on dopamine metabolism both in the peripheral and central nervous system, thus, extending the action of levodopa. The therapy combination allows the reduction of levodopa doses, thus, reducing the risk of both pulsatile dopamine stimulation and dyskinesia. On the other hand, COMT inhibitors work by prolonging the plasma half-life of levodopa and MAO-B inhibitors prevent the degradation of dopamine in the striatum. If these medicines are used wisely, they will result in more "on" time and fewer "off" episodes. Exacting titration is needed to kill the overdose of dopaminergic side effects such as hallucinations, orthostatic hypotension, or impulse control disorders.[29]

2. Wearing-Off Phenomenon

a. Controlled-Release Formulations

The controlled-release and extended-release levodopa drugs are made to give smoother and longer lasting dopaminergic stimulation, and thereby, reducing the “wearing-off” phenomenon that happens between the doses. These drugs keep releasing levodopa bit by bit, so there are no big changes in the plasma levels, and the symptoms are more or less the same all day long. They are not such a good option for every patient, especially when the disease is in the advanced stage, but they can still put off the onset of motor fluctuations. The use of a controlled-release combination with either COMT or MAO-B inhibitors not only increases the duration of the effect but also leads to delayed onset in some cases, which calls for patient-specific timing and individualized adjustment to optimize efficacy while minimizing nocturnal akinesia or morning rigidity.[30]

b. Continuous Infusion Therapies

Advanced Parkinson's disease patients who experience severe motor fluctuations can rely on continuous infusion therapies such as levodopa-carbidopa intestinal gel (LCIG) and subcutaneous apomorphine infusion. These treatments provide a constant supply of dopamine, thus overcoming unstable gastrointestinal absorption and reducing periods of unresponsiveness and movement disorders to a minimum. LCIG treatment involves the use of a jejunal pump that maintains the plasma levels of levodopa constantly, whereas the apomorphine infusion acts as a strong dopamine agonist alternative. The adoption of such therapies for the treatment of Parkinson's disease leads to better motor control, improved daily activities, and enhanced quality of life, but they also necessitate device management and patient training. Side effects are reactions at the infusion site as well as high cost, which limits the treatment's accessibility in places with few resources.[31]

c. Dopamine Agonist Add-On Therapy

Dopamine agonists, which include pramipexole, ropinirole, and rotigotine, have been designated as auxiliary to levodopa medication to extend “on” time and lessen “wearing-off” symptoms. The mechanism of action of these drugs is direct stimulation of dopamine receptors; hence they allow less dependency on the irregular levels of levodopa and facilitate smoother dopaminergic stimulation. Long-acting or transdermal preparations provide an uninterrupted symptom control and also enhance night-time mobility. Dopamine agonists are mainly of advantage in early or mid-stage disease since they are the ones who can delay the start of levodopa therapy, hence delaying the coming of dyskinesia. On the other hand, long-term use of the drug may lead to adverse effects such as sleepiness, hallucinations, or impulse control issues, which will require careful monitoring and individual dosing adjustments to achieve the right balance between effectiveness and safety.[32]

3. Motor Fluctuations and On–Off Periods

a. Pharmacokinetic Optimization

Inconsistent levodopa absorption and fluctuating brain dopamine levels are the primary causes of motor fluctuations. The pharmacokinetic optimization of levodopa dosage schedules involves dosing intervals, controlled release formulations or infusion regimens, all of which aim at providing a stable delivery of the drug. The concomitant use of COMT and MAO-B inhibitors increases the "on" period by lessening the metabolism of dopamine. Careful scheduling helps to obtain the precise timing of “on” states and to reduce unpredictable "off" states to a minimum. Pharmacokinetic refinement is usually practices along with the dietary changes to facilitate absorption. The advanced techniques like intestinal gel infusions or subcutaneous dopamine

agonist delivery provide the approach of continuous dopaminergic stimulation. Proper and individual titration is still crucial in the management of Parkinson's disease, as it is necessary to find the right balance between symptomatic improvement, dyskinesia, and the side effects of dopaminergic drugs.[33]

