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Review

Prodromal Parkinson's Disease: What We Know and What We do Not Know

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Abstract: Prodromal Parkinson's Disease (PD) represents a critical phase preceding the clinical onset of the disease, characterized by subtle and often non-motor symptoms that precede the classic motor manifestations. Understanding this prodromal phase is essential for early diagnosis, intervention, and potentially altering the disease course. This narrative review aims to elucidate the current knowledge on the prodromal phase of PD, highlighting known biomarkers, genetic predispositions, and environmental factors that contribute to early detection. Furthermore, it examines the limitations and gaps in our understanding, including the variability in prodromal symptoms, challenges in identifying definitive biomarkers, and the need for longitudinal studies. By synthesizing the existing literature, this review provides a comprehensive overview of what we know about prodromal PD and underscores the areas that require further research to enhance early diagnostic accuracy and develop preventative strategies.

Keywords: Parkinsons Disease; Prodromal Parkinson; Movement Disorders.

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1. Introduction

Parkinson's disease is a complex progressive neurodegenerative pathology which encompasses a range of clinical, genetic and epidemiological symptoms [1-3]. Its etiology is associated with the deposition of alpha-synuclein in cells, generating oxidative stress, mitochondrial, lysosomal and endosomal malfunction, and these alterations are present both in individuals with positive genetics for the disease, as well as sporadic cases of Parkinson's disease [4]. As the second most common neurodegenerative disease, associated with a significant increase in its prevalence over the last 3 decades [5], the main mechanism of PD is the death of dopaminergic neurons contained in the substantia nigra [6-7], leading to the classic and motor signs of the disease, such as bradykinesia, resting tremor, rigidity and postural instability [3, 4, 8, 9].

Synucleinopathies, such as PD and Lewy Body Dementia, have a slow and progressive scope of subclinical prodromal changes as characteristics that precede the clinical phase of these pathologies, such as REM sleep disturbance, olfactory loss, depression, associated or not with anxiety, autonomic dysfunction and even imaging tests that show hyperechogenicity of the substantia nigra [4, 10, 11]. With this, we realize that certain prodromal markers can be used to screen individuals who have a tendency to develop Parkinson's Disease, and some lines of studies indicate that the pre-pathological phase precedes PD by around 10-20 years, and therefore, when we identify characteristic signs that have an association with a greater probability of developing the disease itself. This

latent phase of neurodegeneration would be of great value in developing neuroprotective therapies that modify the natural history of PD [10, 12-14].

As previously mentioned, PD can be preceded by the appearance of prodromal symptoms before presenting itself as Parkinsonism. However, recent studies indicate that there are subtypes within PD and even its prodrome, which differ in the time of progression of the disease, pathological mechanisms and even its clinic [2, 15]. Factors including beta-amyloid protein and tau, age, environmental factors such as physical exercise and the presence of other pathologies, can divide the PD prodrome into distinct ramifications. An example of this is REM sleep disturbance, which possibly indicates a progression of the pathology with the alpha-synuclein body-first subtype, in which alpha-synuclein originates in the enteric nervous system, while people with mutations in the *LKKR2* gene have a predisposition to the brain-first subtype [2, 16]. Studies also indicate that mutations in the *GBA* genes are closely linked to the body-first profile of PD [2, 16-18].

PD is gradually evolving from a purely clinical diagnosis to a diagnosis supported by early identified biomarkers, possibly in which a diagnosis can be reached in the early stages, focusing on the subtypes with different prognoses, leading to individualized treatment of patients [19, 20]. If we manage to diagnose Parkinson's Disease in its earliest stages, the progression of the pathology and its symptoms could be delayed through appropriate and targeted neuroprotective measures initiated at the most effective stages for treatment [21, 22].

This study aims to highlight some of the new points in relation to Parkinson's Disease prodromes, both pathophysiological and genetic, because by being able to highlight individuals with red flags for the development of PD, we can initiate prevention and even treatment protocols. With this, we would be able to significantly improve the quality of life of patients, as well as possibly modify the natural history of the disease, increasing people's life expectancy. In addition, with new biomarkers for early diagnosis, individualized therapies focused on each patient's specific subtype could be carried out, with a view to improving treatment prospects and outcomes.

