Tuijin Jishu/Journal of Propulsion Technology
ISSN: 1001-4055
Vol. 43 No. 4 (2022)

Parkinson's Disease Demystification: From Molecular to Treatment Strategies

Fahad Hamad Awadh Alharbi[1], Waleed Mohsen Hadi Marwi[1]*, Malek Ahmed Alahmadi[1], Mohammed Eid Altamimi[1], Anas Saad Algarni[1], Sami Salem Alreshidi[1], Mohammed Saud Alahmadi[1], Ismail Jaber Ali[1], Marwan Moslem D Almarwani[1], Ayman Humod Hendi Aljehani[2], Basem Monir G. Alradadi[3], Bashayir Mohammed Al Moghayir[4], Nouf Adel Abdulrahman Albouq[4], Osama Abdulmanim A Alsobhi[4], Zeyiad Abd Arhman Alenazy[5]

[1]King Fahd Hospital-Madinah, Khaled bin Alwaleed Street, Al Jamiah-3177, Madinah- 42351, Kingdom of Saudi Arabia

[2]Prince Abdul Mohsen Hospital - Al Ula, AlUla 43543, Kingdom of Saudi Arabia

[3]Al-Amal Mental Health Hospital Madinah, Alheam Street-42318, Medina-42376, Kingdom of Saudi Arabia

[4]Madinah Health Cluster, Saeed bin Alaas Street, Madinah-42351, Kingdom of Saudi Arabia

[5]Ohud Hospital-Medinah, As Salam-7118, Medina 42354, Kingdom of Saudi Arabia

*Corresponding author

E-mail: marwi@moh.gov.sa (Waleed Mohsen Hadi Marwi)

Submission: Jul. 15; 2022; Accepted: Nov 27, 2022; Published: Dec 03, 2022

Abstract

Parkinson's disease (PD) is a progressive neurological illness that causes symptoms that are both motor and non-motor. It is defined by the death of dopaminergic neurons in the substantia nigra. Parkinson's disease is a progressive neurological illness that causes symptoms that are both motor and non-motor. Despite extensive research, the precise cause of PD remains enigmatic and is thought to involve a complex interplay of genetic vulnerability, environmental factors, and disrupted cellular processes. This review delves into the complex molecular processes, including damage caused by oxidation, misfolded proteins, neuroinflammation, and mitochondrial malfunction, that underlie the development of Parkinson's disease. Additionally, it discusses emerging therapeutic strategies that target these pathways, including gene therapy, stem cell transplantation, and neuroprotective agents. This review highlights the potential and challenges in translating basic research findings into effective clinical interventions for PD. A comprehensive understanding of the disease's complex molecular mechanisms is essential for developing novel therapies that can alleviate symptoms and ultimately halt disease progression.

Keywords: Neurodegenerative disorder, Substantia nigra, Oxidative stress, Neuroinflammation, Genetic susceptibility.

Introduction

Parkinson's disease is a common neurological disorder that is marked by a variety of motor indications, including discomfort, recovery, trembling in the hands, poor and slow movement of the limbs, and issues with posture[1,2]. Its critical to distinguish between parkinsonism, a different name for a syndrome with comparable motor signs that can result from a number of diseases, including PD[3]. Lewy bodies, misfolded α-synuclein intracellular components, and dopaminergic neuron degeneration in the substantia nigra are some of its pathological features[4,5]. Risk factors for Parkinson's disease are associated with both hereditary and biological factors, even though the exact process underlying the condition's progressive loss of neurons is yet unknown. Even so, non-motor symptoms, such as dementia, persist. The clinical diagnosis of PD is predominantly based on its motor indications[6]. Although there are therapies to control motor symptoms, none of them stop the disease's advancement at this time[2,.3,4,6].

EPIDEMIOLOGY

Parkinson's disease is more prevalent in the elderly and rises with longevity (0.1-0.3% of the general population, 1.8% in those over 65, and 2-3% in those over 80).

The complexity of PD, with diverse symptoms, makes diagnosis and management challenging. Research on the relationship between anti-Parkinson medication and mental health symptoms like anxiety and depression has yielded conflicting results, emphasizing the need for individualized treatment approaches based on clinical evaluations[7,8].

CLINICAL MANIFESTATIONS

A challenging neurodegenerative illness, Parkinson's disease is characterized by a wide range of physical and mental signs that all play a part in the disease's progression and clinical presentations[9].

Motor symptoms

Motor grievances, such as poor and slow movement of the limbs, resting tremors, muscle rigidity, and issues with posture[13,14]. These motors impairments are often the most recognizable and are used as primary diagnostic criteria for the disease. However, it is essential to recognize that the severeaty and presentation of motor symptoms can vary widely among individuals with PD[10].

Non-motor symptoms

Non motor symptoms, including hyposmia (reduced sense of smell), constipation, sleep disturbances, and depression. These non motor manifestations often pose substantial challenges in clinical management and may require targeted interventions to alleviate patient Morbidity and mortality[11,12].

Early onset and impact

Non-motor symptoms are an essential indicator for an early diagnosis and subsequent treatment as they can appear far before motor signs do. Improving long-term results in Parkinson's disease and maximizing patient care require a holistic approach to non-motor symptoms[14].

Diagnostic tools

Ocular motor function test has emerged valuable diagnostic tool for PD, with specific eye movement abnormalities being indicative of the disease. These evaluations may assist in the initial diagnosis and advancement of surveillance, along with providing doctors with a better understanding of the neural root of Parkinson's disease [15].

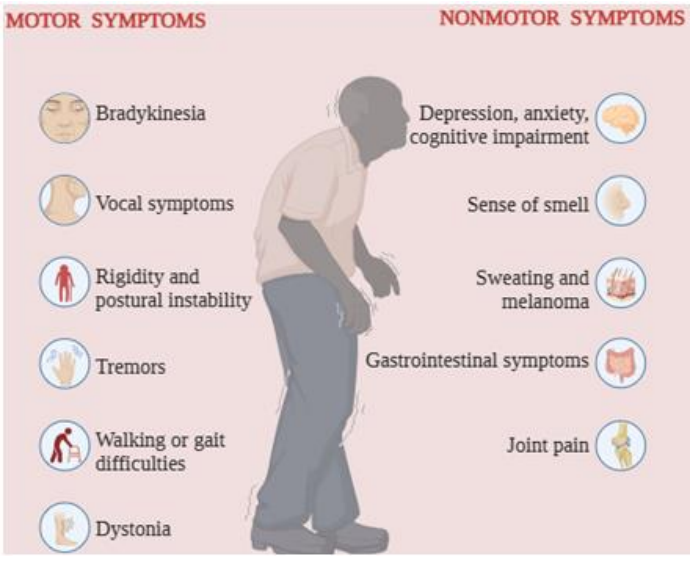

Fig. 1. Clinical manifestations of PD.

Etiology

It involves various factors, including genetic, Environmental, and age-related influences. Genetic aspects contributing to PD have been Confirmed through the discovery of mutations in specific genes like SNCA and GBA, Linked to both familial and sporadic cases of the illness[16]. Nevertheless, genetic factors alone do not account for PD, as indicated by the presence of non-genetic causes and the incomplete expression of known genetic mutations.

Environmental impact on Parkinson's Disease

Environment factors also exert a significant influence on PD's development. Exposure to neurotoxic substances, pesticides, and other environmental toxins has been associated with PD Onset. Evidence suggests that such exposure can cause gradual harm to the substantia nigra, potentially occurring many years before clinical symptoms emerge[17,18,20]. Moreover, epidemiological studies have identified protective effects from Lifestyle factors like smoking and coffee consumption, although the precise mechanism are still unclear.