b. Dietary Adjustments

Dietary protein is a competitor to levodopa when it comes to intestinal absorption and transport through the blood-brain barrier. Thus, it is common for doctors to recommend that their patients take levodopa on an empty stomach or 30 minutes before eating and have their protein intake mainly during evening meals. This method increases the drug's bioavailability and helps to stabilize the patient's motor symptoms. Moreover, water and fiber intake at proper levels make the patient less likely to suffer constipation which, in turn, supports the absorption of levodopa. It is important to keep an eye on vitamin B6 and iron supplements since they have the potential to disrupt levodopa metabolism. All in all, dietary management is a very important support factor in getting the most out of levodopa and keeping the patient's motor function stable during the course of the disease.[34]

c. Continuous Dopaminergic Stimulation

Continuous dopaminergic stimulation (CDS) is a therapeutic concept aimed at keeping the dopamine receptors constantly activated, thereby simulating the natural dopamine transmission in the body. CDS, contrary to the pulsatile stimulation caused by oral levodopa, avoids receptor desensitization and motor complications. It is done with the help of transdermal dopamine agonists, gel infusions into the intestine, or the use of extended-release formulations. CDS strategies will increase the duration of "on" time, decrease the occurrence of dyskinesia, and improve the overall quality of life. They are especially powerful in patients with advanced Parkinson's disease when oral treatments become less predictable. Although there are difficulties in terms of organization and cost, continuous dopaminergic stimulation is still a well-supported method that means a more personal, neurophysiologically stable treatment policy by the end of the day, it can also prevent the long-term occurrence of motor complications and improve the patient's functional independence.[35]

4. Switching Strategies

a. Transition Between Formulations

Switching between oral, transdermal, and infusion formulations is often done in order to control symptoms in the best way possible and also to make the patient stay on the treatment. Those patients who have the problem of irregular absorption or cannot take oral levodopa due to the gastrointestinal side effects may get help from the transition to the use of transdermal dopamine agonists such as rotigotine or infusion-based levodopa-carbidopa intestinal gel (LCIG). This change in treatment ensures that motor fluctuations are minimized because there will be consistent plasma levels and stimulation of dopamine throughout the day. The transitioning will be done by cross-titration which is a slow process, so the patient will not suffer from withdrawal or overstimulation by the dopaminergic effect. The changing of formulations also allows one to adjust the therapy to the patient's lifestyle, cognitive status, and disease severity, thus paving the way for individualized long-term management and the retention of quality of life, as the disease progresses.[36]

b. From Oral to Advanced Therapies

With the progression of Parkinson's disease, a considerable number of patients face insufficient relief from the symptoms with just oral medications. So, it becomes unavoidable to move on to more sophisticated treatments like LCIG infusion, subcutaneous apomorphine infusion, or deep brain stimulation (DBS). Such therapies bring about constant dopaminergic stimulation that cancels out "off" periods and reduces the occurrence of dyskinesias that are typically associated with oral dosing. LCIG avoids the problem of unstable gastric absorption, whereas DBS provides non-invasive modulation of motor circuits. The process of careful patient selection, which considers factors such as motor responsiveness, cognitive status, and comorbidities, is critical to achieving the desired outcome. A multidisciplinary evaluation is the means for a seamless transition and patient education, which in turn will optimize adherence, functional improvement, and long-term stability of conquered symptoms both motor and non-motor.[37]