2. Method

We searched Medline and PubMed from March 2024 to September 2024 for relevant articles using the keywords "Parkinson's Disease," or "prodromal Parkinson's Disease," or "pathophysiology Parkinson's Disease" or "Parkinson's Disease treatment," or "Prodromal symptoms of Parkinson's Disease." The initial search produced 68 hits and, after selection based on the abstracts, a total of – articles on etiology, diagnosis, pathophysiology or treatment were chosen and reviewed, after excluding articles that followed the first set of criteria - exclusion of articles not included in the 2018-2024 search period, as well as articles that were not originally in English. Additional references were obtained from these articles and from the authors of this review.

3. Results

3.1 Preclinical nigrostriatal dysfunction in Parkinson's disease

PD results from the destruction of dopaminergic neurons in the substantia nigra and a decrease in dopamine in this pathway [2, 4, 23]. Oxidative stress, as well as the deposition of elements such as alpha-synuclein, are known to alter the brain neurophysiology of this pathway, and genetic and environmental factors, as well as aging itself, are considered predisposing factors for this pathology [2, 4, 7, 23]. Oxidative stress is a key factor in understanding the destruction of the substantia nigra, with the production of reactive oxygen species eventually overcoming the action of antioxidant enzymes, which leads to their accumulation [23]. Mitochondria are the cell organelles that accumulate the most damage and suffer the most due to reactive oxygen species (ROS). As well as being the

main organelle that regulates the life and death of a cell, there may be an association between alterations in mitochondria and PD [23].

Dopamine transporters (DAT) and the vesicular monoamine transporter (VMAT) represent the major defenses against reactive oxygen species (ROS), by inserting dopamine into vesicles that are resistant to these elements [24]. However, it is known that with natural aging, the expression of DAT suffers a drop in its levels, generating an increase in the degradation of dopamine by ROS, but it has no interaction with VMAT, which ends up suffering due to its interaction with alpha-synuclein in the presynaptic terminal [23].

Lysosomal dysfunctions have also been associated with the development of PD [25]. The lysosomal enzyme glucocerebrosidase-hydroxylase (GCase) has pathogenic mutations that can lead to the development of PD, which is encoded by the GBA gene [26]. In this line of reasoning, they pointed out that Ambroxol could be a potential disease-modifying therapy, since it increases the enzymatic function of GCase, and there are already clinical studies in this direction [25].

It is worth mentioning the distinction between Gut-first type and Brain-first type, or PNS-type (peripheral nervous system) and CNS-type (central nervous system) respectively. There are two hypotheses for differentiating the origin of alpha-synuclein accumulation, which can start in the enteric system and progress retrogradely to the central nervous system, or take the opposite route, from the CNS to the periphery of the body [27]. PNS-type has a higher chance of REM sleep disorders and a lower mutation rate, while CNS-type has a lower incidence of REM sleep disorders and a higher mutation rate [27].

Currently, one of the greatest interests is in the non-invasive early identification of alpha-synuclein, since this deposition precedes parkinsonism by years and for the assessment of disease progression [25]. PET and SPECT have been used in studies to assess the progression of PD [28]. However, the development of methods that specifically target alpha-synuclein for early non-invasive diagnosis is still far from advanced [25].

3.2 Pre-motor symptoms in Parkinson's disease

Pre-motor symptoms in PD can precede the onset of motor disease by around 3 decades. These include gastrointestinal, cardiovascular, genitourinary, thermoregulatory and REM sleep disorders. It can be said that PD patients end up with autonomic alterations divided into at least some of those mentioned above [10, 11, 29]. In a survey of 400 individuals with PD, the authors found a 77.7% prevalence of premotor symptoms and showed that the presence of non-motor symptoms produces a 71.2% prediction success for discriminating between individuals with PD and healthy controls. A very characteristic but not universal symptom is hyposmia, affecting 70-80% of patients [30]. It is a symptom more closely related to the PNS-first type (peripheral nervous system), since in the prodromal phase it is more common to appear in these individuals, while the CNS-first type (central nervous system) is more common to appear later, with the natural evolution of the disease [27].

