An Examination and Treatment of Parkinson's Disease and Its Effects on Enhancing Motor Symptoms at Tertiary Care Hospitals

Mr. Viswanath V. Kandanuru[1*], Mr. Chandu Rachapogu[2], Mr. Swaroop K. R. Rachamreddy[3], Ms. Janani Jadapalli[4], Mr. Kolavali Yalla Reddy[5]

[1,2,3,4] *Student, Srinivasa Institute of Pharmaceutical Sciences, Peddasetty Palli, Proddatur-516361.*

[5] *Professor, Srinivasa Institute of Pharmaceutical Sciences, Peddasetty Palli, Proddatur-516361.*

Abstract: Parkinson's disease (PD) is an age-related neurodegenerative brain disorder caused due to death of dopaminergic neurons that regulate movement in the substantia nigra pars compacta in Basal Ganglia. There is a global prevalence of rising cases of 6.1 million in 2016 to an expected 12 million cases in 2050. This study aims to determine methods to Improve the disorder's symptomatic motor and nonmotor features by collecting 120 cases at tertiary care hospital. Study shows men are affected slightly more rather than females. Elevated motor symptoms are mainly Tremors, rather than rigidity, bradykinesia, and postural instability. Nonmotor symptoms like Depression, Anxiety, sleeplessness, etc., have been observed. This study mostly diagnoses PD by physical observations and MRI scans. Motor improvements are extensively achieved by Levodopa and Carbidopa which are crucial prescribed regimens other than Dopamine Agonists, and MAO/COMT inhibitors. Discharge follow-up is not accompanied in this study. Management of PD is complex, and ongoing research provides significant advancements in the treatment of Parkinson's disease.

Keywords: Parkinson's disease, Levodopa, Carbidopa, Pramipexole, Selegiline, Entacapone.

I. INTRODUCTION

The death of dopaminergic neurons and decrease in dopamine levels, which regulate body movement in the substantia nigra pars compacta in Basal Ganglia, causes unintended or uncontrollable movements is known as Parkinson's Disease (PD). Death occurs due to, reduced brain blood flow and emerging mild strokes in the brain. By Multiple system atrophy as the striatum and the substantia nigra, two regions of the brain, are not connected properly, leading to striatonigral degeneration. Loss of nerve cells and atrophy (shrinkage) of several brain regions, including the cerebral cortex and the basal ganglia known as corticobasal degeneration. And some unidentified etiology i.e. idiopathic PD, by neuroleptic medications e.g. Haloperidol, which block the function of the neurotransmitter dopamine D2 receptors, etc.[1] Symptoms like tremors, rigidity, and issues with maintaining balance and coordination are some notable examples, which were improved by pharmacological treatment. This study seeks to determine the outcomes of the disorder's symptomatic motor and nonmotor features by analysing pharmacological treatments. Motor improvements are extensively achieved by Levodopa and Carbidopa which are crucial prescribed regimens other than Dopamine Agonists, and Monoamine Oxidase-B inhibitors (MAO)/Catechol-O-methyltransferase inhibitors (COMT), etc.

Parkinson's disease (PD), which causes progressive disability due to both motor and non-motor symptoms, has a substantial influence on quality of life (QoL). The motor symptoms, like severe muscle rigidity, unpleasant dystonic postures, and generalized resting tremor, were improved within a few days' usage of Levodopa (400 mg/day) in a 42-year-old patient who had a 20-year medical history and had never been treated. Additionally, a 69-year-old patient who had severe motor impairment and untreated Parkinson's disease for 12 years exhibited a significant improvement 24 hours after starting levodopa.[2] Tremor, a key motor symptom, exhibits variable responsiveness to treatment. This is due to differences in pathophysiology and stress-induced exacerbation. Levodopa is still the mainstay treatment, while dopamine agonists like pramipexole provide further advantages but are less effective than levodopa. Adjuncts like Monoamine Oxidase-B inhibitors (MAO-B) and Catechol-O-

methyltransferase inhibitors (COMT) inhibitors increase levodopa's effectiveness and improve tremor control.[3] One important treatment approach for PD is the combination of levodopa, carbidopa, and entacapone (LCE). By blocking peripheral metabolism and improving levodopa's transport to the brain, entacapone, a catechol-O-methyltransferase (COMT) inhibitor, is added to levodopa and carbidopa to assist in prolonging their effects. According to clinical research, LCE enhances motor function and quality of life (QoL) by decreasing "OFF" time and improving daily "ON" time without raising the risk of dyskinesia, a typical adverse effect of levodopa medication.[4] Dopamine agonists improve more general characteristics of patient well-being in addition to motor symptoms. Pramipexole, a dopamine agonist that can be used as an adjuvant or monotherapy, lowers the motor problems brought on by levodopa. In the meta-analysis, the combined data from six randomized controlled trials (RCTs) with a total of 2000 patients showed that pramipexole significantly improved Parkinson's Disease Questionnaire (PDQ-39) scores on average when compared to a placebo.[5] Selegiline, a selective monoamine oxidase B (MAO-B) inhibitor, has been shown to significantly reduce motor symptoms as assessed by the Unified Parkinson's Disease Rating Scale (UPDRS). But, when used for extended periods of time, its safety profile suggests caution and emphasizes the necessity of customized treatment plans for individual patients.[6]