5. Management of Non-Motor Symptoms Post-Treatment

a. Psychiatric Complications

The use of dopaminergic medications for a long period can have psychiatric complications as hallucinations, psychosis, impulse control disorders and mood changes. All these disturbances are because of the excessive stimulation of the mesolimbic dopamine pathways. The reduction of dose or stopping the dopamine agonist, the one causing the problem, is the first step in the management of these complications. When necessary, the use of atypical antipsychotics, like quetiapine or clozapine, is preferred because of their minor motor side effects. On the other hand, pimavanserin, a selective 5-HT2A inverse agonist, is a new option for Parkinson's disease psychosis. Periodic psychiatric evaluation and participation of the caregiver are very important to detect the symptoms as early as possible. The control of motor and psychiatric symptoms necessitates a very careful titration in order not to worsen either of the symptom domains.[38]

b. Cognitive Decline

Advanced Parkinson's disease typically leads to cognitive impairment and dementia, sometimes worsened by anticholinergic or dopaminergic medications. Treatment consists of optimizing drug

therapy with the intention of minimizing central anticholinergic use and adjusting dopaminergic therapy so as not to cause hallucinations or confusion. In this regard, cholinesterase inhibitors, such as rivastigmine and donepezil, may not only improve cognitive functions but also prolong the decline. Moreover, non-pharmacological approaches, such as the cognitive training and caregiver support, are also very crucial. Monitoring for side effects such as orthostatic hypotension, sleep disturbances, and drug interactions contributes to the cognitive stability. If cognitive impairment is detected early and treated in a personalized manner, it can lead to the maintenance of functional independence and a better quality of life for both patients and caregivers during the late stages of Parkinson's disease.[39]

c. Sleep-Related Issues

In patients suffering from Parkinson's disease, sleep problems like insomnia, vivid dreams, restless legs syndrome, and daytime sleepiness are common; these problems might also get worse after a long period of treatment with dopaminergic agents. Giving nocturnal doses of dopaminergic drugs or transferring to long-acting forms can be very effective in improving nighttime mobility and lessening sleep being broken up. The initial use of dosage adjustments must be done to counteract the sedation caused by the dopamine agonists. Non-medical methods like maintaining sleep hygiene, exercising regularly, and cutting back on daytime naps are still important and they will be able to help the primary treatment significantly. In cases resistant to other treatments, melatonin or clonazepam may be given as an option. The management of sleep-related problems can thus be viewed as a valuable component in the treatment paradigm that not only enhances the patient's compliance to the general treatment, but also benefits the cognitive and emotional aspects of his/her condition.[40]

Advanced and Adjunctive Therapies in Parkinson's Disease

1. Levodopa-Carbidopa Intestinal Gel (LCIG) Therapy

In LCIG therapy continuous infusion of levodopa-carbidopa is delivered directly into the small intestine and this is the way gastric absorption issues are avoided. It levels up stable plasma levels, reduces "off" and dyskinetic periods in patients suffering from advanced Parkinson's disease. However, it is very efficient and it requires invasive tube placement and regular monitoring for infection and mechanical complications, which is why it is the suitable option for patients with severe motor fluctuations.

2. Apomorphine Infusion Therapy

Apomorphine continuous subcutaneous infusion is the most rapid and the most consistent way of dopaminergic stimulation that minimizes "off" episodes in patients suffering from the most severe stages of Parkinson's disease. It will also be a substitute for LCIG or deep brain stimulation. The patients will receive increased motor and mobility capacity but at the same time will also experience adverse effects (nausea, hypotension, and injection site nodules) which require very close monitoring, and pre-treatment with antiemetics may even become necessary for the acceptability of the side effects.[41]

3. Deep Brain Stimulation (DBS)

DBS is a method that utilizes the placement of electrodes in the brain areas like the subthalamic nucleus or globus pallidus interna to manage the irregular neural activity. It has a large positive impact on the symptoms of tremor, rigidity, and bradykinesia, thus leading to a decrease in the dosage of levodopa. In this case, DBS is the treatment for the patients who are taking levodopa and have severe motor fluctuations as a side effect, it can give them long-term improvement with the possibility of reducing the medication-related side effects.