Gastrointestinal dysfunctions range from changes at the beginning of the gastro-digestive tract, such as sialorrhea and dysphagia, to changes during bowel movements, which are present in up to 88.9% of patients before the onset of Parkinson's motor symptoms [29, 31]. Studies indicate that the presence of sialorrhea disorder may be present in 32% to 74% of PD prodromes [32], associated or not with dysphagia, which is commonly progressive with the progression of the disease, affecting 11-81% according to a systematic review [33].

Constipation is certainly a gastrointestinal symptom commonly associated with PD and its prodromal phase, so much so that it was included as a criterion in the MDS-PD to assess the premotor phase of Parkinson's Disease. Around 70% of individuals with the disease suffer from this symptom [10, 29, 32]. Orthostatic hypotension is also another symptom associated both with the prodromal phase and with motor parkinsonism that has already set in, so much so that it is part of the MDS-PD criteria and is the first cardi-

ovascular symptom of PD, affecting up to 40% of individuals [29]. It is worth noting that OH ultimately reduces quality of life and negatively influences the progression of PD, and people with OH should perhaps be closely monitored for possible progression, as some studies have shown [10, 29].

Dysfunctions in the urinary system, mainly nocturia and urinary incontinence, are present in 27-85% of PD patients and in their prodrome, classified primarily as irritative symptoms [34]. Sexual dysfunctions occur in approximately 50% of early PD symptoms [32], but male patients present symptoms such as erectile dysfunction, hypersexuality and even ejaculatory jet dysfunctions, while women primarily present with decreased vaginal lubrication and incontinence during sex [29].

REM sleep disturbance is a strong predictor of PD and Lewy Body Dementia, and studies show that it can precede Parkinsonism by up to 10 years [35]. It is present in 25-58% of patients with PD and up to 90% of patients with Lewy Body Dementia, and cohort studies indicate that up to 80% of individuals with REM sleep disorders may develop alpha synucleinopathies in the future, associated with neurodegeneration [36]. Hyperhidrosis is also associated with alpha-synucleinopathies, which are related to increased dyskinesia and REM sleep disorders, more present in the subtype with greater dysautonomic presentations [37]. Patients who have it also suffer more from anxiety and CNS depression [37].

3.3 Biomarkers for Parkinson's disease

Parkinson's disease begins at the molecular level and is known to result from the destruction of neurons in the substantia nigra and also from the accumulation of alpha-synuclein in the CNS [10, 11, 38, 39]. Other proteins such as beta-amyloid and phosphorylated Tau, mutations in genes such as *LRRK2* and *GBA*, end up differentiating into distinct subtypes of PD presentations, as well as the presentation of its symptoms, and its prodromal period [10, 38, 39]. More than 100 genes or genetic locus have been linked to PD. Approximately 5-10% of PD is caused by monogenes, with the rest probably caused by environmental factors and combinations of genetic susceptible factors [40].

Mutations associated with the autosomal recessive form of PD, such as *PINK-1*, *PRKN*, *PARK-2*, *GBA* and *DJ-1* are the result of a loss of mitochondrial oxidative action resulting in the non-production of their final proteins [41, 42], indicating a strong association with mitochondrial malfunction of neurons in the absence of these [23]. Autosomal dominant PD mutations, such as LRRK2 and SNCA, have a greater relationship with a toxic action of resulting abnormal proteins, which end up disrupting the normal mitochondrial phosphorylation pathway, causing alpha-synuclein accumulation [23].

Studies indicate that GBA mutations are related to REM sleep disturbance in prodromal PD, including that these end up having a shorter prodromal period, but with a faster progression to established PD. The *GBA* also ends up being closer to the primary-body subtype of Parkinson's disease [10, 43]. Altered *GBA* function ultimately allows for an increase in the concentration and deposition of alpha-synuclein in cells [10, 43].