II. EPIDEMIOLOGY

In just 26 years, the number of people affected by Parkinson's disease has more than quadrupled globally, rising from 2.5 million cases (95% confidence interval: 2.0-3.0) in 1990 to 6.1 million cases (5.0-7.3) in 2016. This rise can partly be attributed to population aging, extended illness duration, and potential alterations in social or environmental risk factors. By roughly 2050, we can anticipate that during the following 30 years, there will be more than 12 million patients globally.[7]
Parkinson's disease caused 1,064,753 deaths worldwide. There were significantly more male fatalities (585,321) than female deaths (479,432), resulting in a female-to-male ratio of 0.82. Compared to men, women die at a rate of 18.09% lower.[8]

III. ETIOLOGY

Parkinson's disease is caused in many ways (Fig. 1), which finally results in decreased Patients' Quality of Life (QoL).

1. Mitochondrial Dysfunction

It is well established that mitochondrial dysfunction is the primary source of dopamine neuronal death and malfunction in the substantia nigra pars compacta. Mitochondria control energy production through the processes of aerobic oxidative phosphorylation, intracellular calcium levels, lipid metabolism, and the breakdown of steroids, carbohydrates, and amino acids. Additionally, they serve as gatekeepers for the apoptotic machinery, which completes orderly cell death, and they indicate apoptosis pathways. The dynamics of mitochondrial fusion and fission have a major role in dopamine neuron survival. Mutations in the genes PTEN-induced putative kinase 1 (PINK1), Parkin, and SNCA (alpha-synuclein), which control all mitochondrial processes, are known to produce inherited forms of Parkinson's disease.[9]

2. Mitochondrial DNA damage

There's a chance that the dopaminergic cell disease is exclusive to the mitochondrial DNA (mtDNA) damage. The mitochondrial DNA encodes 37 genes, including 13 protein components for complex I–V of the electron transport chain (ETC). It is situated near the inner mitochondrial membrane, which is the site of oxidative phosphorylation.[9] Mutations in the substantia nigra's dopamine neurons can result from damage to mtDNA, including strand breakage and base alterations, due to the absence of histones and restricted repair processes.[9]

3. Biochemistry Of Oxidative Stress

Oxygen species and redox-active metals can interact directly through processes like the Fenton and Haber-Weiss reactions or indirectly through the activation of enzymes like NADPH oxidases (Nicotinamide adenine dinucleotide phosphate reduced oxidase) or nitric oxide synthase (NOS). Both of these processes have the potential to produce reactive oxygen species (ROS).[10] Although peroxisomes can also manufacture H2O2, the electron transport chain's mitochondrial complexes I and III are the main producers. Catalase is one of the enzymes found in peroxisomes that converts H2O2 to water. However, when peroxisomes are damaged and their enzymes are down-regulated,

H2O2 is released into the cytosol and adds to oxidative stress.[11]

4. Dopamine

While the vesicular monoamine transporter 2 (VMAT2) regulates cytoplasmic dopamine levels and prevents the production of reactive oxygen species (ROS), dopaminergic neurons that have VMAT2 blocked genetically or pharmacologically are more vulnerable to toxic shocks.[12]

