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Depression in prodromal Parkinson's disease: a systematic review

Depressão na doença de Parkinson prodrômica: uma revisão sistemática

Depresión en la enfermedad de Parkinson en fase preclínica: una revisión sistemática

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ABSTRACT:
Introduction: Parkinson's disease (PD) is marked not only by motor symptoms, but non-motor symptoms such as REM sleep disorder, constipation, anosmia, dysautonomia, depression, anxiety, cognitive impairment and others. It is possible that these symptoms precede bradykinesia, forming a condition called Prodromal PD (PPD). Identifying PPD allows optimization of treatment and care. The identification of these patients with PPD remains a challenge, as many of the symptoms listed are prevalent in the elderly population. Depression is highlighted as a prodromal symptom, but identifying patients with depressive symptoms that are part of PPD is a challenging task. **Objectives**: to carry out a systematic review of the literature, aiming to identify advances and updates regarding depression in PPD, allowing the identification of patients with depression who are part of the group of patients with PPD. **Methods**: systematic literature review, following the guidelines of the PRISMA 2020 protocol; searching the descriptors depression, depressive symptoms and prodromal parkinson's disease on the Pubmed Platform. 25 publications were found; In the end, 9 articles remained for inclusion in the review. **Results**: predictive value was observed in the combination of REM sleep disorder and depression for the development of PD; presence of two or more prodromal symptoms combined represented a predictive factor for PD; hospitalization for depression predicted risk of developing PD. **Conclusion**: combination of depression and other prodromal symptoms predicts PD, as well as the severity and refractoriness of the depressive condition. Prodromal symptoms remain a challenge, but can be actively investigated.

Keywords: Parkinson's disease, depression, depressive symptoms

RESUMO:
Introdução: A doença de Parkinson (DP) é marcada não apenas por sintomas motores, mas também por sintomas não motores, como distúrbio do sono REM, constipação intestinal, anosmia, disautonomia, depressão, ansiedade, comprometimento cognitivo e outros. É possível que esses sintomas antecedam a bradicinesia, formando uma condição denominada DP Prodrômica (DPP). A identificação da DPP permite a otimização do tratamento e do cuidado. A identificação desses pacientes com DPP permanece um desafio, visto que muitos dos sintomas listados são prevalentes na população idosa. A depressão é destacada como um sintoma prodrômico, mas identificar pacientes com sintomas depressivos que fazem parte da DPP é uma tarefa desafiadora. **Objetivos**: realizar

uma revisão sistemática da literatura, visando identificar avanços e atualizações em relação à depressão na DPP, permitindo a identificação de pacientes com depressão que fazem parte do grupo de pacientes com DPP. **Métodos**: revisão sistemática da literatura, seguindo as diretrizes do protocolo PRISMA 2020; busca pelos descritores depressão, sintomas depressivos e doença de parkinson prodrômica na Plataforma Pubmed. Foram encontradas 25 publicações; Ao final, restaram 9 artigos para inclusão na revisão. **Resultados**: observou-se valor preditivo na combinação de distúrbio do sono REM e depressão para o desenvolvimento de TP; a presença de dois ou mais sintomas prodrômicos combinados representou um fator preditivo para TP; a hospitalização por depressão previu o risco de desenvolver TP. **Conclusão**: a combinação de depressão e outros sintomas prodrômicos prediz o TP, bem como a gravidade e a refratariedade do quadro depressivo. Os sintomas prodrômicos permanecem um desafio, mas podem ser ativamente investigados.

Palavras-chave: doença de Parkinson, depressão, sintomas depressivos

RESUMEN:
Introducción: La enfermedad de Parkinson (EP) se caracteriza no solo por síntomas motores, sino también por síntomas no motores como trastornos del sueño REM, estreñimiento, anosmia, disautonomía, depresión, ansiedad, deterioro cognitivo, entre otros. Es posible que estos síntomas precedan a la bradicinesia, formando una condición denominada EP en fase preclínica (EPP). Identificar la EPP permite optimizar el tratamiento y la atención. Sin embargo, la identificación de estos pacientes con EPP sigue siendo un desafío, ya que muchos de estos síntomas son frecuentes en la población geriátrica. La depresión se destaca como un síntoma preclínico, pero identificar a los pacientes con síntomas depresivos que forman parte de la EPP es una tarea compleja. **Objetivos**: Realizar una revisión sistemática de la literatura para identificar avances y actualizaciones sobre la depresión en la EPP, con el fin de facilitar la identificación de pacientes con depresión que pertenezcan a este grupo. **Métodos**: Revisión sistemática de la literatura, siguiendo las directrices del protocolo PRISMA 2020; se realizó una búsqueda en PubMed utilizando los descriptores: depresión, síntomas depresivos y enfermedad de Parkinson preclínica. Se encontraron 25 publicaciones; finalmente, se incluyeron 9 artículos en la revisión. **Resultados**: Se observó valor predictivo en la combinación de trastorno del sueño REM y depresión para el desarrollo de la EP; la presencia de dos o más síntomas preclínicos combinados fue un factor predictivo de EP; la hospitalización por depresión

predijo el riesgo de desarrollar EP. **Conclusión**: La combinación de depresión y otros síntomas preclínicos predice la EP, así como la gravedad y la refractariedad de la depresión. Los síntomas preclínicos siguen siendo un desafío, pero su estudio es factible.