LRRK2 mutations end up with a greater increase in cardinal symptoms, such as gait and dyskinesia, but have a better evolution of dementia and non-motor symptoms, such as REM sleep disorder or autonomic dysfunctions and hyposmia [10, 44]. *LRRK2* mutations are more closely associated with the development of "brain-first subtype", with lysosomal dysfunction occurring and leading to the accumulation of alpha-synuclein [10, 44].

Mutations associated with *PRKN* are associated with the early development of PD, reaching 27.6% linkage to autosomal recessive forms in young patients, particularly in European populations [40]. In addition, one study showed that the earlier PD develops, the higher the prevalence of mutations linked to this gene, with up to 42.2% in patients under 20 years old, 29% from 21 to 30 years old, 13% from 31 to 40 years old and only 4.4% from 41 to 60 years old [40, 45].

SNCA is a gene associated with autosomal dominant PD and can be caused by different types of mutations, such as duplication, triplication and loss of part of it [40]. This mutation presents a range of prodromal symptoms of PD, such as orthostatic hypotension, REM sleep disorders and even psychiatric manifestations, showing a good response to treatment with Levodopa at first [46]. This mutation ends up altering the cellular metabolism of dopaminergic neurons, generating mitochondrial alterations and energy deficits, as well as alterations in lipid metabolism [47].

3.4 Treatment in the prodromal phase of Parkinson's disease

The basis for the treatment of PD has already been well established with the use of drugs that increase the concentration of dopamine in the synaptic cleft for years [48, 49]. Medications that either increase the lifespan of dopamine or increase its secretion by the presynaptic neuron, are mainly based on the daily oral use of Carbodopa/Levodopa, associated with behavioral therapies and integrative medicine for a better final result in the treatment of symptoms [50-52].

It can be said that current treatment involves a broad front for the treatment of a multifactorial disease with a wide range of symptoms, focusing mainly on slowing down, or reducing, the progression of PD [53]. According to Church et al. [53], treatment is based on 5 approaches involving behavioral rehabilitation, pharmacological therapy, cardiometabolic restoration, maintenance and Deep Brain Stimulation (DBS). It is worth mentioning that these do not necessarily have to be used concomitantly, but they may or may not complement each other in the treatment of PD [53]. Dopamine agonists such as Apomorphine are drugs used in the early treatment of PD and can even be used as monotherapy in PD and parkinsonism [54]. Their association with Levodopa/Carbodopa leads to an increase in the concentration and duration of the medications, and they are widely used [48]. However, side effects such as compulsion and impulsive disorders can occur [53].

MAO-B inhibitors such as Selegine and Safinamide, as well as COMT inhibitors, are medications used in combination with Levodopa/Carbodopa, as these ultimately decrease the degradation of dopamine in the synaptic cleft, prolonging the effect of dopaminergics [48, 53]. Amantadine is also a medication that has shown a beneficial effect in patients with motor dyskinesia and parkinsonism [55]. The practice of physical exercise has been widely studied to protect against the progression of PD [56-58], and some show that exercise reduces pro-inflammatory markers and helps preserve dopaminergic neurons [59]. In addition, moderate - intense aerobic exercise ends up promoting anti-oxidation and anti-inflammation in patients' bodies [53].

Another drug currently being studied is Vitamin D3, as some studies have indicated that a lack of this implies a greater progression of PD and greater motor symptoms [60], and that individuals with a higher level of vitamin D3 had better neurological performance [61]. Supplementation with vitamin B1 and magnesium L-threonate in some studies has indicated better performance and functioning of neural cells [53].

Another alternative for the treatment of PD is DBS (deep brain stimulation), which directs treatment directly to the globus pallidus, thalamus and subthalamic nucleus [62]. It is a surgical treatment aimed at patients who are refractory to the use of medication or patients who suffer from the disorders and side effects of antiparkinsonian medication [62]. It is worth mentioning that DBS is considered a reversible procedure, since there is no damage to brain tissue, and as the disease progresses, stimulation can be adjusted [62, [62, 63].