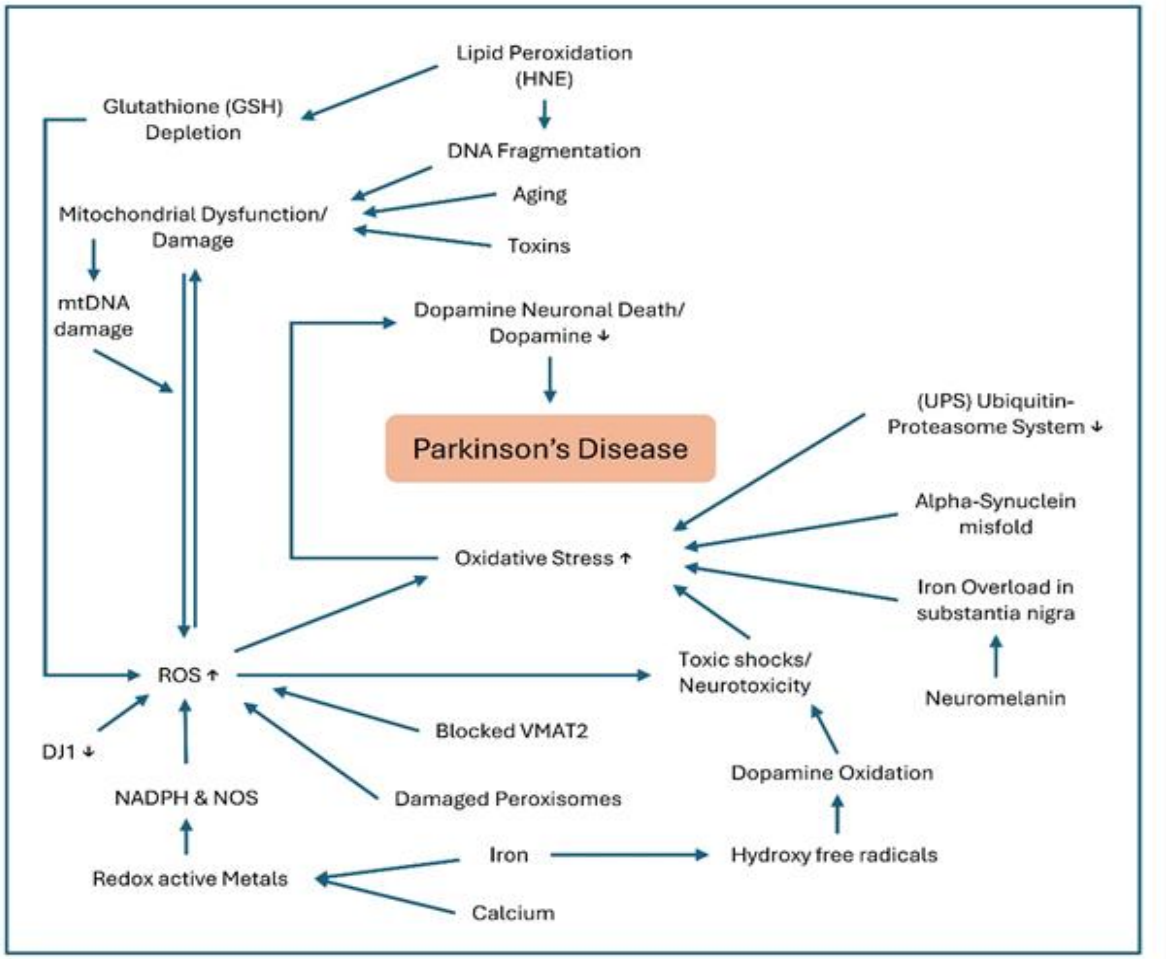

Fig. 1: The underlying causes and contributing factors of Parkinson's disease.

5. Neuromelanin

Neuromelanin is a polymer that increases cellular sensitivity, and there may be a connection between the quantity of this pigment in specific brain areas and neuronal death.[13] Neuromelanin study has shown an early iron overload and accumulation in the substantia nigra (SN) of Parkinson's disease patients, which may result in elevated oxidative stress.[14] The relationship between neuromelanin and alpha-synuclein is another idea regarding how neuromelanin influences neuronal vulnerability.[15]

6. Glutathione

GSH - Glutathione (γ-glutamyl-cysteinyl-glycine) levels are lowered because glutathione inhibits complex I activity, which increases the production of ROS. This drop in GSH levels could be due to either decreased synthesis caused by glutathione reductase inhibition or elevated glutathione disulfide (GSSG) levels and a modified GSH:GSSG ratio.[16] Due to thiol oxidation of key residues, GSH depletion in the SN results in a particular decrease in complex I activity of the mitochondria, which in turn leads to a notable reduction in overall mitochondrial function.[17]

7. Iron

Iron is necessary for almost all cell types, including brain cells. Iron ions can produce reactive oxygen species (ROS) because ferric iron (Fe^{3+}) and ferrous iron (Fe^{2+}) can react with hydrogen peroxide and superoxide, respectively, in a chain reaction that

produces the highly reactive hydroxyl free radical, which when combined with dopamine oxidation can cause neurotoxicity.[18] Aging and degenerative processes are characterized by unusual, progressive iron deposition and increased free iron concentration in the SNPC.[19]

8. Calcium

The primary mesencephalic dopaminergic neurons in culture cause the opening of L-type Ca2+ channels, which leads to raised mitochondrial oxidant stress in dendrites. This regulation of intracellular calcium results in increased mitochondrial activity and concomitant increased generation of reactive oxygen species.[20]

9. Lipids

Lipid peroxidation results in tissue damage and membrane structural damage. 4-hydroxyl-2-nonenal (HNE) not only reduces GSH levels but also activates members of the caspase family and causes DNA fragmentation, which leads to apoptosis.[21] The increased propensity of polyunsaturated fatty acids for peroxidation in oxidative stress conditions further damages neurons and speeds up the progression of Parkinson's disease.[22]

10. Ubiquitin-Proteasome System (Ups)

The ubiquitin-proteasome system (UPS) is the primary mechanism by which cells degrade and remove defective and unwanted proteins.[23] It is believed that the proteasome's efficient elimination of these unwanted compounds during oxidative stress serves as a defence mechanism. Thus, the breakdown of oxidized proteins poses a threat to the creation of toxic aggregations.[24]

11. Alpha-Synuclein

Alpha-synuclein aggregates in Parkinson's disease, causing Lewy bodies to develop in neurons. When alpha-synuclein misfolds, pathogenic clumps are formed that impair cellular activity. These aggregates cause toxicity inflammation, and neurodegeneration.[25]