Palabras clave: Enfermedad de Parkinson, depresión, síntomas depresivos

Introduction

Parkinson's disease (PD) is characterized by bradykinesia, accompanied by akinetic tremor (4 to 6 Hz frequency) and/or muscle rigidity and postural instability (not caused by visual, cerebellar, prociceptive or vestibular disorders); there is a need to exclude other forms of parkinsonism. In addition, according to the UK Parkinson Society Brain Bank criteria (Queen Square Brain Bank Criteria), three other criteria must be present, such as unilateral onset, good response to levodopa, evolution of 10 years or more, persistence of symptom asymmetry, levodopa-induced dyskinesia and resting tremor [1].

Additional tests can reinforce the diagnosis, but are not mandatory for its definition. Absence of atonia during REM sleep can be identified through polysomnography [2]. Cardiac autonomic denervation can be observed by myocardial scintigraphy (MIBG SPECT), reinforcing the diagnostic hypothesis and highlighting one of the non-motor symptoms of PD (dysautonomia) [3]. In addition to Brain Perfusion Scintigraphy with TRODAT (marker of dopamine transport in basal ganglia), which confirms motor symptoms and allows differentiation between primary or induced parkinsonism [4, 5, 6].

The etiopathogenesis of PD is complex, involving the abnormal accumulation of a protein found in the presynaptic terminal, called alpha-synuclein. The accumulation of this protein constitutes a microscopy finding known as a Lewy body. The set of these corpuscles can be found in different locations of the central nervous system (CNS) and explains the symptoms presented during the disease. The olfactory nerve, cerebral cortex, vagus nerve, thalamus, nucleus basalis of Meynert, substantia nigra and other regions may present these corpuscles, which promote cellular suffering and neuronal death.

In short, the accumulation of alpha-synuclein engenders, through various mechanisms, the loss of neurons and, depending on the region, different symptoms will be expressed [7, 8, 9, 10, 11]. This cascade involves

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inflammatory and immunological dysregulation, with activation of glial cells, reduced cellular resilience and loss of adaptive mechanisms. In other words, a “perfect storm” that leads to cell death and the known symptoms of the disease [12, 13, 14].

The motor symptoms, which fundamentally involve bradykinesia, tremor (predominantly asymmetric) and stiffness, are the result of damage to the substantia nigra, with depigmentation and death of dopaminergic neurons; limiting nigro-striatal dopaminergic transport [15 – 16]. When motor symptoms appear, it is estimated that 60% of dopaminergic neurons in this region are lost [15].

In addition to motor impairment, there are non-motor symptoms that involve PD. And its etiology appears to be related to neuronal death, with a decrease in not only dopaminergic transport, but also noradrenergic, cholinergic and serotonergic transport [17]. Almost all (98.6%) of patients with this pathology will develop non-motor symptoms [18 – 19]. They per se are capable of limiting the patient's quality of life and functionality, and are often the main complaint reported during consultations.

This myriad of symptoms involves fatigue, anxiety, depression, sleep disorders, constipation, postural hypotension, urinary urgency, erectile dysfunction and other manifestations of dysautonomia [20]. Braak's evolutionary theory helps support these findings as an integral part of PD, since different locations in the CNS can be affected by Lewy bodies, not just structures related to motor symptoms [19, 21, 22, 23].

Many non-motor symptoms may even be present before the development of bradykinesia and postural instability – being considered prodromal [24]. And again, Braak's evolutionary theory supports these prodromal findings, since the substantia nigra becomes affected only in stage 3 of evolution. That is,previously, other locations in the nervous system have already been affected; for example, olfactory nerve and vagus nerve [25].

The clinical definition of Prodromal Parkinson's Disease (PPD) was made by the International Parkinson and Movement Disorder Society. This study group also defined the concepts of preclinical PD and clinical PD. In the pre-clinical stage, there is already an accumulation of Lewy bodies and neurgeneration, but there are no symptoms. In the prodromal stage, non-motor symptoms appear. And, finally, in the clinical stage, parkinsonism appears, which allows for a complete diagnostic definition [26].

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More recently, the same International Parkinson and Movement Disorder Society constructed the concept of Probable Prodromal Parkinson's disease (probable PPD), denoting a probability of over 80% in the development of PD. This diagnosis is measured using an algorithm (Bayesian), offering the patient's clinical, neuroimaging and genetic data. Among the prodromal symptoms described in this tool, REM sleep disorder (confirmed by polysomnography), anosmia or hyposmia, constipation, daytime drowsiness, symptomatic postural hypotension, erectile dysfunction, urinary dysfunction and diagnosis of depression (with or without anxious symptoms) were listed [27].

Over the last few years, the initially proposed clinical findings have been reviewed, and their predictive potential has been questioned [28]. Reinforcing the challenge in determining which symptoms can predict the onset of PD a posteriori and the challenge in defining prodromal PD.