4. Conclusion

The prodromal phase of Parkinson's Disease (PD) presents a critical window for early interventions that may delay or even prevent the onset of characteristic motor symptoms. While knowledge of this phase has significantly advanced, substantial gaps

remain. The identification of reliable biomarkers and the understanding of underlying mechanisms are essential challenges. Longitudinal studies and multidisciplinary approaches are crucial to enhance diagnostic accuracy and develop effective preventive strategies. This article highlights the need for greater investment in research to fill these gaps, aiming to transform the clinical management of PD and improve the quality of life for affected individuals. Anticipating and intervening in the prodromal phase has the potential to revolutionize PD treatment, making early detection and prevention an achievable reality.

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References

1. Ben-Shlomo Y, Darweesh S, Llibre-Guerra J, Marras C, San Luciano M, Tanner C. The epidemiology of Parkinson's disease. Lancet. 2024;403(10423):283-292. doi:10.1016/S0140-6736(23)01419-8.
2. Morris HR, Spillantini MG, Sue CM, Williams-Gray CH. The pathogenesis of Parkinson's disease. Lancet. 2024;403(10423):293-304. doi:10.1016/S0140-6736(23)01478-2.
3. Hayes MT. Parkinson's Disease and Parkinsonism. Am J Med. 2019;132(7):802-807. doi:10.1016/j.amjmed.2019.03.001.
4. Reich SG, Savitt JM. Parkinson's Disease. Med Clin North Am. 2019;103(2):337-350. doi:10.1016/j.mcna.2018.10.014.
5. Cabreira V, Massano J. Doença de Parkinson: Revisão Clínica e Atualização [Parkinson's Disease: Clinical Review and Update]. Acta Med Port. 2019;32(10):661-670. doi:10.20344/amp.11978.
6. Ding XS, Gao L, Han Z, Eleuteri S, Shi W, Shen Y, et al. Ferroptosis in Parkinson's disease: Molecular mechanisms and therapeutic potential. Ageing Res Rev. 2023;91:102077. doi:10.1016/j.arr.2023.102077.
7. Romano S, Savva GM, Bedarf JR, Charles IG, Hildebrand F, Narbad A. Meta-analysis of the Parkinson's disease gut microbiome suggests alterations linked to intestinal inflammation. NPJ Parkinsons Dis. 2021;7(1):27. doi:10.1038/s41531-021-00156-z.
8. Chu Y, Hirst WD, Federoff HJ, Harms AS, Stoessl AJ, Kordower JH. Nigrostriatal tau pathology in parkinsonism and Parkinson's disease. Brain. 2024;147(2):444-457. doi:10.1093/brain/awad388.
9. Yang Y, Shi Y, Schweighauser M, Zhang X, Kotecha A, Murzin AG, et al. Structures of α-synuclein filaments from human brains with Lewy pathology. Nature. 2022;610(7933):791-795. doi:10.1038/s41586-022-05319-3.
10. Berg D, Borghammer P, Fereshtehnejad SM, Heinzel S, Horsager J, Schaeffer E, et al. Prodromal Parkinson disease subtypes - key to understanding heterogeneity. Nat Rev Neurol. 2021;17(6):349-361. doi:10.1038/s41582-021-00486-9.
11. Joza S, Hu MT, Jung KY, Kunz D, Stefani A, Dušek P, et al. Progression of clinical markers in prodromal Parkinson's disease and dementia with Lewy bodies: a multicentre study. Brain. 2023;146(8):3258-3272. doi:10.1093/brain/awad072.
12. Mahlknecht P, Seppi K, Poewe W. The Concept of Prodromal Parkinson's Disease. J Parkinsons Dis. 2015;5(4):681-697. doi:10.3233/JPD-150685.
13. Elsworth JD. Parkinson's disease treatment: past, present, and future. J Neural Transm (Vienna). 2020;127(5):785-791. doi:10.1007/s00702-020-02167-1.
14. Pajares M, Rojo AI, Manda G, Boscá L, Cuadrado A. Inflammation in Parkinson's Disease: Mechanisms and Therapeutic Implications. Cells. 2020;9(7):1687. doi:10.3390/cells9071687.
15. Vijiaratnam N, Simuni T, Bandmann O, Morris HR, Foltynie T. Progress towards therapies for disease modification in Parkinson's disease. Lancet Neurol. 2021;20(7):559-572. doi:10.1016/S1474-4422(21)00061-2.
16. Horsager J, Knudsen K, Sommerauer M. Clinical and imaging evidence of brain-first and body-first Parkinson's disease. Neurobiol Dis. 2022;164:105626. doi:10.1016/j.nbd.2022.105626.
17. Weintraub D, Aarsland D, Chaudhuri KR, Dobkin RD, Leentjens AF, Rodriguez-Violante M, Schrag A. The neuropsychiatry of Parkinson's disease: advances and challenges. Lancet Neurol. 2022;21(1):89-102. doi:10.1016/S1474-4422(21)00330-6.
18. Abeliovich A, Hefti F, Sevigny J. Gene Therapy for Parkinson's Disease Associated with GBA1 Mutations. J Parkinsons Dis. 2021;11(s2). doi:10.3233/JPD-212739.
19. Tolosa E, Garrido A, Scholz SW, Poewe W. Challenges in the diagnosis of Parkinson's disease. Lancet Neurol. 2021;20(5):385-397. doi:10.1016/S1474-4422(21)00030-2.
20. Church FC. Treatment Options for Motor and Non-Motor Symptoms of Parkinson's Disease. Biomolecules. 2021;11(4):612. doi:10.3390/biom11040612.