12. Parkinson's Pathway Regulators

These are the proteins that regulate mitochondrial quality control, oxidative stress response, and cellular health in neurons. Autosomal recessive early-onset Parkinson's disease (PD) is linked to mutations that impair the E3 ubiquitin ligase activity of the cytoplasmic and nuclear protein *Parkin*.[26] Muscle dysfunction is linked to the drosophila expressing the mutant Parkin, which displays enlarged mitochondria with disruption and disintegration of the cristae, as well as degeneration of dorsomedial dopaminergic neurons.[27] Lack of PTEN-induced putative kinase 1 *(PINK1)* causes the mitochondria in cultivated cells to shrink, bulge, and fragment. It also causes the activity of mitochondrial enzymes, especially Complex I, to decrease. The *PARK7* gene mutations cause *DJ-1* to stop functioning which is a neuroprotective protein that controls the anti-inflammatory, anti-oxidant, and anti-apoptotic pathways.[28] An increase in Leucine-rich repeat kinase 2 *(LRRK2)* activity causes neuronal death through mitochondrial-dependent apoptosis.[29]

13. Aging

Neurodegenerative diseases are triggered by an age-related decrease in mitochondrial activity high amount of (mtDNA) deletions and a rise in the production of ROS as a result.[30]

14. Toxins

Pesticides such as herbicide paraquat and rotenone can easily penetrate cell membranes and gather in mitochondria, where they inhibit Complex I by compromising oxidative phosphorylation, which leads to oxidative stress and the death of dopamine neurons in PD.[31]

IV. PATHOPHYSIOLOGY

Lewy bodies (LB), which are neuronal inclusions primarily composed of Alpha-synuclein protein aggregations, are the pathological hallmark of Parkinson's disease. Due to this aggregation of LB, it leads a high chance of impaired motor function due to a shortage of dopamine-producing neurons. In particular, the Alpha-synuclein protein (SNCA) causes self-aggregation aberrantly. In LB aggregations, the presence of proteins like ubiquitin and ubiquitin alpha-synuclein impedes neuronal activity. In the case of neuron degradation, gene mutations encoding proteins that were found in the central nervous system play a role effectively.[32]

In general, cells of dopaminergic neurons, which are situated in the substantia nigra pars compacta (SNpc) in the basal ganglia, were destroyed. Then it causes dopamine stock lesion due to precipitation of nigrostriatal tract degeneration and leads to acetylcholine imbalance, which shows modulatory

or inhibitory effects on dopamine, because the corpus striatum's basic function relies on a balance between the excitatory effects of acetylcholine. This entire process causes extrapyramidal system impairment, which is responsible for complex body movements and results in symptoms of PD.[32]

V. MECHANISM OF ACTION

Levodopa functions as a precursor to dopamine that has the ability to enter the brain, something that dopamine is unable to achieve. The enzyme aromatic L-amino acid decarboxylase (AADC) in surviving dopaminergic neurons transforms it into dopamine once it passes across the blood–brain barrier. In addition to activating D1 and D2 receptors, which are necessary for appropriate motor communication within the basal ganglia, the dopamine produced by this mechanism aids in restoring depleted striatal reserves. Levodopa helps alleviate the main motor issues associated with Parkinson's disease, such as tremor, rigidity, and slowed movement, through this repair. Levodopa is nearly always used in conjunction with carbidopa to increase its efficacy. By preventing its breakdown in peripheral tissues, carbidopa minimizes adverse effects including nausea and hypotension while increasing the amount of levodopa that reaches the brain.[33] In order to make up for the loss of natural dopamine in Parkinson's disease, the dopamine agonist pramipexole acts by directly stimulating dopamine receptors in the brain, particularly the D3 receptor. It helps alleviate motor symptoms by binding most strongly to D3 receptors and somewhat activating D2 receptors. It protects the nigrostriatal pathway by reducing endogenous dopamine production and oxidative stress through its action on presynaptic dopamine autoreceptors. Apart from its motor advantages, pramipexole also affects dopaminergic pathways in the mesolimbic system, which helps explain its antidepressant effects in major depression and Parkinson's disease.[34] The MAO-B enzyme in the brain is selectively and permanently inhibited by selegiline. Dopamine is generally broken down by MAO-B, thus when this enzyme is inhibited, dopamine remains active longer. This helps in raising dopamine levels in the brain. It enters the body and is converted into amphetamine, methamphetamine, and desmethylselegiline, which mostly support its dopaminergic action but may also provide minor stimulant qualities.[35] The enzyme catechol-O-methyltransferase (COMT), which typically converts levodopa (LD) into the metabolite 3-OMD in peripheral tissues, is selectively and reversibly blocked by entacapone. Entacapone prolongs the duration of levodopa's circulation and increases its availability in the body by blocking this metabolic route. Levodopa levels in the bloodstream stabilize as a result, giving the brain dopaminergic effects that are smoother and longer-lasting. Entacapone's effects are limited to the peripheral nervous system since it cannot pass through the blood–brain barrier. It is frequently used with levodopa and a dopa-decarboxylase inhibitor, like carbidopa, particularly in Parkinson's disease patients who are experiencing "wearing-off" symptoms.[36]

VI. MATERIALS

1. Materials

A Prospective case-series (Case-Cohort) study was conducted with a sample size of 120 following one small group of subjects, concerned with the frequency and amount of exposure in subjects with a specific disease. To determine the management of Parkinson’s disease, with Pharmacological treatment at the site of Andhra Pradesh Vaidya Vidhana Parishad (APVVP) Govt. District Hospital, Proddatur, India.