As expressed, depression has been identified as a prodromal symptom [28], but it can often be confused with apathy, anhedonia, bradyphrenia or other anxiety and psychopathological disorders [29]. This adds another challenge: how to diagnose and identify patients with depression who are, in fact, at greater risk of developing PD.

Furthermore, the delay in identifying the prodromal phase of this disease and depressive symptoms generates clear losses in quality of life and initiation of treatment [30].

Objectives

The objective of this article is to carry out a systematic review of the literature that covers the diagnosis of depression in Prodromal Parkinson's disease (PPD). To do this, two questions need to be answered: how is depression diagnosed in prodromal Parkinson's disease? When should depression be suspected as a prodromal symptom of Parkinson's disease?

Materials and Methods

The study design consists of a systematic review of the literature, using the PRISMA 2020 (Preferred Reporting Items for a Systematic Review and Meta-Analysis) guidelines. The articles included had to be original and deal with “depression in prodromal Parkinson's disease”. Reviews or meta-analyses and other articles whose main theme was not depression in prodromal PD were excluded.

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A search was carried out on the PubMed data platform, using the descriptors "depression", "depressive symptoms" and "prodromal parkinson's disease". A total of 25 articles were found and all had their title and abstract analyzed.

Of the 25 articles listed, 9 were review articles (systematic, integrative or meta-analysis) and another 2 addressed depression as a manifestation of PD in its motor phase. Therefore, 13 of the 25 articles were excluded from the sample based only on reading their abstracts.

The remaining 12 articles were read in full. Three of them also addressed PD in its motor phase (although early). Therefore, as they did not address PPD, they were excluded. Therefore, nine articles remained. Figure 1 below shows the process of searching and excluding the articles found.

Results

Of the nine articles selected for the review, four consisted of cohorts, three were case-control studies and two were cross-sectional studies. One of them had an international and multicenter database as its database, another was carried out in China and the rest were carried out in Europe (with Germany highlighting three of the studies).

The number of patients evaluated in each of the studies was heterogeneous, 36 individuals were evaluated in the cross-sectional study by Kazmi et al., while the case-control study by Schrag included 46,755 controls and 8,166 patients with PD [31 - 32].

The diversity of tools for diagnosing depression, among the articles included in the review, was remarkable. Two of them used the Geriatric Depression Scale (GDS), two the Beck Depression Scale, another three used the International Classification of Diseases criteria (ICD 9 or 10) or the Diagnostic and Statistical Manual of Mental Disorders (DSM IV). Others used reports of depression in medical records (without using psychometric scales). Below is a table with the most relevant information obtained in each of the studies. Frame 1.

Ma et al. correlated REM sleep disorders with depressive symptoms in prodromal PD in a cohort study in which patients were followed for 5 years, concluding a correlation between depressive symptoms and behavioral changes in REM sleep in a patient with prodromal PD. Furthermore, using the RBD Screening Questionnaire Score scale, individuals with higher

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scores on this scale had more prominent depressive symptoms – especially in PD patients, when compared to controls [33].

Other authors such as Roos et al., Schrag et al., Gaenslen et al. and Bohlken et al. correlated different prodromal symptoms such as hyposmia, sleep disorders, urinary symptoms (such as urge incontinence), anxiety, fatigability, dizziness, hypotension and depression; seeking to evaluate their impact on the development of PD [31, 32, 33, 34].

The study by Roos et al. concluded that the combination of prodromal symptoms (two or more) increased the risk of developing PD and worse motor outcomes. The authors highlighted that, in the absence of pathognomonic symptoms, prodromal PD should be considered in view of the combination of different suggestive findings. The presence of depressive symptoms is no exception to this logic [35]. The study by Bohlken et al. highlighted that depression, dizziness, insomnia and constipation were predictors for the development of PD, but its prevalence in the general population was also high.

The work of Scharg et al. It was based on a database from The Health Improvement Network (THIN), from the United Kingdom. In this study, data from the medical records of patients with or without PD, between 1996 and 2012, were collected and retrospectively evaluated. Possible prodromal symptoms are listed for analysis – including autonomic, neuropsychiatric, motor and others [31]. For individuals who developed PD, the relative risk and incidence of each of the symptoms were calculated for various periods: two, five, or ten years before diagnosis. Two years before the diagnosis of PD, the most relevant symptoms were tremor (isolated, without establishing a diagnosis of parkinsonism), constipation (as the most relevant dysautonomic symptom), depression and anxiety (especially when starting after the age of 50). Five years before the diagnosis of PD, the incidence of depression, fatigability, dizziness and other symptoms was higher among individuals who would later develop PD. Ten years before the diagnosis of PD, the incidence of tremor (isolated) and constipation was higher among individuals who would develop PD compared to controls.

The Tübinger Evaluation of Risk Factors for Early Detection of Neurodegeneration (TREND) study served as the database for the work of Gaenslen et al. (2014); including individuals aged between 50 and 80 years, without a diagnosis of Parkinson's disease or other neurodegenerative diseases. In this prospective cohort, markers and 23

possible prodromal symptoms for Alzheimer's disease and PD were investigated, including eight motor and fifteen non-motor symptoms. Motor symptoms included: hypophonia, bradyphrenia, reduced limb swing when walking, micrographia, dysarthria and akinetic tremor. Non-motor symptoms were: perception of visuospatial impairment, painful muscle tension, sleep disturbances, constipation, urinary dysfunction, erectile dysfunction, orthostatic dizziness, amnesic impairment, anxiety. The presence of two or three of these motor or non-motor symptoms increased the risk of presenting PD later [32].