21. Bang Y, Lim J, Choi HJ. Recent advances in the pathology of prodromal non-motor symptoms olfactory deficit and depression in Parkinson's disease: clues to early diagnosis and effective treatment. Arch Pharm Res. 2021;44(6):588-604. doi:10.1007/s12272-021-01337-3.
22. Mestre TA, Fereshtehnejad SM, Berg D, Bohnen NI, Dujardin K, Erro R, et al. Parkinson's Disease Subtypes: Critical Appraisal and Recommendations. J Parkinsons Dis. 2021;11(2):395-404. doi:10.3233/JPD-202472.
23. Trist BG, Hare DJ, Double KL. Oxidative stress in the aging substantia nigra and the etiology of Parkinson's disease. Aging Cell. 2019;18(6). doi:10.1111/acel.13031.
24. Exner N, Lutz AK, Haass C, Winklhofer KF. Mitochondrial dysfunction in Parkinson's disease: molecular mechanisms and pathophysiological consequences. EMBO J. 2012;31(14):3038-3062. doi:10.1038/emboj.2012.170.
25. Haider A, Elghazawy NH, Dawoud A, et al. Translational molecular imaging and drug development in Parkinson's disease. Mol Neurodegener. 2023;18(1):11. doi:10.1186/s13024-023-00600-z.
26. Gan-Or Z, Liong C, Alcalay RN. GBA-Associated Parkinson's Disease and Other Synucleinopathies. Curr Neurol Neurosci Rep. 2018;18(8):44. doi:10.1007/s11910-018-0860-4.
27. Borghammer P, Van Den Berge N. Brain-First versus Gut-First Parkinson's Disease: A Hypothesis. J Parkinsons Dis. 2019;9(s2). doi:10.3233/JPD-191721.
28. Zhu L, Ploessl K, Kung HF. PET/SPECT imaging agents for neurodegenerative diseases. Chem Soc Rev. 2014;43(19):6683-6691. doi:10.1039/c3cs60430f.
29. Chen Z, Li G, Liu J. Autonomic dysfunction in Parkinson's disease: Implications for pathophysiology, diagnosis, and treatment. Neurobiol Dis. 2020;134:104700. doi:10.1016/j.nbd.2019.104700.
30. Kim JS, Park HE, Park IS, et al. Normal 'heart' in Parkinson's disease: is this a distinct clinical phenotype?. Eur J Neurol. 2017;24(2):349-356. doi:10.1111/ene.13206.
31. Sung HY, Park HE, Kim HW. The Frequency and Severity of Gastrointestinal Symptoms in Patients with Early Parkinson's Disease. J Mov Disord. 2014;7(1):7-12.
32. Malek N, Lawton MA, Grosset KA, Bajaj N, Barker RA, Burn DJ, et al.; PRoBaND Clinical Consortium. Autonomic Dysfunction in Early Parkinson's Disease: Results from the United Kingdom Tracking Parkinson's Study. Mov Disord Clin Pract. 2017;4(4):509-516. doi:10.1002/mdc3.12454.
33. Takizawa C, Gemmell E, Kenworthy J, Speyer R. A Systematic Review of the Prevalence of Oropharyngeal Dysphagia in Stroke, Parkinson's Disease, Alzheimer's Disease, Head Injury, and Pneumonia. Dysphagia. 2016;31(3):434-441. doi:10.1007/s00455-016-9695-9.
34. McDonald C, Winge K, Burn DJ. Lower urinary tract symptoms in Parkinson's disease: Prevalence, aetiology and management. Parkinsonism Relat Disord. 2017;35:8-16. doi:10.1016/j.parkreldis.2016.10.024.