4. Adenosine A2A Receptor Antagonists

Adenosine A2A receptor antagonists such as istradefylline can be counted upon to alleviate the "off" period by regulating basal ganglia neurotransmission without having a direct impact on the dopamine receptors. They help in the development of the dopamine signaling and the overall motor function, thus acting as a great relief together with the levodopa. Their low chances of causing dyskinesia and psychosis make them very well accepted as a support for people suffering from the long-term side effects of levodopa treatment.[42]

5. Continuous Subcutaneous Levodopa Delivery Systems

The latest subcutaneous levodopa delivery systems are capable of providing continuous non-invasive dopaminergic stimulation through the use of portable pumps. These substances (foslevodopa/foscarbidopa) keep plasma levels constant and therefore minimize motor fluctuations and "off" periods. They negate the need for surgical treatments by being a better option than intestinal infusions. There may be mild local reactions but they are a sign of an encouraging and patient-friendly future therapy option.

6. Gene and Stem Cell-Based Adjunctive Therapies

Gene therapy increases dopamine production or delivers neuroprotective factors, at the same time stem cell therapy replaces the lost dopaminergic neurons. All treatments are aimed at disease modification instead of just relieving symptoms. They have started showing motor benefits and possible neuroprotection in early clinical trials but ethical and safety issues still persist. These developments represent a shift towards regenerative treatment for Parkinson's disease.[43]

COMPARATIVE EFFECTIVENESS OF DRUG CLASSES

1. Levodopa vs. Dopamine Agonists

Levodopa is still the most powerful medication for the motor symptoms control if the patient does not respond to it. It has a rapid and strong impact on bradykinesia and rigidity. On the other hand, the effects of dopamine agonists are weaker but they have the advantage of being longer-lasting and causing fewer motor complications at the beginning. Long-term treatment with levodopa leads to dyskinesia while the patients on dopamine agonists are more prone to impulse-control disorders and hallucinations.

2. Levodopa vs. MAO-B Inhibitors

Levodopa is a potent motor reliever, but its duration of action is shorter than MAO-B inhibitors like selegiline or rasagiline. MAO-B inhibitors give a minor benefit of symptoms thus postponing the start of levodopa treatment in early Parkinson's disease. Their combined use leads to the expansion of "on" periods and the reduction of "off" time which means that the levodopa's effect will be stronger while fluctuations related to the dosage will be less.[44]

3. Levodopa vs. COMT Inhibitors

Levodopa is the best option for controlling symptoms, but its short half-life leads to motor fluctuations. By blocking the breakdown of levodopa in the body, COMT inhibitors like entacapone or opicapone can effectively raise the drug's plasma half-life. The use of this drug combination results in better stability, a longer "on" period, and a smaller dosage frequency, but it also poses the risk of making dyskinesia worse since more levodopa is present in the body.

4. Dopamine Agonists vs. MAO-B Inhibitors

Dopamine agonists such as pramipexole are more effective in the control of motor symptoms and thus, can be recommended as early single medicines or in combination with other treatments. On the other hand, MAO-B inhibitors only provide a small degree of symptom relief, albeit they are associated with fewer and less severe adverse effects. Thus, the use of dopamine agonists might lead to the delay of levodopa start, but they also bring the risks of drowsiness, swelling, and loss of control over one's behavior which would limit their application in older patients.[45]

5. Anticholinergics vs. Amantadine

The use of Anticholinergics in younger patients leads to an improvement in the trembling of the hands and fingers, but it also results in the kids of the old having a hard time thinking. On the other hand, Amantadine, through NMDA antagonism, gives only slight improvement in the case of motor rigidity and tremor, while it is very effective in relieving the movements that are caused by levodopa medication. Overall, it is less disturbing than anticholinergic medication and it also makes the protecting of the nervous system a possibility; thus, it is the most desirable partner in the treatment of motor complications of Parkinson's disease.