Study by Kazmi et al. demonstrated that patients with depressive symptoms that began after the age of 55 more frequently presented deficits in dopamine transport in the basal ganglia, when compared to healthy individuals. For this purpose, 28 individuals with depression and 30 controls were recruited and examined; 24% of individuals with depressive symptoms had deficits in dopamine transport (measured using single-photon emission computed tomography with ioflupane 123) compared to only 4% of controls [36].

The severity of depressive symptoms presented in this prodromal context appears to be related to negative motor outcomes and worse quality of life during the clinical phase of the disease. This was concluded in the prospective cohort study by Gustafsson et al., which included 140,688 individuals with depression and 421,943 controls [37]. Likewise, anxious symptoms comorbid with depressive symptoms can predict worse outcome, as found in the work of Roos et al [37 - 38].

Study by Liu et al. concluded that siblings of patients with PD are more likely to suffer from depression, anxiety and REM sleep behavior disorder [39]. Indicating the presence of shared genetic factors and heredity.

Discussion

Depressive symptoms may precede motor symptoms of PD by 1 to 36 years [40]. This chronology is based on Braak's evolutionary theory, which correlates depressive symptoms with involvement of the raphe nuclei and locus coeruleus [23]. Furthermore, the earlier the appearance of these symptoms, the greater the window of opportunity for diagnosis, assertive treatment and diagnostic suspicion.

The presence of other prodromal symptoms such as hyposmia, anosmia, insomnia, sleep disorders (especially REM sleep), urinary symptoms (urge incontinence), fatigability, family history of PD appear as risk markers for

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the development of PD [33, 35, 38, 41, 42, 43, 44, 45]. And, among the symptoms presented by the studies, all of them can be actively identified, classified and treated in general clinical practice.

The tool presented in the study by Kazmi et al. (SPECT) demonstrated deficits in dopamine transport in basal ganglia in patients with depressive symptoms [36]; indicating the possibility of a new propaedeutic tool. However, its applicability in clinical practice is limited – either due to access or cost.

Other prodromal symptoms of PD that are strongly related to depression are sleep disorders. Examples range from excessive daytime drowsiness, difficulty changing position due to dystonia and the off effect of medications (already in the motor phase), restless leg syndrome, myoclonus and the absence of atonia during REM sleep [46]. Furthermore, approximately half of individuals with some alpha-synucleinopathy may experience REM sleep disorders [43].

The correlation between sleep disorders and depressive symptoms is not just epidemiological. Patients with sleep disorders may experience more intense depressive symptoms (and worse quality of life); as well as both disorders may have a common cause – especially in the prodromal context of alpha-synucleinopathies [43]. That is, the relationship between depression and sleep disorders is bidirectional, as demonstrated by Ma et al [46]. And the combination of sleep disorders and depression in elderly patients can increase diagnostic suspicion.

More severe depressive episodes, which lead to psychiatric hospitalization, seem to have a greater impact on the subsequent development of PD. In addition to this factor, resistance and recurrence of depressive symptoms also seem to increase the risk [37]. In fact, the severity and resistance of depressive symptoms are often related to the emergence of neurodegenerative disorders (and dementia) in the elderly population [43]. Reinforcing diagnostic suspicion in cases that are difficult to manage and have a low therapeutic response.

The concomitant presence of depression and anxiety was frequent in the study by Roos et al. and this combination negatively impacted the physical performance of the patients studied [45]. Reinforcing the impact of psychopathological symptoms on functional performance and the need for clinical identification and rapid treatment. A study by Orayj et al., for example, highlights the use of MAOIs as an effective alternative for the

treatment of depressive symptoms, including recently diagnosed PD (within one year of the onset of motor symptoms) [47].

The mechanisms involving depressive conditions in the context of prodromal PD are still unknown – depression may be an independent risk factor, be the early expression of the disease itself or both conditions may present common causal factors [42]. In this sense, the detection of depressive symptoms, which will be part of PD in the future, remains a challenge.

A study included in the review concluded that siblings of PD patients are more likely to suffer from depression, anxiety, and REM sleep behavior disorder [39]. Reinforcing the presence of shared genetic factors. Other studies included in the work did not address the prevalence of depression or PD in first-degree relatives.

Another nosological challenge involving depression in PD consists of differentiating and identifying apathy and major depressive disorder. Apathy can be a symptom within a depressive syndrome or a syndrome per se. It involves affective and motor hyporeactivity to stimuli, as well as reduced initiative and pragmatism when performing tasks. Rarely responds to levodopa replacement therapy, unlike motor symptoms. It may respond to antidepressant treatment if it is linked to depression. It may also be a prodrome of dementia [44, 45]. None of the studies present in the review specifically addressed this symptom.