Age related Aspects

Gerontology greatly complicates the association between environmental exposure and hereditary propensity. The primary risk factor for Parkinson's is years of age, as this disease is far more frequently diagnosed in elderly individuals. This suggest that age related cellular changes may heighten the susceptibility of dopaminergic neurons to various insults, thereby contributing to PD's development[19].

Interplay and covering pathways

In essence, PD is a multifaceted condition with a complex etiology that cannot be attributed to single cause. It's development likely involve a combination of genetic susceptibility, environmental exposure, age related factors. Converging pathways such as mitochondrial malfunction, oxidative stress and neuroinflammation play a pivotal role in the disease process[20,21]. Comprehending this intricate interaction is essential for devising effective therapeutic interventions to prevent or alter the progression of PD.

Understanding Parkinson's Disease Pathology

Parkinson's disease is characterized by Lewy bodies, which are intercellular inclusions mainly composed of fragmented alpha-synuclein, and a gradual degeneration of dopamine-producing neurons in the substantia nigra[22, 23]. The motor symptoms of PD, such as hardness, shaking hands, and poor and slow limb movement, are related to these pathological characteristics. Moreover, the pathology of Parkinson's affects the peripheral and enteric neural systems, in addition to the central nervous system, suggesting multisystem involvement [24].

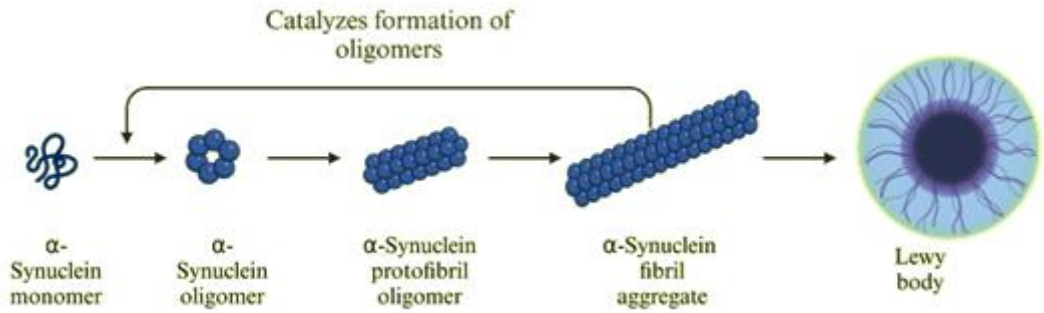

Fig. 2. Initially, alpha-synuclein monomers form smaller oligomers, which can be toxic to cells. These oligomers then aggregate further to form larger fibrils, which ultimately accumulate in neurons and disrupt cellular function.

Role of alpha-synuclein mutations

There's on going debate regarding this significance of specific alpha-synuclein mutations in PD. While certain familial PD cases are associated with mutation in the alpha-synuclein generate, such mutations are uncommon in sporadic PD[25]. However, the initiation of Parkinson's appears to progress in an observable way, potentially

including the intraneuronal transmission of alpha-synuclein clumps from the lower brainstem to the neocortex. The potential use of alpha-synuclein pathology in the peripheral nervous system as a diagnostic marker for prodromal illness lends legitimacy to this notion.[26].

Complex pathological mechanisms

While familial PD maybe linked to specific genetic mutations, pathology of sporadic PD is more intricate, involving multiple systems. The potential for alpha-synuclein aggregate to propagate through neural network provide insights into disease progression and offer avenues for early diagnosis through the detection of peripheral alpha-synuclein pathology[23,25,26,44].

Elaborating and Lewy bodies and dopaminergic neuron loss

This accumulation of proteins is considered to impede typical cell turnover while sustaining the neurons of the substantia nigra. The brain's ability to produce dopamine diminishes as these neurons become less effective, triggering the motor symptoms of Parkinson's disease [27,28,].

Multisystem involvement in Parkinson's pathology

Although PD is categorized as a central nervous system condition, research shows that its pathology may not be solely confined to the brain.[29,30]. The diverse spectrum of symptoms that people with Parkinson's disease endure, including non-motor symptoms like gastrointestinal issues and mental retardation along with to neurological symptoms, may be attributed to multisystem involvement.[33-37].

Parkinson's genesis involves connections between biology and the environment.

This condition possesses an enigmatic path that is influenced by both hereditary and external factors. Genetic involvement has been confirmed through the identification of PARK genes and a mutations in genes like SNCA, LRRK2, and GBA, associated with both familial and sporadic cases of the disease[38,39,40]. Additionally environmental factors, such as exposure to toxins and lifestyle choices, play a role in PD etiology with some studies proposing that environmental toxins could be play a role in PD etiology with some studies proposing that environmental toxins could induce epigenetic alterations contributing to the disease[31]. Notably, evidence suggests that genetic predisposition may modify an individual 's susceptibility to environmental risk factors, with genetic mutation influencing the impact of oxygen environment factors affecting the expression of PD related genes[42,43]. This interplay is further supported by observations of epigenetic modifications such as DNA methylation changes in genes involved in neurogenesis, possibly triggered by environmental exposures[32]. In summary, PD pathogenesis likely arises from a complex interaction between genetic prepositions and environment exposure with both contributing to the disease, potentially through epigenetic modification and Gene environment in interactions[41,42,43].

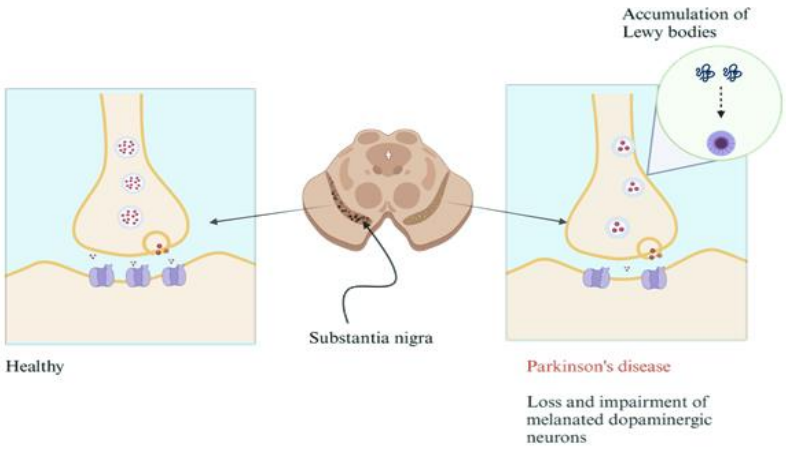

Fig. 3. progression of the illness in the (Lewy bodies, unstable protein aggregates within neurons, are prognostic of the onset of Parkinson's disease in the substantia nigra). The Lewy bodies, that are speculated to play a role in the neuronal malfunction and eventual cell death seen in Parkinson's illness, consist mainly of misfolded alpha-synuclein protein.

Pathogenesis

It has grown in popularity that dysfunction in mitochondria serves an essential part in the progression of Parkinson's disease. Research indicate that the neurodegenerative process observed may be mainly caused by oddities in mitochondrial function. The acquisition of mitochondrial contaminants, such as N-methyl-4-Phenyl-1,2,3,6-tetrahydropyridine (the compound MPTP), which elicits Parkinsonism and illustrates the susceptibility of dopaminergic neurons to mitochondrial collisions, supports this idea. Further emphasizing the vital function of mitochondrial abnormalities in the development and progression of Parkinson's disease is the fact that genetic research has associated specific mutations to defective mitochondria in both hereditary and atypical PD patients.