6. Adjunctive COMT/MAO-B Inhibitors vs. Deep Brain Stimulation (DBS)

Besides the use of adjunctive COMT or MAO-B inhibitors, which offer pharmacological control of the motor fluctuations, the latter is done through surgical intervention, where long-term symptom relief is obtained by altering the neural circuits. The superiority of DBS is manifested in the significant decrease of both dyskinesias and drug dependence, but it requires surgery. Drug therapy is still the method of choice in moderate cases while DBS is for those patients who have advanced disease and unmanageable symptoms.[46]

FUTURE DIRECTIONS

1. Disease-Modifying Therapies

Presently, the medications provide only symptomatic relief without stopping the neurodegeneration process. Controversial research will be focusing on the development of therapies that will modify disease by acting on α-synuclein aggregation, mitochondrial dysfunction, oxidative stress, and neuroinflammation. Along with the ones mentioned above, other agents such as monoclonal antibodies (prasinezumab, cinpanemab) and gene-editing techniques are very promising but still need to go through large-scale and long-term trials to prove their clinical efficacy and safety.

2. Neuroprotective and Regenerative Approaches

Doctors are trying to use stem cell therapy along with the neurotrophic factor, GDNF (glial cell-derived neurotrophic factor), to treat the condition by rejuvenating the dopamine-producing neurons. The use of sophisticated delivery systems, for instance, viral vectors and nanocarriers, is meant to ensure better targeting of the central nervous system. Nevertheless, inconsistency in clinical results and the immune response over the long term continue to be significant hurdles for research.[47]

3. Personalized and Precision Medicine

The selection of therapy based on genetics and biomarkers is a major area of research that is receiving more attention. Discovering the patient-specific genetic changes (e.g., LRRK2, GBA) and the related molecular signatures can possibly indicate the drug sensitivity and the rate of disease progression. The combination of pharmacogenomics with clinical phenotyping might result in individual treatment plans that would not only prevent adverse effects but also enhance the patient's overall long-term outcomes.

4. Advanced Drug Delivery Systems

Innovative delivery systems such as transdermal patches, intranasal sprays, and continuous subcutaneous infusions are being created to provide consistent dopaminergic stimulation. These methods have the potential to diminish motor fluctuations and consequently, patient

loyalty to treatment will be increased. However, more clinical trials are required to assess bioavailability, the economic aspect, and improvements in the patient's quality of life.[48]

5. Digital Health and Artificial Intelligence

The use of AI tools, wearable sensors, and telemedicine systems is playing a major role in the transformation of Parkinson's disease monitoring and treatment. Constant monitoring of gait, tremors, and sleep helps in the early detection of symptoms and prompt changes in therapy. Although it is possible that the machine learning models will be able to ascertain the disease's progression and the patient's responsiveness to the treatment, the industry is still waiting for the digital biomarkers that will be universally accepted and the ethical data frameworks that will support them.

6. Non-Motor Symptom Research

Concerning the treatment/prevention of motor disorders, the research done on non-motor symptoms has not kept pace with the development of motor control techniques. Besides, a research paradigm supporting these manifestations as integral to the whole patient management, better psycho-neuro-physiology-based consumer treatment methods will result from the development of integrated neuropsychiatric management approaches to improve holistic patient outcomes.

7. Long-Term Outcomes and Real-World Evidence

There is a tendency for most clinical trials to evaluate the efficacy of a drug only for a short period, thus leaving the long-term effects less studied or completely ignored. In addition, researchers in the future are advised to take into account real-world evidence, people's assessments of their health and quality of life, and partnerships among several centers in order to determine the long-term effectiveness, tolerability, and socio-economic impacts of different treatment methods.[49,50]

CONCLUSION

This review highlights the current pharmacological treatment strategies and necessary post-treatment modifications in managing Parkinson’s disease. Although levodopa remains the cornerstone of therapy, its long-term complications necessitate adjunctive use of dopamine agonists, MAO-B inhibitors, COMT inhibitors, and amantadine to optimize outcomes. Post-treatment adjustments—such as dose fractionation, infusion therapies, and advanced delivery systems—play a crucial role in minimizing motor fluctuations and dyskinesias. Emerging therapies targeting neuroprotection, gene regulation, and precision medicine promise future advancements. A patient-centered, adaptive treatment approach integrating pharmacological innovations with technological support is essential for improving long-term outcomes and quality of life in Parkinson’s disease.