Anxious symptoms can also be confused or even comorbid with depressive symptoms. During the motor phase of PD, such symptoms may be associated with periods off medication, which may exacerbate bradykinesia, tremor and functional limitations [48]. It is no surprise that prodromal anxious and depressive symptoms and apathy suggest a worse response to levodopa therapy and greater complications [38].

Population cohort studies, such as those presented in this review, seek to determine the identification of prodromal PD. However, even though clinical criteria are proposed, the specificity and predictive value of some of these tests are limited [48]. Higher and more robust predictive values are often obtained in studies including high-risk populations, such as individuals with hyposmia and idiopathic REM sleep disorders [49 - 50].

The International Parkinson and Movement Disorder Society (MDS) Task Force sought to list symptoms and criteria to define prodromal PD [50].

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Probable prodromal PD was defined as an 80% probability of developing PD. The choice of criteria involved meta-analyses and reviews that indicated which variables could have a greater probability of impact.

Among the non-motor risk markers, the first version of the MDS Task Force for diagnosing prodromal PD listed: REM sleep disorder (diagnosed by polysomnography), anosmia or hyposmia, constipation, daytime sleepiness, symptomatic postural hypotension, erectile dysfunction, urinary dysfunction and diagnosis of depression (with or without anxious symptoms) [51]. It is important to highlight that the diagnosis of depression did not have such a high predictive potential; given its high prevalence in the general population.

Furthermore, none of the studies included in the review, nor other guidelines, proposed special criteria for diagnosing depression in this context. That is, even though depression is a recognized risk marker and is linked to the premotor phase of PD [52]; There are no specific criteria for its diagnosis. Therefore, unless the patient presents other clinical complications (such as hyposmia, sleep disorders, constipation and others); the diagnostic presumption in the face of depressive symptoms is the responsibility of the examiner. Lacking specific criteria to guide the propaedeutics.

Mortality is high in individuals with PD and comorbid depression (2.66 times compared to individuals without depression) [52]. Furthermore, suicidal ideation is twice as high in individuals with PD compared to the general population [53]. Reinforcing the importance and need for assertive treatment, whether in the clinical phase or in the prodromal phase of the disease; mitigating losses and risks afterwards.

Conclusion

The review demonstrated that the combination of depression and other symptoms can increase diagnostic suspicion and indicate a context of prodromal PD. The use of subsidiary tests such as SPECT with a tracer of dopamine transport in the basal ganglia is a tool that, in the future, could form part of the therapeutic arsenal in a more accessible way.

Other points of greater suspicion in relation to prodromal PD involve the refractoriness and severity of depressive conditions, especially when combined with anxious symptoms, sleep disorders and late onset (after the age of 50).

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The review also highlighted the challenge in identifying patients with PPD, delaying guidance, care and treatment. Even so, many of the prodromal symptoms highlighted by the studies included in the review can be actively investigated in general medical consultations; highlighting the possibility of rapid management and treatment of these; allowing better quality of life for patients who will develop PD.

References

1. Alves, GS, Tíbor Rilho P, Sudo FK. Psicogeriatria: Diagnóstico e Manejo. São Paulo: Artmed Editora; 2022.

2. Sommerauer M, Fedorova TD, Hansen AK, Knudsen K, Otto M, Jeppesen J, Frederiksen Y, Blicher JU, Geday J, Nahimi A, Damholdt MF, Brooks DJ, Borghammer P. Evaluation of the noradrenergic system in Parkinson's disease: an 11C-MeNER PET and neuromelanin MRI study. Brain. 2018;141(2):496-504. https://doi.org/10.1093/brain/awx348 PMid:29272343

3. Rascol O, Schelosky L, 123I-metaiodobenzylguanidine scintigraphy in Parkinson's disease and related disorders. Mov Disord. 2009,24(Suppl 2):S732-41. https://doi.org/10.1002/mds.22499 PMID: 19877202

4. Nandhagopal R, Kuramoto L, Schulzer M, Mak E, Cragg J, Lee CS, McKenzie J, McCormick S, Samii A, Troiano A, Ruth TJ, Sossi V, de la Fuente-Fernandez R, Calne DB, Stoessl AJ. Longitudinal progression of sporadic Parkinson's disease: a multi-tracer positron emission tomography study. Brain. 2009;132(Pt 11):2970-9. https://doi.org/10.1093/brain/awp209 PMid:19690093

5. Hoehn MM, Yahr MD. Parkinsonism: onset, progression and mortality. Neurology. 1967;17(5):427-42. https://doi.org/10.1212/WNL.17.5.427 PMid:6067254

6. Poewe W, Seppi K, Tanner CM, Halliday GM, Brundin P, Volkmann J, Schrag AE, Lang AE. Parkinson disease. Nat Rev Dis Primers.

2017;3:17013. https://doi.org/10.1038/nrdp.2017.13 PMid:28332488

7. Lewy FH. Paralysis agitans. I. Pathologische Anatomie. In: Lewandowsky M. editor. Handbuch der Neurologie. Berlin: Springer; 1912. p. 920-33.