2. Inclusion Criteria

- Adults with a diagnosis of Parkinson’s disease.
- Patients who are willing to participate in the study procedure.

3. Exclusion Criteria

- Supranuclear gaze palsy or saccades diagnosed patients.
- Probable behavioural variant frontotemporal dementia or primary progressive aphasia diagnosed patients.
- Parkinsonian features in <18 y People.
- No response to high-dose levodopa despite at least moderate severity of disease.
- Unequivocal cortical sensory loss, clear limb ideomotor apraxia, or progressive aphasia.
- Pregnancy and Lactating Women.

4. Study Procedure:

Data from individual patients were collected from specially designed patient data entry Case Reports. The outcomes will be Analysed by using the following data:

- Demographic details of the patient.
- Patient Medical History.
- Patient Medication History.
- Personal Habitat and Lifestyle of the patient.
- Patient Family History.
- Diagnosis of the patients.
- Pharmacological Treatment.
- Length of the story in Hospital.

VII. METHODS

The patient underwent a Physical examination for the diagnosis of PD. We observed Tremors, Rigidity, Bradykinesia, and Postural instability by physical examination. The tremors were observed as uncontrollable shaking by allowing the patient, to be seated in a chair and both hands are comfortably resting on their thighs, completely extend their elbow and flex their arm forward at a 90° angle to check for postural tremor. To evaluate the stiffness, flexion and extension of the wrist forearm, and lower limbs were done. The slow movements were observed by allowing the patient to open and close the fist, by pronating and supinating the hand, and by tapping the toe while seated in a chair and placing both feet on the floor. The stability abnormalities were observed with loss of balance and arm swings examined by free-standing and walking. The Imaging examination with an MRI Scan was also performed. Examinations like Complete blood picture, C-reactive protein, Erythrocyte sedimentation rate, Liver and Renal function test, Electrocardiogram, Blood pressure, and Fasting and Post Prandial Blood Sugar Test are done as a common clinical procedure.

In this prospective study, we evaluated all patients who met the inclusion criteria and were admitted as inpatients to APVVP Hospital in various wards based on their gender and idiopathic Parkinson's disease diagnosis. The first occurrence of any motor symptom as described by the patient, a family member, or a doctor was considered the disease's onset. To guarantee supervision, patients with incapacitating symptoms were admitted to the hospital. Clinical information was documented 24 hours following the start of levodopa treatment in these instances. The clinical examination covered the development of motor signs after therapeutic procedures. Symptoms were evaluated at baseline visits by combining 10g of carbidopa with 100 mg of levodopa.

Following the first levodopa-carbidopa dose ever taken in the morning, patients received one or two further doses of the medication that day (Day 1), and then began taking it three or four times a day starting the following day (Day 2-3). They then continued to adhere to this dosage schedule. (Dopamine agonists) - Pramipexole 0.25 mg, (Monoamine Oxidase-B inhibitors (MAO)) - selegiline 5 mg, (Catechol-O-methyltransferase inhibitors (COMT)) - Entacapone 200 mg, and an extra 50/5 mg of levodopa-carbidopa or further dose might be administered during the follow-up, as required, to obtain satisfactory control of motor symptoms if additional treatment was needed. At every follow-up schedule, all patients were evaluated for the existence of motor fluctuations at least eight hours after levodopa withdrawal (overnight OFF), 90 minutes after levodopa ingestion (ON state), and with different therapies based on patient status.

VIII. RESULTS

The progression of symptoms in patients who were diagnosed with PD was confirmed by physical examination – with observed results of involuntary, stiff, slow - movements and loss of balance and leaning postures. And by imaging examination with the help of MRI which is only limited to ruling out structural abnormalities, confirming age-related cerebral atrophy in 12 patients in our study. Gradual improvements of motor manifestations were observed by pharmacological treatment. The patients diagnosed with clinical features and given treatment regimens can see in (Table: 02), with a stay period of 97 patients 06-10 days and 23 patients 11-15 days. About 77 patients are Men diagnosed with PD than women (Table: 01). Patients were highly diagnosed with tremors along with/without other conditions. A patient who was diagnosed with PD was prescribed Levodopa + Carbidopa LD/CD (100/10mg) with variable doses and frequencies based on their conditions. About 11 patients received 110mg × 02 frequencies, 30 patients received 110mg × 03, 67 patients received 110mg × 04, and 12 patients received 110mg × 05 doses. Along with levodopa + carbidopa, several patients were prescribed adjuvants like pramipexole 0.25mg once a day (OD) 1 hour before bedtime, selegiline 5mg OD, and Entacapone 200mg OD after 3 days of initial therapy of LD/CD. Patients who experienced – weakness and were diagnosed with age-related cerebral atrophy were administered Vitamin B12

and Multivitamin tablets OD at noon time. And the Betahistine 8mg OD or BD, or 16 mg OD prescribed for vertigo and anxiety disorders. Deriphyllin® taken for Shortness of Breath. In contrast, azithromycin has been used for throat infections. The NSAIDs and Gastritis regimens were prescribed usually according to the patient's conditions. Abnormal motor symptoms with following therapeutic regimens by day-by-day follow-up show significant improvements in patients diagnosed with PD. About 25% after 5 days of follow-up showed slight and 67% after 10 days of follow-up showed moderate - PD symptom reduction along with other clinical features associated with it. In contrast 25% of patients show symptomatic improvement when treated without LD/CD adjuvants.