REFERENCES

1. Kalia LV, Lang AE. Parkinson’s disease. Lancet, Aug. 29, 2015; 386(9996): 896–912.
2. Tanner CM, Goldman SM. Epidemiology of Parkinson’s disease. Neurol Clin., May 1996; 14(2): 317–35.
3. Nussbaum RL, Ellis CE. Alzheimer’s disease and Parkinson’s disease. N Engl J Med., Apr. 3, 2003; 348(14): 1356–64.
4. Chen RC, Chang SF, Su CL, Chen TH, Yen MF, Wu HM, et al. Prevalence, incidence, and mortality of PD: A door-to-door survey in Ilan county, Taiwan. Neurology, Nov. 13, 2001; 57(9): 1679–86.
5. Mhyre TR, Boyd JT, Hamill RW, Maguire-Zeiss KA. Parkinson's disease. Subcell Biochem, 2012; 65: 389-455.
6. Tolosa E, Martí MJ, Valldeoriola F, Molinuevo JL. History of levodopa and dopamine agonists in Parkinson's disease treatment. Neurology, Jun. 1998; 50(6,6): S2-10; discussion S44-8.
7. Huang Z, de la Fuente-Fernández R, Stoessl AJ. Etiology of Parkinson's disease. Can J Neurol Sci., Mar. 2003; 3(1): S10-8.
8. Mary Brenda Ogwang, and Deepak Kumar Jha. “An Integrated Review of Parkinson’s Disease: Etiology, Differential Diagnosis, Biomarkers, Emerging Therapeutic Approaches, and Translational Models”. Journal of Advances in Medical and Pharmaceutical Sciences, 2025; 27(8): 1–22.
9. MacMahon Copas AN, McComish SF, Fletcher JM, Caldwell MA. The Pathogenesis of Parkinson's Disease: A Complex Interplay Between Astrocytes, Microglia, and T Lymphocytes? Front Neurol, May 26, 2021; 12: 666737.
10. Morris HR, Spillantini MG, Sue CM, Williams-Gray CH. The pathogenesis of Parkinson's disease. Lancet, Jan. 20, 2024; 403(10423): 293-304.
11. Leak RK, Clark RN, Abbas M, Xu F, Brodsky JL, Chen J, Hu X, Luk KC. Current insights and assumptions on α-synuclein in Lewy body disease. Acta Neuropathol, Aug. 14, 2024; 148(1): 18.
12. Ramesh S, Arachchige ASPM. Depletion of dopamine in Parkinson's disease and relevant therapeutic options: A review of the literature. AIMS Neurosci, Aug. 14, 2023; 10(3): 200-231.
13. Subramaniam SR, Chesselet MF. Mitochondrial dysfunction and oxidative stress in Parkinson's disease. Prog Neurobiol, Jul-Aug., 2013; 106-107: 17-32.
14. Wang Q, Liu Y, Zhou J. Neuroinflammation in Parkinson's disease and its potential as therapeutic target. Transl Neurodegener, Oct. 12, 2015; 4: 19.
15. Hung AY, Schwarzschild MA. Treatment of Parkinson's disease: what's in the non-dopaminergic pipeline? Neurotherapeutics, Jan. 2014; 11(1): 34-46.
16. Sveinbjornsdottir S. The clinical symptoms of Parkinson's disease. J Neurochem, Oct. 2016; 139(1): 318-324.