Despite it is typical in several neurological diseases, PD exhibits a specific kind of mitochondrial impairment resulting from diminished complex I activity and elevated stress levels. In spite of affecting energy production, this defect additionally impacts other critical mitochondrial activities like cell death, ferroptosis, the inflammasome activation all of which contribute to the progress of Parkinson's disease.

The observed electron transport patterns in multiple tissues and tissue cultivation data support a relationship between complex I deficiency and PD. Mendelian sequences of inheritance seldom occur in monozygotic twins despite the fact that nuclear genes encode a significant number of complexes I subunits. This finding may indicate a lack of concordance. It is vital keep in mind that the genome of a mitochondrial cell produces seven complex I subunits, which might clarify the reason complex 1 lesion show up intermittently in the disease. Reactive oxygen species could be generating as the consequence of complex I disarray, which could aid in the onset of Parkinson's disease. Reactive oxygen species (ROS) the generation pathway impacts mitochondrial DNA (mtDNA), that contains a replacement version of complex I subunits.

Fortunately, it is unusual for mitochondrial DNA or mtDNA mutations to be transferred from spouses in the case of PD, and genetic data indicate that mt variations in DNA might contribute to the pathology of TD. A single case resulting from a finding of a new point mutation in the mitochondrial 12 Sr RNA in a pedigree manifesting neuropathy, parkinsonism, and deafness. Furthermore, Parkinsonism has been associated with the G11778A mitochondrial mutation in Laber's optical atrophy. No homoplasmic point deletions were identified in the coding fields of mtDNA from PD subjects. PD was observed to be associated with low-level heterozymic mutations in the ND5 subunit of complex I, yet at far lower levels than in issues carried on by mtDNA mutations.

Evidence demonstrates that mitochondrial permeability plays a role in both congenital and random varieties of PD, with the latter emerging as a significant pathological marker. The potential for therapeutic intervention to target malfunctioning mitochondria is demonstrated by the overlapping of genetic compromise and external factors in mitochondrial pathways. However, further studies are required to identify the specific process by which the breakdown of mitochondria causes Parkinson's illness and to design an effective therapy based on these findings. The primary roles of oxidative stress and mitochondrial malfunction in Parkinson's disease (PD) are supported by mutations in the nuclear encoder mitochondrial genes, including PINK1, DJ-1, and Omi/HtrA2. Protecting mitochondria from damage caused by oxygen and cell death requires the mitochondrial protein kinase PINK1. The G309D missense mutation in the PINK1 gene reduces its kinase activity, which could impair neural protection from oxidative stress. [45-54].

Complications

The longevity of PD patients is markedly lesser than that of the general population. PD mostly affects the nervous system and is a neuro degenerative illness, though it may additionally trigger non-neurological symptoms and difficulties. Lewy bodies, which are symptomatic of Parkinson's condition, for instance, to imply a more pervasive systemic involvement than mere a neurological condition. Studies on GB A1 a mutation careers show the affect of environmental as well as genetic variables on the neurological spectrum that further demonstrates its clinical diversity. Genetic and external variables work together to contribute to these issues, which reinforces the requirement for extensive treatment approaches that satisfy the numerous requirements individuals with PD[55-59].

Clinical Diagnosis

Rigidity involves consistent resistance to passive moment of a linked to "lead pipe' rigidity while tremor typically occurs at rest[63]. These motor symptoms are crucial for diagnosing PD and are often accompanied by postural instability. However, that clinical presentation of PD[61] can be intricate. Non motor symptoms are increasingly recognized and included in diagnostic criteria reflecting PD's diverse nature with both motor and non-motor effects[60]. Moreover, differential diagnosis is vital, another form of Parkinsonism can mimic PD but have different causes and outlooks. Diagnosis is supported by clinical criteria[62,64-66].

Asymmetrical clinical findings play a significant role in diagnosing

Parkinsonism should be diagnosed to obtain an accurate diagnosis, which entails poor and slow limb movement, and possibly shaking at rest or stiffness. A supportive criterion that increases optimism regarding prognosis is the appearance of imbalance, whereas the opposite side of the body has a greater impact than the other side of the body. This accumulation is frequently apparent when the condition first begins, and can continue to occur as it develops[68,69]. While asymmetry supports PD diagnosis other criteria are also considered. For example, the presence of unusual neurological signs like early dementia or a typical Parkinsonism may complicate the diagnosis[70]. The criteria aim to maximize specificity, especially for early or new cases of PD, by excluding cases where disease duration components are present and by modifying red flags to be absolute exclusions[67].

A critically important instrument for the detection and management of Parkinson's disease (PD) is the unified Parkinson's disease rating scale (UPDRS).[71,72], offering a holistic assessment of the condition's severity and progression, while the UPDRS scale is a cornerstone in PD assessment, it's predictive power of certain aspects of the disease such as peak aerobic capacity, KS is not always robust, this underscores the complexity of PD and the need for a comprehensive diagnostic approach. Expert diagnosis remains crucial, as the UPDRS scale is typically administered by a specialist who evaluates motor and behavioral symptoms through observation. The UPDRS scale goes beyond symptom assessment, it also aids in predicting functional capacities like aerobic capacity and ambulatory function, albeit with limitations. To enhance its predictive capabilities, the UPDRS scale is often used alongside other, such as the Hoehn and Yahr scale. This highlights the importance of a multifaceted diagnostic approach in PD management[73].

Table. 1. Diagnostic method of pakinson’s disease.

S.no	Diagnostic method	Description	References
1	Healthcare history	Extensive healthcare history, including the initial onset and progression of symptoms, how well the individual behaved to medication, the presence of risk factors, and any familial history of Parkinson's disease.	[116]
2	Physical assessment	Motor manifestations were examined physiologically.	[117]
3	Neurological examination	Evaluation of gait, balance, coordination, and other neurological signs to assess the extent of motor impairment.	
4	Response to Dopaminergic therapy	Improvement in motor symptoms following a trial of dopaminergic medications can support the diagnosis of parkinson’s disease.	[60]
5	Diagnostic procedures included magnetic resonance imaging (MRI) and DAT tests.	MRI: To examine abnormalities in the brain and rule out possible root causes of Parkinsonism. DAT test: To determine dopamine transporter levels in the brain.	[118]

Management of PD

Managing is effectively requiring a comprehensive, multidisciplinary. This approach involves a team of health care professionals, including neurologists, psychiatrists, physical therapists, and others working together to address the multifaceted challenges of the disease[74,76,79]. Palliative care concepts have shown promise in improving symptoms in advanced PD patients, like the benefits observed in patients with metastatic cancer, highlighting the importance of a holistic approach to management. Day-Clinic models that offer multidisciplinary care have also been effective in improving both motor and non-motor symptoms, underscoring the value of integrated care approaches in PD management[75,77,78,80]

Noteworthy that while adherence to pharmacological treatment is crucial for symptom management, non-adherence remains a significant issue. Interventions aimed at improving adherence have been shown to lead to better clinical outcomes and QOL[82-86]. For instance, physiotherapy interventions have demonstrated effectiveness in reducing falls, improving posture, and enhancing QOL in PD patients[81]. Surgical intervention such as deep brain simulation offer promise in outcomes for selected patient, particularly when medication alone is insufficient[87].