8. Adler CH, Dugger BN, Hentz JG, Hinni ML, Lott DG, Driver-Dunckley E, Mehta S, Serrano G, Sue LI, Duffy A, Intorcia A, Filon J, Pullen J, Walker DG, Beach TG. Peripheral synucleinopathy in early Parkinson's disease: submandibular gland Needle biopsy findings. Mov Disord. 2016;31(2):250-6. https://doi.org/10.1002/mds.26476 PMID: 26799362 PMCID: PMC4747813

9. Campo F, Carletti R, Fusconi M, Pellicano C, Pontieri FE, Di Gioia CR, Vincentiis M. Alpha-synuclein in salivary gland as biomarker for Parkinson's disease. Rev Neurosci. 2019;30(5):455-462. https://doi.org/10.1515/revneuro-2018-0064 PMID: 30471223

10. Sian J, Dexter DT, Lees AJ, Daniel S, Agid Y, Javoy-Agid F, Jenner P, Marsden CD. Alterations in glutathione levels in Parkinson's disease and other neurodegenerative disorders affecting basal ganglia. Ann Neurol. 1994;36(3):348-55. https://doi.org/10.1002/ana.410360305 PMid:8080242

11. Greenfield JG, Bosanquet FD. The brain-stem lesions in parkinsonism. J Neurol Neurosurg Psychiatry. 1953;16(4):213-26. https://doi.org/10.1136/jnnp.16.4.213 PMID: 13109537 PMCID: PMC503142

12. Zavariz RC, Limeira DM. Possíveis etiologias para a Doença de Parkinson: Uma breve revisão bibliográfica. Saúde Pesqui. 2012;5(2):388-98. https://periodicos.unicesumar.edu.br/index.php/saudpesq/article/view/1818

13. Da Silva Correia MDG, de Jesus AVF, Messias GMS, Nunes TLGM, Gomes MZ, da Paixão AO, Silva FS, Nunes TLGM, Santos TBG. Doença de Parkinson: uma desordem neurodegenerativa. Cad. Grad. Ciênc Biol Saúde Unit. 2013;1(2),57-65. https://periodicos.set.edu.br/cadernobiologicas/article/view/290

14. Tansey MG, Wallings RL, Houser MC, Herrick MK, Keating CE, Joers V. Inflammation and immune dysfunction in Parkinson disease. Nat Rev Immunol. 2022;22(11):657-73. https://doi.org/10.1038/s41577-022-00684-6 PMid:35246670 PMCid:PMC8895080

15. Souza CFM, Almeida HCP, Sousa JB, Costa PH, Silveira YSS, Bezerra JCL. A doença de Parkinson e o processo de envelhecimento motor: uma revisão de literatura. Rev Neurocienc. 2011;19(4):718-23. https://doi.org/10.34024/rnc.2011.v19.8330

16. Alves SCC. Fisiopatologia dos gânglios base na doença de Parkinson [master's thesis on internet]. Coimbra: Faculdade de Medicina da Universidade de Coimbra; 2012. https://hdl.handle.net/10316/84946

17. Jankovic J, Hallett M, Okun MS, Comella CL, Fahn S, Goldman J. Principles and practice of movement disorders. 3a ed. London: Elsevier Health Sciences; 2021. Chapter 26, Peripheral movement disorders; p. 585-90. https://doi.org/10.1016/B978-0-323-31071-0.00026-3

18. Barone P, Antonini A, Colosimo C, Marconi R, Morgante L, Avarello TP, Bottacchi E, Cannas A, Ceravolo G, Ceravolo R, Cicarelli G, Gaglio RM, Giglia RM, Iemolo F, Manfredi M, Meco G, Nicoletti A, Pederzoli M, Petrone A, Pisani A, Pontieri FE, Quatrale R, Ramat S, Scala R, Volpe G, Zappulla S, Bentivoglio AR, Stocchi F, Trianni G, Del Dotto P. The PRIAMO study: a multicenter assessment of nonmotor symptoms and their impact on quality of life in Parkinson's

disease. Mov Disord. 2009;24(11):1641-9. https://doi.org/10.1002/mds.22643 PMid:19514014

19. O'Sullivan SS, Williams DR, Gallagher DA, Massey LA, Silveira-Moriyama L, Lees AJ. Nonmotor symptoms as presenting complaints in Parkinson's disease: a clinicopathological study. Mov Disord. 2008;23(1):101-6. https://doi.org/10.1002/mds.21813 PMid:17994582

20. Goetz CG, Tilley BC, Schaftman S. Clinimetric testing of the new UPDRS (MDS-UPDRS) vs original version. Movement Disorders. 2007;22 (Suppl. 16): S6.