17. Váradi C. Clinical Features of Parkinson's Disease: The Evolution of Critical Symptoms. Biology, 2020; 9(5): 103.
18. Kempster PA. Understanding the progression of Parkinson's disease: a review. BMJ Neurol Open, Sep. 8, 2025; 7(2): e001215.
19. Krüger R, Klucken J, Weiss D, Tönges L, Kolber P, Unterecker S, Lorrain M, Baas H, Müller T, Riederer P. Classification of advanced stages of Parkinson's disease: translation into stratified treatments. J Neural Transm (Vienna), Aug. 2017; 124(8): 1015-1027.
20. Riederer P, Strobel S, Nagatsu T, Watanabe H, Chen X, Löschmann PA, Sian-Hulsmann J, Jost WH, Müller T, Dijkstra JM, Monoranu CM. Levodopa treatment: impacts and mechanisms throughout Parkinson's disease progression. J Neural Transm (Vienna), Jun. 2025; 132(6): 743-779.
21. Kim TY, Lee BD. Current therapeutic strategies in Parkinson's disease: Future perspectives. Mol Cells, Sep. 4, 2025; 48(11): 100274.
22. Jankovic J, Aguilar LG. Current approaches to the treatment of Parkinson's disease. Neuropsychiatr Dis Treat., Aug. 2008; 4(4): 743-57.
23. Gerretsen P, Pollock BG. Drugs with anticholinergic properties: a current perspective on use and safety. Expert Opin Drug Saf., Sep. 2011; 10(5): 751-65.
24. Brocks DR. Anticholinergic drugs used in Parkinson's disease: An overlooked class of drugs from a pharmacokinetic perspective. J Pharm Pharm Sci., May-Aug., 1999; 2(2): 39-46.
25. Stayte S, Vissel B. Advances in non-dopaminergic treatments for Parkinson's disease. Front Neurosci, May 22, 2014; 8: 113.
26. Uchida S, Soshiroda K, Okita E, Kawai-Uchida M, Mori A, Jenner P, Kanda T. The adenosine A2A receptor antagonist, istradefylline enhances anti-parkinsonian activity induced by combined treatment with low doses of L-DOPA and dopamine agonists in MPTP-treated common marmosets. Eur J Pharmacol, Nov. 5, 2015; 766: 25-30.
27. Nyholm D, Stepien V. Levodopa fractionation in Parkinson's disease. J Parkinsons Dis., 2014; 4(1): 89-96.
28. Blanpied TA, Clarke RJ, Johnson JW. Amantadine inhibits NMDA receptors by accelerating channel closure during channel block. J Neurosci, Mar. 30, 2005; 25(13): 3312-22.
29. Regensburger M, Ip CW, Kohl Z, Schrader C, Urban PP, Kassubek J, Jost WH. Clinical benefit of MAO-B and COMT inhibition in Parkinson's disease: practical considerations. J Neural Transm (Vienna), Jun. 2023; 130(6): 847-861.
30. Fabbri M, Barbosa R, Rascol O. Off-time Treatment Options for Parkinson's Disease. Neurol Ther., Apr. 2023; 12(2): 391-424.
31. Abbruzzese G, Barone P, Bonuccelli U, Lopiano L, Antonini A. Continuous intestinal infusion of levodopa/carbidopa in advanced Parkinson's disease: efficacy, safety and patient selection. Funct Neurol, Jul-Sep, 2012; 27(3): 147-54.
32. Riederer P, Horowski R. L-DOPA-therapy in Parkinson's disease: some personal reflections on L-DOPA therapy from Vienna and Berlin. J Neural Transm (Vienna), Nov. 2023; 130(11): 1323-1335.
33. Fabbrini G, Juncos J, Mouradian MM, Serrati C, Chase TN. Levodopa pharmacokinetic mechanisms and motor fluctuations in Parkinson's disease. Ann Neurol, Apr. 1987; 21(4): 370-6.
34. Pedrosa de Menezes AL, Bloem BR, Beckers M, Piat C, Benarroch EE, Savica R. Molecular Variability in Levodopa Absorption and Clinical Implications for the Management of Parkinson's Disease. J Parkinsons Dis., 2024; 14(7): 1353-1368.
35. Stocchi F. The therapeutic concept of continuous dopaminergic stimulation (CDS) in the treatment of Parkinson's disease. Parkinsonism Relat Disord, Dec. 2009; 15(3): S68-71.
36. Antonini A, Chaudhuri KR, Martinez-Martin P, Odin P. Oral and infusion levodopa-based strategies for managing motor complications in patients with Parkinson's disease. CNS Drugs, Feb. 2010; 24(2): 119-29.
37. Dijk JM, Espay AJ, Katzenschlager R, de Bie RMA. The Choice Between Advanced Therapies for Parkinson's Disease Patients: Why, What, and When? J Parkinsons Dis., 2020; 10(s1): S65-S73.
38. Weintraub D. Management of psychiatric disorders in Parkinson's disease : Neurotherapeutics - Movement Disorders Therapeutics. Neurotherapeutics, Oct. 2020; 17(4): 1511-1524.
39. Meireles J, Massano J. Cognitive impairment and dementia in Parkinson's disease: clinical features, diagnosis, and management. Front Neurol, May 25, 2012; 3: 88.
40. Zuzuárregui JRP, During EH. Sleep Issues in Parkinson's Disease and Their Management. Neurotherapeutics, Oct. 2020; 17(4): 1480-1494.
41. Pålhagen SE, Sydow O, Johansson A, Nyholm D, Holmberg B, Widner H, Dizdar N, Linder J, Hauge T, Jansson R, Bergmann L, Kjellander S, Marshall TS. Levodopa-carbidopa intestinal gel (LCIG) treatment in routine care of patients with advanced Parkinson's disease: An open-label prospective observational study of effectiveness, tolerability and healthcare costs. Parkinsonism Relat Disord, Aug. 2016; 29: 17-23.
42. Lozano AM, Lipsman N, Bergman H, Brown P, Chabardes S, Chang JW, Matthews K, McIntyre CC, Schlaepfer TE, Schulder M, Temel Y, Volkmann J, Krauss JK. Deep brain stimulation: current challenges and future directions. Nat Rev Neurol, Mar. 2019; 15(3): 148-160.
43. Olanow CW, Espay AJ, Stocchi F, Ellenbogen AL, Leinonen M, Adar L, Case RJ, Orenbach SF, Yardeni T, Oren S, Poewe W; 006 study group. Continuous Subcutaneous Levodopa Delivery for Parkinson's Disease: A Randomized Study. J Parkinsons Dis., 2021; 11(1): 177-186.