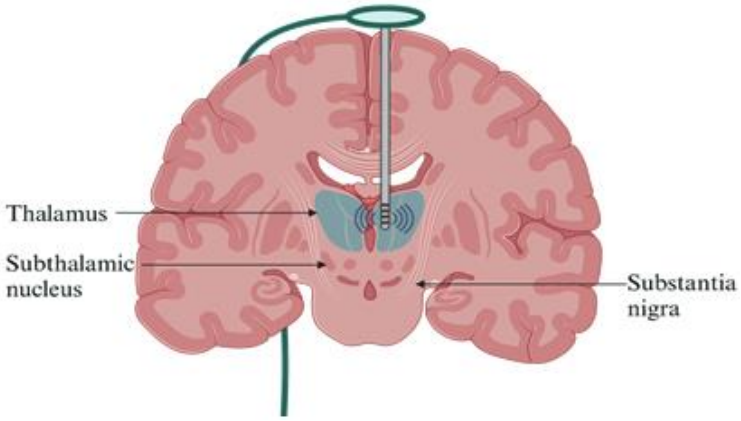

Fig. 4. Deep brain stimulation works by modulating the activity of these brain regions, helping to restore more normal patterns of neural activity. This can lead to a reduction in motor symptoms and, in some cases, a decrease in the need for medication.

One of the most significant challenges in the field of Parkinson's is the absence of neuroprotective agents. No treatment has been proven for neuroprotection or to slow down the disease, despite substantial studies and clinical trials[88,89.] The complicated pathogenesis mechanism of PD, lack of an accurate animal model that mimics the human condition, and scarcity of beneficial biomarkers to track the development of the illness all contribute to this issue.

Although alternative treatment with levodopa has been beneficial for managing the symptoms of Parkinson's disease, it fails to alter the course of the disease. Additional drugs, such as monoamine oxidase (MAO) B agents and dopamine agonists, have demonstrated symptomatic relief, but not definitive neuroprotective properties. Various methods of neuroimaging, particularly SPECT and PET imaging, MRI, and CT, are being examined for the possibility of being used to diagnose at an early stage and follow the successful outcome of neuroprotective treatments. Efforts to develop indications for PD are currently underway[92]. In conclusion, the search for neuroprotective therapy in PD remains a significant challenge with current treatments primary focus on managing symptoms rather than modifying the underlying disease process. Research on indicators is still a vital area with the goal of improving early identification and monitoring the progress of disease, neither of which is crucial for the development of preventative indicators in the decades to come.[90,91,92].

Table. 2. Treatment of Parkinson's disease.

S.no	Treatment	Description	References
1	Levodopa	Levodopa precursor of dopamine, which relieves motor symptoms by	[103,104]

		converting to dopamine after crossing the blood-brain barrier.	
2	Dopamine agonist	bind to dopamine receptors and replicate adrenaline's effects	[105,106]
3	MAO-B Blockers	Blocking the monoamine oxidase-B enzyme, which breaks down antagonists of MAO-B, increases the amount of dopamine in the brain.	[106,107]
4	COMT inhibitors	Levodopa's actions can be further sustained by decreasing an enzyme called catechol-O-methyltransferase, it tears down its active ingredient.	[106,108]
5	Anticholinergics	Minimize trembling and rigidity in the muscles by decreasing the action of excess cholinergic in Parkinson's disease.	[106]
6	Amantadine	NMDA receptor antagonist and weak dopamine agonist, used to improve motor function and reduce dyskinesias	[109]
7	Deep brain stimulation	Before surgery, sedation is used to place electrodes in specific parts of the brain in order to regulate aberrant impulses.	[110,111]
8	Physical therapy	Helps maintain mobility, range of motion, and overall physical fitness.	[112,113]
9	Speech therapy	Improves speech and swallowing difficulties often associated with PD.	[114]

Table. 3. These investigations have shed insight into the obstacles and accomplishments that accompany establishing effective treatments for the illness, which has significantly improved knowledge about the condition.

S.No	Study	Intervention	Outcome measures	Results	References
1	DATATOP study	Deprenyl vs. Placebo	Time to disability requiring levodopa	Deprenyl delayed onset of disability in early PD patients	[93]
2	ADAGIO	Rasagiline vs. placebo	Changes in UPDRS score over 72 weeks	Rasagiline showed significant reduction in UPDRS scores	[94]
3	TEMPO study	Rasagiline vs.entacapone	Changes in total UPDRS scores after 18 weeks	Rasagiline demonstrated non-inferiority to entacapone in PD treatment	[95]
4	CALM-PD study	Coenzyme Q10 vs. placebo	Changes in UPDRS score over 16 months	Coenzyme Q10 showed no significant	[96]

				difference compared to placebo	
5	REAL-PET study	Levodopa vs. pramipexole	Change in dopaminetransporter binding using PET	Pramipexole showed similar effects on dopamine transporter binding as levodopa	[97]
6	ELLDOPA study	Levodopa vs. Placebo	Change in UPDRS score over 40 weeks	Levodopa significantly improved motor function compared to placebo	[98]
7	ADAGIO-LFS study	Rasagiline vs. placebo	Change in UPDRS score over 76 weeks	Rasagiline showed a significant reduction in UPDRS scores	[99]
8	PRECEPT study	Creatine vs. placebo	Rate of clinical decline using the UPDRS	Creatine showed no significant effect on the rate of clinical decline	[100]
9	QE2 study	Coenzyme Q10 vs.placebo	Change in UPDRS score after 16 months	Coenzyme Q10 showed no significant difference compared to placebo	[101]
10	NET-PD LS-1 study	Creatine vs. placebo	Rate of clinical decline using the UPDRS	There was no discernible effect of creatine on the individual's rate of clinical decline.	[102]

Discussion

A complex neurodegenerative medical condition is distinguished by the gradual mortality of neurons producing dopamine in the substantia nigra. Despite extensive research on PD, its specific pathogenesis remains unidentified, despite the hypothesis of both genetic and environmental factors. Establishing optimal plans for therapy requires an understanding of the molecular processes underlying the condition known as PD.

Molecular pathways of Parkinson' disease

One pathogenic aspect of Parkinson's disease (PD) is the deposition of misfolded alpha-synuclein proteins, which results in the development of Lewy bodies. These protein complexes are implicated in cell death and brain injury. The onset of illness has also been associated with oxidative stress, mitochondrial deficiency, and accelerated disintegration of protein networks[119,120].

Biological elements

Although nearly all PD circumstances are will, a number of genetic anomalies have been demonstrated to increase the risk of the condition. Parental variants of PD have been shown to involve polymorphisms in genes including SNCA (encoding alpha-synuclein), LRRK2, PARKIN, and PINK 1. Several genetic advances have shed significant light on the molecular processes that drive the clinical manifestations of the illness[121,122].

Environment-related components

Many testimonies have associated the consumption of particular contaminants in the environment, such as herbicides and toxic metals, with an increased risk of developing Parkinson's disease. The beginning and course of an illness are caused by the association of these external variables with inherited aspects[123,124,125].

Modalities of therapy

The principal objectives of presently accessible PD therapy are alleviating symptoms and the standard of life augmentation. Levodopa along with other dopamine receptor agonists are examples of cholinergic medicines, that constitute the mainstay of medical care for motor signs and symptoms. However, additionally, the growth of the condition. or its non-motor manifestations are efficiently treated with these therapies.

Conclusion

Demystifying Parkinson's disease requires a comprehensive understanding of its molecular pathways and the complex interplay between genetic and environmental factors. Advances in research are paving the way for more effective treatments that target the underlying pathophysiology of PD, offering hope for improved outcomes for patients in the future. There's a growing interest in developing disease - modifying therapies that Target the underlying molecular pathways of PD. Strategies aimed at reducing alpha- synuclein aggregation, enhancing mitochondrial function, and reducing neuroinflammation are being actively investigated. Additionally, advances in genes therapy and stem cell research hold promise for restoring dopaminergic function in PD patients.

Acknowledgments

All the authors are thankful to database open access library like DOAJ etc and publication, for providing the useful information to complete article.