Table No.: 01, Diagnosed patients based on Age and Gender.

Age	Male	Female	NO. OF. PATIENTS
20-39	04	02	06
40-59	24	13	37
60-79	43	21	64
80+	06	07	13
Total	77	43	120

Table No.: 02, Diagnosed patient's clinical features and pharmacological treatment data.

Disease-dependent Clinical Features	No. Of. Patients	Other Clinical Features	No. Of. Patients	Pharmacological treatment	No. Of. Patients
Tremor	22	Bloating and Gastric Problems	18	Levodopa and Carbidopa - 100/10mg.	120
Rigidity	13	Abdominal Spasms	07	Pramipexole - 0.25mg	37
Bradykinesia	06	Anxiety & Depression	13	Selegiline - 5mg	19
Postural Instability	08	Restlessness and sleep disturbances	16	Entacapone - 200mg	34
Tremor + Rigidity	24	Confusion and unusual behaviors	15	Azithromycin – 500mg	06
Tremor + Bradykinesia	12	Vertigo	11	Betahistine - 8,16 mg	31
Tremor + Rigidity + Bradykinesia	08	Shortness of Breath	09	Etofylline and theophylline – 77&23mg (Deriphyllin®)	10
Tremor + Postural Instability	07	Speech difficulties	17	Vitamin B12 and Multivitamins	40
Rigidity + Postural Instability	07	Loss of Smell	08	Diclofenac - 50mg	97
Bradykinesia + Postural Instability	13	Difficulty in Swallowing	06	Ranitidine -150mg /Pantoprazole - 40 mg	120
Total	120	Total	120	Individual patients are administered Multiple medications according to disease state and conditions.	

IX. DISCUSSION

The progressive death of dopaminergic neurons in the substantia nigra pars compacta is the hallmark of Parkinson's disease (PD). This complex neurodegenerative illness causes both motor and non-motor symptoms. In this study, Levodopa has been a major advancement in the pharmacological treatment of Parkinson's disease. Even in patients with chronic, untreated PD, levodopa significantly reduced motor symptoms. Management of tremors is still difficult because of their inconsistent response to therapy. While dopamine agonists like pramipexole offered excellent alleviation for severe cases, in treating motor symptoms and enhancing quality of life for both early and advanced stages of Parkinson's disease, the improvements last for different lengths of time. selegiline, a selective MAO-B inhibitor, also provided long-lasting relief from motor symptoms. Levodopa with carbidopa and entacapone in one combination therapy that has shown improvement in quality of life and motor function. Entacapone is a good long-term management option because it prolongs levodopa's effects without appreciably increasing the risk of dyskinesia. However, other COMT inhibitors, such as opicapone, might provide longer-lasting advantages. Even though PD is not curable permanently, providing treatment for extended periods improves motor symptoms and patients' quality of life.

X. CONCLUSION

This study presents that, even in a setting with limited resources, pharmacological interventions - specifically, Levodopa-Carbidopa (LC) therapy significantly improve motor symptoms of Parkinson's disease. Levodopa-carbidopa, along with the combination of adjuvants like Pramipexole, selegiline, and Entacapone, improves the efficacy of LC treatment, which aids in the enhancement of normal motor features. However, even while short-term results are encouraging, future studies are required in order to improve patients' quality of life. Long-term follow-up management techniques may be helpful with complete care regimens that address both motor and nonmotor symptoms.

REFERENCES

[1] Saeedi, H., Remington, G., & Christensen, B. K. (2006). Impact of haloperidol, a dopamine D2 antagonist, on cognition and mood. Schizophrenia research, 85(1-3), 222–231. https://doi.org/10.1016/j.schres.2006.03.033

[2] Cilia, R., Cereda, E., Akpalu, A., Sarfo, F. S., Cham, M., Laryea, R., Obese, V., Oppon, K., Del Sorbo, F., Bonvegna, S., Zecchinelli, A. L., & Pezzoli, G. (2020). Natural history of motor symptoms in Parkinson's disease and the long-duration response to levodopa. Brain : a journal of neurology, 143(8), 2490–2501. https://doi.org/10.1093/brain/awaa181

[3] Pirker, W., Katzenschlager, R., Hallett, M., & Poewe, W. (2023). Pharmacological Treatment of Tremor in Parkinson's Disease Revisited. Journal of Parkinson's disease, 13(2), 127–144. https://doi.org/10.3233/JPD-225060

[4] Reichmann H. (2023). Real-world considerations regarding the use of the combination of levodopa, carbidopa, and entacapone (Stalevo®) in Parkinson's disease. European journal of neurology, 30 Suppl 2, 15–20. https://doi.org/10.1111/ene.15992