44. Ruan X, Lin F, Wu D, Chen L, Weng H, Yu J, Wang Y, Chen Y, Chen X, Ye Q, Meng F, Cai G. Comparative Efficacy and Safety of Dopamine Agonists in Advanced Parkinson's Disease With Motor Fluctuations: A Systematic Review and Network Meta-Analysis of Double-Blind Randomized Controlled Trials. Front Neurosci, Oct. 29, 2021; 15: 728083.
45. Binde CD, Tvete IF, Gåsemyr J, Natvig B, Klemp M. A multiple treatment comparison meta-analysis of monoamine oxidase type B inhibitors for Parkinson's disease. Br J Clin Pharmacol, Sep. 2018; 84(9): 1917-1927.
46. McEvoy JP. A double-blind crossover comparison of antiparkinson drug therapy: amantadine versus anticholinergics in 90 normal volunteers, with an emphasis on differential effects on memory function. J Clin Psychiatry, Sep. 1987; 48: 20-3.
47. Akerud P, Canals JM, Snyder EY, Arenas E. Neuroprotection through delivery of glial cell line-derived neurotrophic factor by neural stem cells in a mouse model of Parkinson's disease. J Neurosci, Oct. 15, 2001; 21(20): 8108-18.
48. Rideout HJ, Chartier-Harlin MC, Fell MJ, Hirst WD, Huntwork-Rodriguez S, Leyns CEG, Mabrouk OS, Taymans JM. The Current State-of-the Art of LRRK2-Based Biomarker Assay Development in Parkinson's Disease. Front Neurosci, Aug. 18, 2020; 14: 865.
49. Twala B. AI-driven precision diagnosis and treatment in Parkinson's disease: a comprehensive review and experimental analysis. Front Aging Neurosci, Jul. 28, 2025; 17: 1638340.
50. Murakami H, Shiraishi T, Umehara T, Omoto S, Iguchi Y. Recent Advances in Drug Therapy for Parkinson's Disease. Intern Med., Jan. 1, 2023; 62(1): 33-42.