Authors Contribution

All authors are contributing and involved in the preparation of manuscript including table, data and figures editing the manuscript for the preparation of final draft.

Conflict of interest statement

Authors declare they do not have any conflict of interest.

References

1. Jellinger KA. Neuropathology and pathogenesis of extrapyramidal movement disorders: a critical update I. Hypokinetic-rigid movement disorders. Journal of Neural Transmission. 2019 Aug 1;126(8):933-95.
2. Balestrino R, Schapira AH. Parkinson disease. European journal of neurology. 2020 Jan;27(1):27-42.
3. Ruiz-Lopez M, Freitas ME, Oliveira LM, Munhoz RP, Fox SH, Rohani M, Rogaeva E, Lang AE, Fasano A. Diagnostic delay in Parkinson's disease caused by PRKN mutations. Parkinsonism & Related Disorders. 2019 Jun 1;63:217-20.

4. Roos DS, Twisk JW, Raijmakers PG, Doty RL, Berendse HW. Hyposmia as a marker of (non-) motor disease severity in Parkinson's disease. Journal of Neural Transmission. 2019 Nov;126:1471-8.

5. Rojas JC, Wang P, Staffaroni AM, Heller C, Cobigo Y, Wolf A, Goh SY, Ljubenkov PA, Heuer HW, Fong JC, Taylor JB. Plasma neurofilament light for prediction of disease progression in familial frontotemporal lobar degeneration. Neurology. 2021 May 4;96(18):e2296-312.

6. Bucur MS, Sylvester H, Hategan A. Essential Medical Work-Up and Rule Outs. Inpatient Geriatric Psychiatry: Optimum Care, Emerging Limitations, and Realistic Goals. 2019:3-25.

7. Chuquilín-Arista F, Álvarez-Avellón T, Menéndez-González M. Prevalence of depression and anxiety in Parkinson disease and impact on quality of life: a community-based study in Spain. Journal of geriatric psychiatry and neurology. 2020 Jul;33(4):207-13.

8. Li L, Guo P, Ding D, Lian T, Zuo L, Du F, Zhang W. Parkinson's disease with orthostatic hypotension: analyses of clinical characteristics and influencing factors. Neurological Research. 2019 Aug 3;41(8):734-41.Gong S, Gao Y, Liu J, Li J, Tang X, Ran Q, Tang R, Liao C. The prevalence and associated factors of dysphagia in Parkinson's disease: A systematic review and meta-analysis. Frontiers in Neurology. 2022 Oct 6;13:1000527.

9. Huang H, Yang X, Zhao Q, Chen Y, Ning P, Shen Q, Wang H, An R, Xu Y. Prevalence and risk factors of depression and anxiety in essential tremor patients: a cross-sectional study in Southwest China. Frontiers in Neurology. 2019 Nov 15;10:1194.

10. Margolesky J, Fleming N, Shpiner D, Luca C, Moore H, Singer C. Blepharoclonus in Parkinson's Disease: a prevalent and meaningful finding?(2174).

11. Hussein M, Koura R. Auditory and vestibular dysfunction in patients with Parkinson's disease. The Egyptian Journal of Otolaryngology. 2019 Jul;35:313-21.

12. Sung MS, Choi SM, Kim J, Ha JY, Kim BC, Heo H, Park SW. Inner retinal thinning as a biomarker for cognitive impairment in de novo Parkinson's disease. Scientific reports. 2019 Aug 14;9(1):11832.

13. Chen Z, Liu J. The identification and diagnosis of preclinical and premotor Parkinson's disease. Chinese Journal of Neurology. 2018:486-91.

14. Yase CH, Xiaoting ZH, Qiying SU, Qian XU, Jifeng GU, Beisha TA, Xinxiang YA. Research progress of oculomotor disorder in Parkinson's disease. Chinese Journal of Neurology. 2019:143-6.

15. Hategan A, Bourgeois JA, Cheng T, Young J, Hategan A, Bourgeois JA, Cheng T, Young J. Common Major and Mild Neurocognitive Disorders: Alzheimer Disease, Frontotemporal, Lewy Body, and Vascular Types. Geriatric Psychiatry Study Guide: Mastering the Competencies. 2018:203-42.

16. Petrucci S, Consoli F, Valente EM. Parkinson disease genetics: a "continuum" from Mendelian to multifactorial inheritance. Current molecular medicine. 2014 Sep 1;14(8):1079-88.

17. Logroscino G. The role of early life environmental risk factors in Parkinson disease: what is the evidence?. Environmental health perspectives. 2005 Sep;113(9):1234-8.

18. Jackson-Lewis V, Lester D, Kozina E, Przedborski S, Smeyne RJ. From man to mouse: The MPTP model of Parkinson disease. InMovement Disorders 2015 Jan 1 (pp. 287-306). Academic Press.

19. Zhang L, Deng J, Pan Q, Zhan Y, Fan JB, Zhang K, Zhang Z. Targeted methylation sequencing reveals dysregulated Wnt signaling in Parkinson disease. Journal of Genetics and Genomics. 2016 Oct 20;43(10):587-92.

20. Eriksen JL, Wszolek Z, Petrucelli L. Molecular pathogenesis of Parkinson disease. Archives of neurology. 2005 Mar 1;62(3):353-7.

21. Landrigan PJ, Sonawane B, Butler RN, Trasande L, Callan R, Droller D. Early environmental origins of neurodegenerative disease in later life. Environmental health perspectives. 2005 Sep;113(9):1230-3.

22.Pang SY, Ho PW, Liu HF, Leung CT, Li L, Chang EE, Ramsden DB, Ho SL. The interplay of aging, genetics and environmental factors in the pathogenesis of Parkinson's disease. Translational Neurodegeneration. 2019 Dec;8:1-1.

23.Hernandez SM, Tikhonova EB, Karamyshev AL. Protein-protein interactions in alpha-synuclein biogenesis: new potential targets in Parkinson's disease. Frontiers in Aging Neuroscience. 2020 Mar 17;12:72.

24.Braak H, Del Tredici K. Invited Article: Nervous system pathology in sporadic Parkinson disease. Neurology. 2008 May 13;70(20):1916-25.

25.Higuchi S, Arai H, Matsushita S, Matsui T, Kimpara T, Takeda A, Shirakura K. brief communication Mutation in the α-Synuclein Gene and Sporadic Parkinson's Disease, Alzheimer's Disease, and Dementia with Lewy Bodies. Experimental neurology. 1998 Sep 1;153(1):164-6.

26.Al-Qassabi A, Tsao TS, Racolta A, Kremer T, Cañamero M, Belousov A, Santana MA, Beck RC, Zhang H, Meridew J, Pugh J. Immunohistochemical detection of synuclein pathology in skin in idiopathic rapid eye movement sleep behavior disorder and parkinsonism. Movement Disorders. 2021 Apr;36(4):895-904.

27.Lo Bianco C, Ridet JL, Schneider BL, Deglon N, Aebischer P. α-Synucleinopathy and selective dopaminergic neuron loss in a rat lentiviral-based model of Parkinson's disease. Proceedings of the National Academy of Sciences. 2002 Aug 6;99(16):10813-8.

28.Inden M, Kondo JI, Kitamura Y, Takata K, Nishimura K, Taniguchi T, Sawada H, Shimohama S. Proteasome inhibitors protect against degeneration of nigral dopaminergic neurons in hemiparkinsonian rats. Journal of pharmacological sciences. 2005 Jan 1;97(2):203-11.