35. Joza S, Hu MT, Jung KY, Kunz D, Arnaldi D, Lee JY, et al.; International REM Sleep Behavior Disorder Study Group. Prodromal dementia with Lewy bodies in REM sleep behavior disorder: A multicenter study. Alzheimers Dement. 2024;20(1):91-102. doi:10.1002/alz.13386.
36. Hu MT. REM sleep behavior disorder (RBD). Neurobiol Dis. 2020;143:104996. doi:10.1016/j.nbd.2020.104996.
37. van Wamelen DJ, Leta V, Podlewska AM, et al. Exploring hyperhidrosis and related thermoregulatory symptoms as a possible clinical identifier for the dysautonomic subtype of Parkinson's disease. J Neurol. 2019;266(8):1736-1742. doi:10.1007/s00415-019-09325-w.
38. Siderowf A, Concha-Marambio L, Lafontant DE, et al.; Parkinson's Progression Markers Initiative. Assessment of heterogeneity among participants in the Parkinson's Progression Markers Initiative cohort using α-synuclein seed amplification: a cross-sectional study. Lancet Neurol. 2023;22(5):407-417. doi:10.1016/S1474-4422(23)00109-6.
39. Rutledge J, Lehallier B, Zarifkar P, et al. Comprehensive proteomics of CSF, plasma, and urine identify DDC and other biomarkers of early Parkinson's disease. Acta Neuropathol. 2024;147(1):52. doi:10.1007/s00401-024-02706-0.
40. Jia F, Fellner A, Kumar KR. Monogenic Parkinson's Disease: Genotype, Phenotype, Pathophysiology, and Genetic Testing. Genes (Basel). 2022;13(3):471. doi:10.3390/genes13030471.
41. Blesa J, Trigo-Damas I, Quiroga-Varela A, Jackson-Lewis VR. Oxidative stress and Parkinson's disease. Front Neuroanat. 2015;9:91. doi:10.3389/fnana.2015.00091.
42. Gegg ME, Schapira AH. Mitochondrial dysfunction associated with glucocerebrosidase deficiency. Neurobiol Dis. 2016;90:43-50. doi:10.1016/j.nbd.2015.09.006.
43. Ye H, Robak LA, Yu M, Cykowski M, Shulman JM. Genetics and Pathogenesis of Parkinson's Syndrome. Annu Rev Pathol. 2023;18:95-121. doi:10.1146/annurev-pathmechdis-031521-034145.
44. Domenicale C, Magnabosco S, Morari M. Modeling Parkinson's disease in LRRK2 rodents. Neuronal Signal. 2023;7(3). doi:10.1042/NS20220040.
45. Lesage S, Lunati A, Houot M, et al.; French Parkinson Disease Genetics Study Group. Characterization of Recessive Parkinson Disease in a Large Multicenter Study. Ann Neurol. 2020;88(4):843-850. doi:10.1002/ana.25787.
46. Liu H, Koros C, Strohäker T, et al. A Novel SNCA A30G Mutation Causes Familial Parkinson's Disease. Mov Disord. 2021;36(7):1624-1633. doi:10.1002/mds.28534.
47. Barbuti PA, Ohnmacht J, Santos BF, et al. Gene-corrected p.A30P SNCA patient-derived isogenic neurons rescue neuronal branching and function. Sci Rep. 2021;11(1):21946. doi:10.1038/s41598-021-01505-x.