21. Teive HAG. Etiopatogenia da doença de Parkinson. Rev Neurocienc. 2005;13:201-14. https://doi.org/10.34024/rnc.2005.v13.8794

22. Dickson DW, Braak H, Duda JE, Duyckaerts C, Gasser T, Halliday GM, Litvan I. Neuropathological assessment of Parkinson's disease: refining the diagnostic criteria. Lancet Neurol. 2009;8(12):1150-7. https://doi.org/10.1016/S1474-4422(09)70238-8 PMid:19909913

23. Braak H, Del Tredici K, Rub U, de Vos RA, Jansen Steur EN, Braak E. Staging of brain pathology related to sporadic Parkinson's disease. Neurobiol Aging. 2003;24(2):197-211 https://doi.org/10.1016/S0197-4580(02)00065-9 PMid:12498954

24. Postuma RB, Berg D. Advances in markers of prodromal Parkinson disease. Nat Rev Neurol. 2016;12(11):622-34. https://doi.org/10.1038/nrneurol.2016.152 PMid:27786242

25. Braak H, Del TK. Invited article: nervous system pathology in sporadic Parkinson disease. Neurology. 2008;70(20):1916-25. https://doi.org/10.1212/01.wnl.0000312279.49272.9f PMid:18474848

26. Berg D, Postuma RB, Bloem B, Chan P, Dubois B, Gasser T, Goetz CG, Halliday GM, Hardy J, Lang AE, Litvan I, Marek K, Obeso J, Oertel W, Olanow CW, Poewe W, Stern M, Deuschl G. Time to redefine PD? Introductory statement of the MDS Task Force on the definition of Parkinson's disease. Mov Disord. 2014;29(4):454-62 https://doi.org/10.1002/mds.25844 PMid:24619848 PMCid:PMC4204150

27. Berg D, Postuma RB, Adler CH, Bloem BR, Chan P, Dubois B, Gasser T, Goetz CG, Halliday G, Joseph L, Lang AE, Liepelt-Scarfone I, Litvan I, Marek K, Obeso J, Oertel W, Olanow CW, Poewe W, Stern M, Deuschl G. MDS research criteria for prodromal Parkinson's disease. Mov Disord. 2015;30(12):1600-11. https://doi.org/10.1002/mds.26431 PMid:26474317

28. Heinzel S, Berg D, Gasser T, Chen H, Yao C, Postuma RB. Update of the MDS research criteria for prodromal Parkinson's disease. Mov Disord. 2019;34(10):1464-70. https://doi.org/10.1002/mds.27802 PMid:31412427

29.Starkstein SE, Brockman S. Management of depression in Parkinson's disease: a systematic review. Mov Disord Clin Pract. 2017;4:470-77. https://doi.org/10.1002/mdc3.12507 PMid:30363415 PMCid:PMC6174394

30. Ravina B, Camicioli R, Como PG, Marsh L, Jankovic J, Weintraub D, Elm J. The impact of depressive symptoms in early Parkinson disease. Neurology. 2007;69(4):342-7. https://doi.org/10.1212/01.wnl.0000268695.63392.10 PMid:17581943 PMCid:PMC2031220

31. Schrag A, Horsfall L, Walters K, Noyce A, Petersen I. Apresentações pré-diagnósticas da doença de Parkinson na atenção primária: um estudo caso-controle. Lancet Neurol. 2015;14(1):57-64. https://doi.org/10.1016/S1474-4422(14)70287-X PMid:25435387

32. Gaenslen A, Wurster I, Brockmann K, Huber H, Godau J, Faust B, Lerche S, Eschweiler GW, Maetzler W, Berg D. Prodromal features for Parkinson's disease--baseline data from the TREND study. Eur J Neurol. 2014;21(5):766-72. https://doi.org/10.1111/ene.12382 PMid:24612314

33. Ma J, Dou K, Liu R, Liao Y, Yuan Z, Xie A. Associations of Sleep Disorders With Depressive Symptoms in Early and Prodromal Parkinson's Disease. Front Aging Neurosci. 2022;14:898149. https://doi.org/10.3389/fnagi.2022.898149 PMid:35754965 PMCid:PMC9226450

34. Bohlken J, Schrag A, Riedel-Heller S, Kostev K. Identification of Prodromal Presentations of Parkinson's Disease among Primary Care Outpatients in Germany. Neuroepidemiology. 2022;56(1):41-9. https://doi.org/10.1159/000520574 PMid:34724667

35. Roos DS, Klein M, Deeg DJH, Doty RL, Berendse HW. Prevalence of Prodromal Symptoms of Parkinson's Disease in the Late Middle-Aged Population. J Parkinsons Dis. 2022;12(3):967-74. https://doi.org/10.3233/JPD-213007 PMid:35180132 PMCid:PMC9108586

36. Kazmi H, Walker Z, Booij J, Khan F, Shah S, Sudre CH, Buckman JEJ, Schrag AE. Late onset depression: dopaminergic deficit and clinical features of prodromal Parkinson's disease: a cross-sectional study. J Neurol Neurosurg Psychiatry. 2021;92(2):158-64. https://doi.org/10.1136/jnnp-2020-324266 PMid:33268471 PMCid:PMC7841491

37. Gustafsson H, Nordström A, Nordström P. Depression and subsequent risk of Parkinson disease: A nationwide cohort study. Neurology. 2015;84(24):2422-9. https://doi.org/10.1212/WNL.0000000000001684 PMid:25995056 PMCid:PMC4478031

38. Hinkle JT, Perepezko K, Gonzalez LL, Mills KA, Pontone GM. Apathy and Anxiety in De Novo Parkinson's Disease Predict the Severity of Motor Complications. Mov Disord Clin Pract. 2020;8(1):76-84. https://doi.org/10.1002/mdc3.13117 PMid:33426161 PMCid:PMC7780944