29.Zhou ZD, Selvaratnam T, Lee JC, Chao YX, Tan EK. Molecular targets for modulating the protein translation vital to proteostasis and neuron degeneration in Parkinson's disease. Translational neurodegeneration. 2019 Dec;8:1-4.

30.Kawamura M, Sato S, Matsumoto G, Fukuda T, Shiba-Fukushima K, Noda S, Takanashi M, Mori N, Hattori N. Loss of nuclear REST/NRSF in aged-dopaminergic neurons in Parkinson's disease patients. Neuroscience Letters. 2019 Apr 23;699:59-63.

31.McNaught KS, Shashidharan P, Perl DP, Jenner P, Olanow CW. Aggresome-related biogenesis of Lewy bodies. European Journal of Neuroscience. 2002 Dec;16(11):2136-48.

32.Liu M, Liu C, Xiao X, Han SS, Bi MX, Jiao Q, Chen X, Yan CL, Du XX, Jiang H. Role of upregulation of the KATP channel subunit SUR1 in dopaminergic neuron degeneration in Parkinson's disease. Aging Cell. 2022 May;21(5):e13618.

33.Pan L, Meng L, He M, Zhang Z. Tau in the pathophysiology of Parkinson's disease. Journal of Molecular Neuroscience. 2021 Jan 18:1-3.

34.Wang N, Gibbons CH, Freeman R. Cutaneous α-synuclein and Parkinson disease, a biomarker of disease severity. Autonomic Neuroscience: Basic and Clinical. 2013 Aug 1;177(1):27-8.

35.Prada CE, Grabowski GA. Neuronopathic lysosomal storage diseases: clinical and pathologic findings. Developmental disabilities research reviews. 2013 Jun;17(3):226-46.

36.Wang KK, Zhang Z, Kobeissy FH, editors. Biomarkers of brain injury and neurological disorders. CRC Press; 2014 Oct 28.

37.Ying Z, Wang H, Wang G. The ubiquitin proteasome system as a potential target for the treatment of neurodegenerative diseases. Current pharmaceutical design. 2013 Jun 1;19(18):3305-14.

38.Bekris LM, Mata IF, Zabetian CP. The genetics of Parkinson disease. Journal of geriatric psychiatry and neurology. 2010 Dec;23(4):228-42.

39.Petrucci S, Consoli F, Valente EM. Parkinson disease genetics: a "continuum" from Mendelian to multifactorial inheritance. Current molecular medicine. 2014 Sep 1;14(8):1079-88.

40.Warner TT, Schapira AH. Genetic and environmental factors in the cause of Parkinson's disease. Annals of Neurology: Official Journal of the American Neurological Association and the Child Neurology Society. 2003;53(S3):S16-25.

41.Zhang L, Deng J, Pan Q, Zhan Y, Fan JB, Zhang K, Zhang Z. Targeted methylation sequencing reveals dysregulated Wnt signaling in Parkinson disease. Journal of Genetics and Genomics. 2016 Oct 20;43(10):587-92.

42.Pang SY, Ho PW, Liu HF, Leung CT, Li L, Chang EE, Ramsden DB, Ho SL. The interplay of aging, genetics and environmental factors in the pathogenesis of Parkinson's disease. Translational Neurodegeneration. 2019 Dec;8:1-1.

42.Kline EM, Houser MC, Herrick MK, Seibler P, Klein C, West A, Tansey MG. Genetic and Environmental Factors in P arkinson's Disease Converge on Immune Function and Inflammation. Movement Disorders. 2021 Jan;36(1):25-36.

43.Vance JM, Ali S, Bradley WG, Singer C, Di Monte DA. Gene–environment interactions in Parkinson's disease and other forms of parkinsonism. Neurotoxicology. 2010 Sep 1;31(5):598-602.

44.Chung KK, Zhang Y, Lim KL, Tanaka Y, Huang H, Gao J, Ross CA, Dawson VL, Dawson TM. Parkin ubiquitinates the α-synuclein–interacting protein, synphilin-1: implications for Lewy-body formation in Parkinson disease. Nature medicine. 2001 Oct 1;7(10):1144-50.

45.Eriksen JL, Wszolek Z, Petrucelli L. Molecular pathogenesis of Parkinson disease. Archives of neurology. 2005 Mar 1;62(3):353-7.

46.Rocha EM, De Miranda B, Sanders LH. Alpha-synuclein: Pathology, mitochondrial dysfunction and neuroinflammation in Parkinson's disease. Neurobiology of disease. 2018 Jan 1;109:249-57.

47.Schapira AH, Gegg M. Mitochondrial contribution to Parkinson's disease pathogenesis. Parkinson's disease. 2011 Jan 1;2011.

48.Vicario M, Cieri D, Brini M, Calì T. The close encounter between alpha-synuclein and mitochondria. Frontiers in Neuroscience. 2018 Jun 7;12:380543.

49.Kulikova OI, Fedorova TN, Kuznetsov VI, Orlova VS. Exogenous factors of parkinson's disease development. Ekologiya cheloveka (Human Ecology). 2019 Jan 15;26(1):34-9.

50.Masato A, Plotegher N, Boassa D, Bubacco L. Impaired dopamine metabolism in Parkinson's disease pathogenesis. Molecular neurodegeneration. 2019 Aug 20;14(1):35.

51.Simon DK, Tanner CM, Brundin P. Parkinson disease epidemiology, pathology, genetics, and pathophysiology. Clinics in geriatric medicine. 2020 Feb 1;36(1):1-2.

52.Perfeito R, Cunha-Oliveira T, Rego AC. Revisiting oxidative stress and mitochondrial dysfunction in the pathogenesis of Parkinson disease resemblance to the effect of amphetamine drugs of abuse. Free Radical Biology and Medicine. 2012 Nov 1;53(9):1791-806.

53.Smith L, Schapira AH. GBA variants and Parkinson disease: mechanisms and treatments. Cells. 2022 Apr 8;11(8):1261.

54.Muñoz P, Melendez C, Paris I, Segura-Aguilar J. Molecular and neurochemical mechanisms dopamine oxidation to o-quinones in Parkinson's disease pathogenesis. Toxicity and Autophagy in Neurodegenerative Disorders. 2015:205-23.

55.Weintraub D, Stern MB. Psychiatric complications in Parkinson disease. The American journal of geriatric psychiatry. 2005 Oct 1;13(10):844-51.

56.Karceski S. Parkinson disease and mortality: Understanding how the two are connected. Neurology. 2018 Nov 27;91(22):e2106-8.

57.Lopez G, Steward A, Ryan E, Groden C, Wiggs E, Segalà L, Monestime GM, Tayebi N, Sidransky E. Clinical evaluation of sibling pairs with gaucher disease discordant for parkinsonism. Movement Disorders. 2020 Feb;35(2):359-65.

58.Kim JS, Youn J, Shin H, Cho JW. Nonmotor symptoms in drug-induced parkinsonism and drug-naïve Parkinson disease. Canadian journal of neurological sciences. 2013 Jan;40(1):36-41.

59.Braak H, Del Tredici K. Invited Article: Nervous system pathology in sporadic Parkinson disease. Neurology. 2008 May 13;70(20):1916-25.

60.Postuma RB, Berg D, Stern M, Poewe W, Olanow CW, Oertel W, Obeso J, Marek K, Litvan I, Lang AE, Halliday G. MDS clinical diagnostic criteria for Parkinson's disease. Movement disorders. 2015 Oct;30(12):1591-601.

61.Zijlmans JC. The role of imaging in the diagnosis of vascular parkinsonism. Neuroimaging Clinics. 2010 Feb 1;20(1):69-76.

62.Rizek P, Kumar N, Jog MS. An update on the diagnosis and treatment of Parkinson disease. Cmaj. 2016 Nov 1;188(16):1157-65.