[5] Li, T., Zou, S., Zhang, Z., Liu, M., & Liang, Z. (2022). Efficacy of pramipexole on quality of life in patients with Parkinson's disease: a systematic review and meta-analysis. BMC neurology, 22(1), 320. https://doi.org/10.1186/s12883-022-02830-y

[6] Wang, K., Liu, Z. H., Li, X. Y., Li, Y. F., Li, J. R., Hui, J. J., Li, J. X., Zhou, J. W., & Yi, Z. M. (2023). Efficacy and safety of selegiline for the treatment of Parkinson's disease: A systematic review and meta-analysis. Frontiers in aging neuroscience, 15, 1134472. https://doi.org/10.3389/fnagi.2023.1134472

[7] Rocca, W. A. (2018, November). The burden of Parkinson's disease: a worldwide perspective. The Lancet Neurology, 17(11), 928–929. https://doi.org/10.1016/s1474-4422(18)30355-7

[8] Lampropoulos, I. C., Malli, F., Sinani, O., Gourgoulianis, K. I., & Xiromerisiou, G. (2022). Worldwide trends in mortality related to Parkinson's disease in the period of 1994–2019: Analysis of vital registration data from the WHO Mortality Database. Frontiers in Neurology, 13, 956440. https://doi.org/10.3389/fneur.2022.956440

[9] B. R. de Miranda and J. T. Greenamyre, in Oxidative Stress and Redox Signalling in Parkinson's Disease, ed. R. Franco, J. A. Doorn, and J. Rochet, The Royal Society of Chemistry, 2017, pp. 1-26.

[10] Smith, D. G., Cappai, R., & Barnham, K. J. (2007). The redox chemistry of the Alzheimer's disease amyloid beta peptide. Biochimica et biophysica acta, 1768(8), 1976–1990. https://doi.org/10.1016/j.bbamem.2007.02.002

[11] Valko, M., Leibfritz, D., Moncol, J., Cronin, M. T., Mazur, M., & Telser, J. (2006). Free radicals and antioxidants in normal physiological functions and human disease. The International Journal of Biochemistry & Cell Biology, 39(1), 44-84. https://doi.org/10.1016/j.biocel.2006.07.001

[12] Uhl, G. R., Li, S., Takahashi, N., Itokawa, K., Lin, Z., Hazama, M., & Sora, I. (2000). The VMAT2 gene in mice and humans: amphetamine responses, locomotion, cardiac arrhythmias, aging, and vulnerability to dopaminergic toxins. FASEB journal : official publication of the Federation of American Societies for Experimental Biology, 14(15), 2459–2465. https://doi.org/10.1096/fj.00-0205rev

[13] Kastner, A., Hirsch, E. C., Lejeune, O., Javoy-Agid, F., Rascol, O., & Agid, Y. (1992). Is the vulnerability of neurons in the substantia nigra of patients with Parkinson's disease related to their neuromelanin content?. Journal of neurochemistry, 59(3), 1080–1089. https://doi.org/10.1111/j.1471-4159.1992.tb08350.x

[14] Double, K. L., Gerlach, M., Schünemann, V., Trautwein, A. X., Zecca, L., Gallorini, M., Youdim, M. B., Riederer, P., & Ben-Shachar, D. (2003). Iron-binding characteristics of neuromelanin of the human substantia nigra. Biochemical pharmacology, 66(3), 489–494. https://doi.org/10.1016/s0006-2952(03)00293-4

[15] Gründemann, J., Schlaudraff, F., & Liss, B. (2011). UV-laser microdissection and mRNA expression analysis of individual neurons from postmortem Parkinson's disease brains. Methods in molecular biology (Clifton, N.J.), 755, 363–374. https://doi.org/10.1007/978-1-61779-163-5_30

[16] Genestra M. (2007). Oxyl radicals, redox-sensitive signalling cascades and antioxidants. Cellular signalling, 19(9), 1807–1819. https://doi.org/10.1016/j.cellsig.2007.04.009

[17] Chinta, S. J., Kumar, M. J., Hsu, M., Rajagopalan, S., Kaur, D., Rane, A., Nicholls, D. G., Choi, J., & Andersen, J. K. (2007). Inducible alterations of glutathione levels in adult dopaminergic midbrain neurons result in nigrostriatal degeneration. The Journal of neuroscience: the official journal of the Society for Neuroscience, 27(51), 13997–14006. https://doi.org/10.1523/JNEUROSCI.3885-07.2007

[18] Jomova, K., & Valko, M. (2011). Advances in metal-induced oxidative stress and human disease. Toxicology, 283(2-3), 65–87. https://doi.org/10.1016/j.tox.2011.03.001

[19] Sian-Hülsmann, J., Mandel, S., Youdim, M. B., & Riederer, P. (2011). The relevance of iron in the pathogenesis of Parkinson's disease. Journal of neurochemistry, 118(6), 939–957. https://doi.org/10.1111/j.1471-4159.2010.07132.x

[20] Dryanovski, D. I., Guzman, J. N., Xie, Z., Galteri, D. J., Volpicelli-Daley, L. A., Lee, V. M., Miller, R. J., Schumacker, P. T., & Surmeier, D. J. (2013). Calcium entry and α-synuclein inclusions elevate dendritic mitochondrial oxidant stress in dopaminergic neurons. The Journal of neuroscience: the official journal of the Society for Neuroscience, 33(24), 10154–10164. https://doi.org/10.1523/JNEUROSCI.5311-12.2013