48. Armstrong MJ, Okun MS. Diagnosis and Treatment of Parkinson Disease: A Review. JAMA. 2020;323(6):548-560. doi:10.1001/jama.2019.22360.
49. Cattaneo C, Jost WH. Pain in Parkinson's Disease: Pathophysiology, Classification and Treatment. J Integr Neurosci. 2023;22(5):132. doi:10.31083/j.jin2205132.
50. Jang Y, Koo JH, Kwon I, et al. Neuroprotective effects of endurance exercise against neuroinflammation in MPTP-induced Parkinson's disease mice. Brain Res. 2017;1655:186-193. doi:10.1016/j.brainres.2016.10.029.
51. Johansson H, Freidle M, Ekman U, et al. Feasibility Aspects of Exploring Exercise-Induced Neuroplasticity in Parkinson's Disease: A Pilot Randomized Controlled Trial. Parkinsons Dis. 2020;2020:2410863. doi:10.1155/2020/2410863.
52. Paillard T, Rolland Y, de Souto Barreto P. Protective Effects of Physical Exercise in Alzheimer's Disease and Parkinson's Disease: A Narrative Review. J Clin Neurol. 2015;11(3):212-219. doi:10.3988/jcn.2015.11.3.212.
53. Church FC. Treatment Options for Motor and Non-Motor Symptoms of Parkinson's Disease. Biomolecules. 2021;11(4):612. doi:10.3390/biom11040612.
54. Carbone F, Djamshidian A, Seppi K, Poewe W. Apomorphine for Parkinson's Disease: Efficacy and Safety of Current and New Formulations. CNS Drugs. 2019;33(9):905-918. doi:10.1007/s40263-019-00661-z.
55. Perez-Lloret S, Rascol O. Efficacy and safety of amantadine for the treatment of L-DOPA-induced dyskinesia. J Neural Transm (Vienna). 2018;125(8):1237-1250. doi:10.1007/s00702-018-1869-1.
56. Ernst M, Folkerts AK, Gollan R, et al. Physical exercise for people with Parkinson's disease: a systematic review and network meta-analysis. Cochrane Database Syst Rev. 2023;1(1). doi:10.1002/14651858.CD013856.pub2.
57. Ellis TD, Colón-Semenza C, DeAngelis TR, et al. Evidence for Early and Regular Physical Therapy and Exercise in Parkinson's Disease. Semin Neurol. 2021;41(2):189-205. doi:10.1055/s-0041-1725133.
58. Ashburn A, Pickering R, McIntosh E, et al. Exercise- and strategy-based physiotherapy-delivered intervention for preventing repeat falls in people with Parkinson's: the PDSAFE RCT. Health Technol Assess. 2019;23(36):1-150. doi:10.3310/hta23360.
59. Jang Y, Koo JH, Kwon I, et al. Neuroprotective effects of endurance exercise against neuroinflammation in MPTP-induced Parkinson's disease mice. Brain Res. 2017;1655:186-193. doi:10.1016/j.brainres.2016.10.029.
60. Ding H, Dhima K, Lockhart KC, et al. Unrecognized vitamin D3 deficiency is common in Parkinson disease: Harvard Biomarker Study. Neurology. 2013;81(17):1531-1537. doi:10.1212/WNL.0b013e3182a95818.
61. Peterson AL, Murchison C, Zabetian C, et al. Memory, mood, and vitamin D in persons with Parkinson's disease. J Parkinsons Dis. 2013;3(4):547-555. doi:10.3233/JPD-130206.
62. Cernera S, Eisinger RS, Wong JK, et al. Long-term Parkinson's disease quality of life after staged DBS: STN vs GPi and first vs second lead. NPJ Parkinsons Dis. 2020;6:13. doi:10.1038/s41531-020-0115-3.
63. Sharma VD, Patel M, Miocinovic S. Surgical Treatment of Parkinson's Disease: Devices and Lesion Approaches. Neurotherapeutics. 2020;17(4):1525-1538. doi:10.1007/s13311-020-00939-x.