63.Shin HW, Hong SW, Youn YC. Clinical aspects of the differential diagnosis of Parkinson's disease and parkinsonism. Journal of Clinical Neurology (Seoul, Korea). 2022 May;18(3):259.

64.Li J, Jin M, Wang L, Qin B, Wang K. MDS clinical diagnostic criteria for Parkinson's disease in China. Journal of neurology. 2017 Mar;264:476-81.

65.Thenganatt MA, Jankovic J. Psychogenic (functional) parkinsonism. Handbook of clinical neurology. 2016 Jan 1;139:259-62.

66.Connolly B, Fox SH. Treatment of cognitive, psychiatric, and affective disorders associated with Parkinson's disease. Neurotherapeutics. 2014 Jan 1;11(1):78-91.

67.Berg D, Adler CH, Bloem BR, Chan P, Gasser T, Goetz CG, Halliday G, Lang AE, Lewis S, Li Y, Liepelt-Scarfone I. Movement disorder society criteria for clinically established early Parkinson's disease. Movement Disorders. 2018 Oct;33(10):1643-6.

68.Heinzel S, Berg D, Gasser T, Chen H, Yao C, Postuma RB, MDS Task Force on the Definition of Parkinson's Disease. Update of the MDS research criteria for prodromal Parkinson's disease. Movement Disorders. 2019 Oct;34(10):1464-70.

69.Pilotto A, Heinzel S, Suenkel U, Lerche S, Brockmann K, Roeben B, Schaeffer E, Wurster I, Yilmaz R, Liepelt-Scarfone I, von Thaler AK. Application of the movement disorder society prodromal Parkinson's disease research criteria in 2 independent prospective cohorts. Movement Disorders. 2017 Jul;32(7):1025-34.

70.Hategan A, Bourgeois JA, Cheng T, Young J, Hategan A, Bourgeois JA, Cheng T, Young J. Other Major and Mild Neurocognitive Disorders: Parkinson Disease, Atypical Parkinsonism, and Traumatic Brain Injury Types. Geriatric Psychiatry Study Guide: Mastering the Competencies. 2018:243-68.

71.Kupryjanow A, Kunka B, Kostek B. Updrs tests for diagnosis of parkinson's disease employing virtual-touchpad. In2010 Workshops on Database and Expert Systems Applications 2010 Aug 30 (pp. 132-136). IEEE.

72.Ivey FM, Katzel LI, Sorkin JD, Macko RF, Shulman LM. The Unified Parkinson's Disease Rating Scale as a predictor of peak aerobic capacity and ambulatory function. Journal of rehabilitation research and development. 2012;49(8):1269.

73.Lee YE, Lee DH, Lee JH, Lu HY, Cho SY, Park JM, Ko CN, Bae HS, Park SU. Three case reports of postural instability and gait difficulty in parkinson's disease patients treated with korean and western medicine. Korean Journal of Acupuncture. 2014;31(1):40-7.

74.Hwang H, Norris SA. Managing advanced Parkinson disease. Journal of geriatric psychiatry and neurology. 2021 Jul;34(4):289-300.

75.Dickson DW. Parkinson's disease and parkinsonism: neuropathology. Cold Spring Harbor perspectives in medicine. 2012 Aug 1;2(8):a009258.

76.Taylor J, Anderson WS, Brandt J, Mari Z, Pontone GM. Neuropsychiatric complications of Parkinson disease treatments: importance of multidisciplinary care. The American Journal of Geriatric Psychiatry. 2016 Dec 1;24(12):1171-80.

77.Miyasaki JM, Long J, Mancini D, Moro E, Fox SH, Lang AE, Marras C, Chen R, Strafella A, Arshinoff R, Ghoche R. Palliative care for advanced Parkinson disease: an interdisciplinary clinic and new scale, the ESAS-PD. Parkinsonism & related disorders. 2012 Dec 1;18:S6-9.

78.Scherbaum R, Hartelt E, Kinkel M, Gold R, Muhlack S, Tönges L. Parkinson's Disease Multimodal Complex Treatment improves motor symptoms, depression and quality of life. Journal of neurology. 2020 Apr;267(4):954-65.

79.Tosserams A, de Vries NM, Bloem BR, Nonnekes J. Multidisciplinary care to optimize functional mobility in Parkinson disease. Clinics in Geriatric Medicine. 2020 Feb 1;36(1):159-72.

80.Isaacson SH. Effective treatment strategies for motor and nonmotor symptoms of Parkinson disease. The Journal of Clinical Psychiatry. 2020 Jan 7;81(1):26546.

81.Shaikh HA, Masood S. Effects of physiotherapy interventions on fall, posture and quality of life in parkinson disease. Pakistan journal of rehabilitation. 2019;8(1):04-12.

82.Kamatchi K, Priya S, Senthilnathan CV, Kumar GM, Tharani G, Yuvarani G. A Comparative Study to Analyse the Effectiveness of PNF Versus Balance Exercises in Parkinsonism. Indian Journal of Public Health Research & Development. 2019 Dec 1;10(12).

83.Marumoto K, Yokoyama K, Inoue T, Yamamoto H, Kawami Y, Nakatani A, Fukazawa Y, Hosoe Y, Yamasaki A, Domen K. Inpatient enhanced multidisciplinary care effects on the quality of life for Parkinson disease: a quasi-randomized controlled trial. Journal of geriatric psychiatry and neurology. 2019 Jul;32(4):186-94.

84.Stuijt C, Karapinar-Çarkit F, van den Bemt B, van Laar T. Effect of pharmacist-led interventions on (non) motor symptoms, medication-related problems, and quality of life in Parkinson disease patients: a pilot study. Clinical neuropharmacology. 2018 Jan 1;41(1):14-9.

85.Rodriguez-Oroz MC, Moro E, Krack P. Long-term outcomes of surgical therapies for Parkinson's disease. Movement Disorders. 2012 Dec;27(14):1718-28.

86.Aaroe AE, Henchcliffe C. Promises and Challenges of MSC-Based Therapies: Parkinson Disease and Parkinsonism. InA Roadmap to Non-Hematopoietic Stem Cell-based Therapeutics 2019 Jan 1 (pp. 297-320). Academic Press.

87.Ossig C, Reichmann H. Treatment strategies in early and advanced Parkinson disease. Neurologic clinics. 2015 Feb 1;33(1):19-37.

88.AlDakheel A, Kalia LV, Lang AE. Pathogenesis-targeted, disease-modifying therapies in Parkinson disease. Neurotherapeutics. 2014 Jan 1;11(1):6-23.

89.Athauda D, Foltynie T. The ongoing pursuit of neuroprotective therapies in Parkinson disease. Nature Reviews Neurology. 2015 Jan;11(1):25-40.

90.Löhle M, Reichmann H. Clinical neuroprotection in Parkinson's disease—still waiting for the breakthrough. Journal of the neurological sciences. 2010 Feb 15;289(1-2):104-14.

91.de la Fuente-Fernández R, Schulzer M, Mak E, Sossi V. Trials of neuroprotective therapies for Parkinson's disease: problems and limitations. Parkinsonism & related disorders. 2010 Jul 1;16(6):365-9.

92Hellman AM, Morley JF, Duda JE. Disease modification in Parkinson's disease: are we there yet with currently available therapies?. Neurodegenerative Disease Management. 2012 Aug;2(4):379-87.

93. Parkinson Study Group*. Effect of deprenyl on the progression of disability in early Parkinson's disease. New England Journal of Medicine. 1989 Nov 16;321(20):1364-71.