[21] Liu, W., Kato, M., Akhand, A. A., Hayakawa, A., Suzuki, H., Miyata, T., Kurokawa, K., Hotta, Y., Ishikawa, N., & Nakashima, I. (2000). 4-hydroxynonenal induces a cellular redox status-related activation of the caspase cascade for apoptotic cell death. Journal of cell science, 113 (Pt 4), 635–641. https://doi.org/10.1242/jcs.113.4.635

[22] Montine, K. S., Quinn, J. F., Zhang, J., Fessel, J. P., Roberts, L. J., 2nd, Morrow, J. D., & Montine, T. J. (2004). Isoprostanes and related products of lipid peroxidation in neurodegenerative diseases. Chemistry and physics of lipids, 128(1-2), 117–124. https://doi.org/10.1016/j.chemphyslip.2003.10.010

[23] Olanow, C. W., & McNaught, K. S. (2006). Ubiquitin-proteasome system and Parkinson's disease. Movement disorders: official journal of the Movement Disorder Society, 21(11), 1806–1823. https://doi.org/10.1002/mds.21013

[24] Davies K. J. (2001). Degradation of oxidized proteins by the 20S proteasome. Biochimie, 83(3-4), 301–310. https://doi.org/10.1016/s0300-9084(01)01250-0

[25] Braak, H., Rüb, U., Gai, W. P., & Del Tredici, K. (2003). Idiopathic Parkinson's disease: possible routes by which vulnerable neuronal types may be subject to neuroinvasion by an unknown pathogen. Journal of neural transmission (Vienna, Austria: 1996), 110(5), 517–536. https://doi.org/10.1007/s00702-002-0808-2

[26] Zhang, Y., Gao, J., Chung, K. K., Huang, H., Dawson, V. L., & Dawson, T. M. (2000). Parkin functions as an E2-dependent ubiquitin- protein ligase and promotes the degradation of the synaptic vesicle-associated protein, CDCrel-1. Proceedings of the National Academy of Sciences of the United States of America, 97(24), 13354–13359. https://doi.org/10.1073/pnas.240347797

[27] Whitworth, A. J., Theodore, D. A., Greene, J. C., Benes, H., Wes, P. D., & Pallanck, L. J. (2005). Increased glutathione S-transferase activity rescues dopaminergic neuron loss in a Drosophila model of Parkinson's disease. Proceedings of the National Academy of Sciences of the United States of America, 102(22), 8024–8029. https://doi.org/10.1073/pnas.0501078102

[28] Kahle, P. J., Waak, J., & Gasser, T. (2009). DJ-1 and prevention of oxidative stress in

Parkinson's disease and other age-related disorders. Free radical biology & medicine, 47(10), 1354–1361. https://doi.org/10.1016/j.freeradbiomed.2009.08.003

[29] Iaccarino, C., Crosio, C., Vitale, C., Sanna, G., Carrì, M. T., & Barone, P. (2007). Apoptotic mechanisms in mutant LRRK2-mediated cell death. Human Molecular Genetics, 16(11), 1319-1326. https://doi.org/10.1093/hmg/ddm080

[30] Reeve, A. K., Krishnan, K. J., Elson, J. L., Morris, C. M., Bender, A., Lightowlers, R. N., & Turnbull, D. M. (2008). Nature of mitochondrial DNA deletions in substantia nigra neurons. American journal of human genetics, 82(1), 228–235. https://doi.org/10.1016/j.ajhg.2007.09.018

[31] Perier, C., Bové, J., Vila, M., & Przedborski, S. (2003). The rotenone model of Parkinson's disease. Trends in neurosciences, 26(7), 345–346. https://doi.org/10.1016/S0166-2236(03)00144-9

[32] Sayyaed, A., Saraswat, N., Vyawahare, N., & Kulkarni, A. (2023). A detailed review of pathophysiology, epidemiology, cellular and molecular pathways involved in the development and prognosis of Parkinson's disease with insights into screening models. Bulletin of the National Research Centre, 47(1), 1-16. https://doi.org/10.1186/s42269-023-01047-4

[33] Vaziri, E. H., Jalali Rad, K., & Mohasseb, A. (2025). A Comprehensive Review on Levodopa Pharmacology and Its Drug Delivery Methods. Journal of Chemical Technology, 1(1), 1-6.

[34] Singh, R., & Parmar, M. (2023). Pramipexole. In StatPearls. StatPearls Publishing.

[35] Rinaldi, D., Alborghetti, M., Bianchini, E., Sforza, M., Galli, S., & Pontieri, F. E. (2023). Monoamine-oxidase Type B Inhibitors and Cognitive Functions in Parkinson's Disease: Beyond the Primary Mechanism of Action. Current neuropharmacology, 21(5), 1214–1223.

[36] Habet S. (2022). Clinical Pharmacology of Entacapone (Comtan) From the FDA Reviewer. The international journal of neuropsychopharmacology, 25(7), 567–575.