94. Olanow CW, Stern MB, Sethi K. The scientific and clinical basis for the treatment of Parkinson disease (2009). Neurology. 2009 May 26;72(21_supplement_4):S1-36.

95. Rascol O, Brooks DJ, Melamed E, Oertel W, Poewe W, Stocchi F, Tolosa E. Rasagiline as an adjunct to levodopa in patients with Parkinson's disease and motor fluctuations (LARGO, Lasting effect in Adjunct therapy with Rasagiline Given Once daily, study): a randomised, double-blind, parallel-group trial. The Lancet. 2005 Mar 12;365(9463):947-54.

96. Shults CW, Oakes D, Kieburtz K, Beal MF, Haas R, Plumb S, Juncos JL, Nutt J, Shoulson I, Carter J, Kompoliti K. Effects of coenzyme Q10 in early Parkinson disease: evidence of slowing of the functional decline. Archives of neurology. 2002 Oct 1;59(10):1541-50.

97. Al W. Slower progression of Parkinson's disease with ropinirole versus levodopa: The REAL-PET study. Ann Neurol.2003;54:93-101.

98. Parkinson Study Group. Levodopa and the progression of Parkinson's disease. New England Journal of Medicine. 2004 Dec 9;351(24):2498-508.

99. Olanow CW, Kieburtz K, Odin P, Espay AJ, Standaert DG, Fernandez HH, Vanagunas A, Othman AA, Widnell KL, Robieson WZ, Pritchett Y. Continuous intrajejunal infusion of levodopa-carbidopa intestinal gel for patients with advanced Parkinson's disease: a randomised, controlled, double-blind, double-dummy study. The Lancet Neurology. 2014 Feb 1;13(2):141-9.

100. Kieburtz K, Tilley BC, Elm JJ, Babcock D, Hauser R, Ross GW, Augustine AH, Augustine EU, Aminoff MJ, Bodis-Wollner IG, Boyd J. Effect of creatine monohydrate on clinical progression in patients with Parkinson disease: a randomized clinical trial. Jama. 2015 Feb 10;313(6):584-93.

101. Parkinson Study Group. A controlled trial of rasagiline in early Parkinson disease: the TEMPO Study. Archives of neurology. 2002 Dec 1;59(12):1937-43

102. Wills AM, Elm JJ, Ye R, Chou KL, Parashos SA, Hauser RA, Bodis-Wollner I, Hinson VK, Christine CW, Schneider JS, NINDS NET-PD Investigators. Cognitive function in 1736 participants in NINDS Exploratory Trials in PD Long-term Study-1. Parkinsonism & related disorders. 2016 Dec 1; 33: 127-33.

103. Olanow CW, Obeso JA, Stocchi F. Continuous dopamine-receptor treatment of Parkinson's disease: scientific rationale and clinical implications. The Lancet Neurology. 2006 Aug 1;5(8):677-87.

104. Lees AJ, Hardy J, Revesz T. Parkinson's disease. The Lancet. 2009 Jun 13;373(9680):2055-66.

105. Connolly BS, Lang AE. Pharmacological treatment of Parkinson disease: a review. Jama. 2014 Apr 23;311(16):1670-83.

106. Rascol O, Hauser RA, Stocchi F, Fitzer-Attas CJ, Sidi Y, Abler V, Olanow CW, AFU Investigators. Long-term effects of rasagiline and the natural history of treated Parkinson's disease. Movement Disorders. 2016 Oct;31(10):1489-96

107. Reichmann F, Holzer P. Neuropeptide Y: A stressful review. Neuropeptides. 2016 Feb 1;55:99-109.

108. Ferreira LG, Dos Santos RN, Oliva G, Andricopulo AD. Molecular docking and structure-based drug design strategies. Molecules. 2015 Jul 22;20(7):13384-421.

109. Pahwa R, Lyons KE, Hauser RA, Fahn S, Jankovic J, Pourcher E, Hsu A, O'Connell M, Kell S, Gupta S, APEX-PD Investigators. Randomized trial of IPX066, carbidopa/levodopa extended release, in early Parkinson's disease. Parkinsonism & Related Disorders. 2014 Feb 1;20(2):142-8.

110. Deuschl G, Schade-Brittinger C, Krack P, Volkmann J, Schäfer H, Bötzel K, Daniels C, Deutschländer A, Dillmann U, Eisner W, Gruber D. A randomized trial of deep-brain stimulation for Parkinson's disease. New England Journal of Medicine. 2006 Aug 31;355(9):896-908.

111. Follett KA, Weaver FM, Stern M, Hur K, Harris CL, Luo P, Marks Jr WJ, Rothlind J, Sagher O, Moy C, Pahwa R. Pallidal versus subthalamic deep-brain stimulation for Parkinson's disease. New England Journal of Medicine. 2010 Jun 3;362(22):2077-91.

112. Goodwin VA, Richards SH, Taylor RS, Taylor AH, Campbell JL. The effectiveness of exercise interventions for people with Parkinson's disease: A systematic review and meta-analysis. Movement disorders. 2008 Apr 15;23(5):631-40.

113. Tomlinson CL, Herd CP, Clarke CE, Meek C, Patel S, Stowe R, Deane KH, Shah L, Sackley CM, Wheatley K, Ives N. Physiotherapy for Parkinson's disease: a comparison of techniques. Cochrane Database of Systematic Reviews. 2014(6).

114. Ramig LO, Sapir S, Fox C, Countryman S. Changes in vocal loudness following intensive voice treatment (LSVT®) in individuals with Parkinson's disease: A comparison with untreated patients and normal age-matched controls. Movement disorders: official journal of the Movement Disorder Society. 2001 Jan;16(1):79-83.

115. Jankovic J. Parkinson's disease and movement disorders: moving forward. The Lancet Neurology. 2008 Jan 1;7(1):9-11.

116. Goetz CG. The history of Parkinson's disease: early clinical descriptions and neurological therapies. Cold Spring Harbor perspectives in medicine. 2011 Sep 1;1(1):a008862.

117. Tanner CM, Goldman SM. Epidemiology of Parkinson's disease. Neurologic clinics. 1996 May 1;14(2):317-35.

118. Hughes AJ, Ben-Shlomo Y, Daniel SE, Lees AJ. What features improve the accuracy of clinical diagnosis in Parkinson's disease: a clinicopathologic study. Neurology. 1992 Jun;42(6):1142-.

119. Zaman V, Shields DC, Shams R, Drasites KP, Matzelle D, Haque A, Banik NL. Cellular and molecular pathophysiology in the progression of Parkinson's disease. Metabolic brain disease. 2021 Jun;36:815-27.

120.Goiran T, Eldeeb MA, Zorca CE, Fon EA. Hallmarks and molecular tools for the study of mitophagy in Parkinson's disease. Cells. 2022 Jul 2;11(13):2097.

121.Day JO, Mullin S. The genetics of Parkinson's disease and implications for clinical practice. Genes. 2021 Jun 30;12(7):1006.

122.Puschmann A. New genes causing hereditary Parkinson's disease or parkinsonism. Current neurology and neuroscience reports. 2017 Sep;17:1-1.

123.Pyatha S, Kim H, Lee D, Kim K. Association between heavy metal exposure and Parkinson's disease: a review of the mechanisms related to oxidative stress. Antioxidants. 2022 Dec 15;11(12):2467.

124.Subramaniam SR, Chesselet MF. Mitochondrial dysfunction and oxidative stress in Parkinson's disease. Progress in neurobiology. 2013 Jul 1;106:17-32.

125.Gravitz L. The promise and potential of stem cells in Parkinson's disease. Nature. 2021;597(7878):8-10.