39. Liu JB, Leng JL, Zhang XJ, Wang ZX, Duan ZW, Mao CJ, Liu CF. Investigation of non-motor symptoms in first-degree relatives of patients with Parkinson's disease. Parkinsonism Relat Disord. 2018;52:62-8. https://doi.org/10.1016/j.parkreldis.2018.03.021 PMid:29606605

40. Leentjens AF, Van den Akker M, Metsemakers JF, Lousberg R, Verhey FR. Higher incidence of depression preceding the onset of Parkinson's disease: a register study. Mov Disord. 2003;18(4):414-8. https://doi.org/10.1002/mds.10387 PMid:12671948

41. Heinzel S, Berg D, Gasser T, Chen H, Yao C, Postuma RB. Update of the MDS research criteria for prodromal Parkinson's disease. Mov Disord. 2019;34(10):1464-70. https://doi.org/10.1002/mds.27802 PMid:31412427

42. Walter U, Heilmann R, Kaulitz L, Just T, Krause BJ, Benecke R, Höppner J. Prediction of Parkinson's disease subsequent to severe depression: a ten-year follow-up study. J Neural Transm (Viena). 2015;122(6):789-97. https://doi.org/10.1007/s00702-014-1313-0 PMid:25217967

43. Karlsen KH, Larsen JP, Tandberg E, Maeland JG. Influence of clinical and demographic variables on quality of life in patients with Parkinson's disease. J Neurol Neurosurg Psychiatry. 1999;66(4):431-5. https://doi.org/10.1136/jnnp.66.4.431 PMid:10201412 PMCid:PMC1736304

44. Kirsch-Darrow L, Fernandez HH, Marsiske M, Okun MS, Bowers D. Dissociating apathy and depression in Parkinson disease.

Neurology. 2006;67(1):33-8. https://doi.org/10.1212/01.wnl.0000230572.07791.22 PMid:16832074 PMCid:PMC2911155

45. Dujardin K, Sockeel P, Delliaux M, Destée A, Defebvre L. Apathy may herald cognitive decline and dementia in Parkinson's disease. Mov Disord. 2009;24(16):2391-7. https://doi.org/10.1002/mds.22843 PMid:19908317

46. Barone D. A., Henchcliffe C. Rapid eye movement sleep behavior disorder and the link to alpha-synucleinopathies. Clin Neurophysiol. 2018;129(8):1551-64. https://doi.org/10.1016/j.clinph.2018.05.003 PMid:29883833 PMCid:PMC6495539

47. Orayj K, Almeleebia T, Vigneshwaran E, Alshahrani S, Alavudeen SS, Alghamdi W. Trend of recognizing depression symptoms and antidepressants use in newly diagnosed Parkinson's disease: Population-based study. Brain Behav. 2021;11(8):e2228. https://doi.org/10.1002/brb3.2228 PMid:34124851 PMCid:PMC8413829

48. Nissenbaum H, Quinn NP, Brown RG, Toone B, Gotham AM, Marsden CD. Mood swings associated with the 'on-off' phenomenon in Parkinson's disease. Psychol Med. 1987;17(4):899-904. https://doi.org/10.1017/S0033291700000702 PMid:3432464

49. Postuma RB, Gagnon J-F, Bertrand J-A, Genier Marchand D, Montplaisir JY. Parkinson risk in idiopathic REM sleep behavior disorder: preparing for neuroprotective trials. Neurology 2015;84:1104-1113. https://doi.org/10.1212/WNL.0000000000001364 PMid:25681454 PMCid:PMC4371408

50. Mahlknecht P, Iranzo A, Hogl B, Frauscher B, Müller C, Santamaría J, Tolosa E, Serradell M, Mitterling T, Gschliesser V,

Goebel G, Brugger F, Scherfler C, Poewe W, Seppi K. Olfactory dysfunction predicts early transition to a Lewy body disease in idiopathic RBD. Neurology. 2015;84(7):654-8. https://doi.org/10.1212/WNL.0000000000001265 PMid:25609758

51. Berg D, Postuma RB, Adler CH, Bloem BR, Chan P, Dubois B, Gasser T, Goetz CG, Halliday G, Joseph L, Lang AE, Liepelt-Scarfone I, Litvan I, Marek K, Obeso J, Oertel W, Olanow CW, Poewe W, Stern M, Deuschl G. MDS research criteria for prodromal Parkinson's disease. Mov Disord. 2015;30(12):1600-11. https://doi.org/10.1002/mds.26431 PMid:26474317

52. Bareeqa SB, Samar SS, Kamal S, Masood Y, Allahyar Ahmed SI, Hayat G. Prodromal depression and subsequent risk of developing Parkinson's disease: a systematic review with meta-analysis. Neurodegener Dis Manag. 2022;12(3):155-64. https://doi.org/10.2217/nmt-2022-0001 PMid:35512296

53. Lee T, Lee HB, Ahn MH, Kim J, Kim MS, Chung SJ, Hong JP. Increased suicide risk and clinical correlates of suicide among patients with Parkinson's disease. Parkinsonism Relat Disord. 2016;32:102-07. https://doi.org/10.1016/j.parkreldis.2016.09.006 PMid:27637284

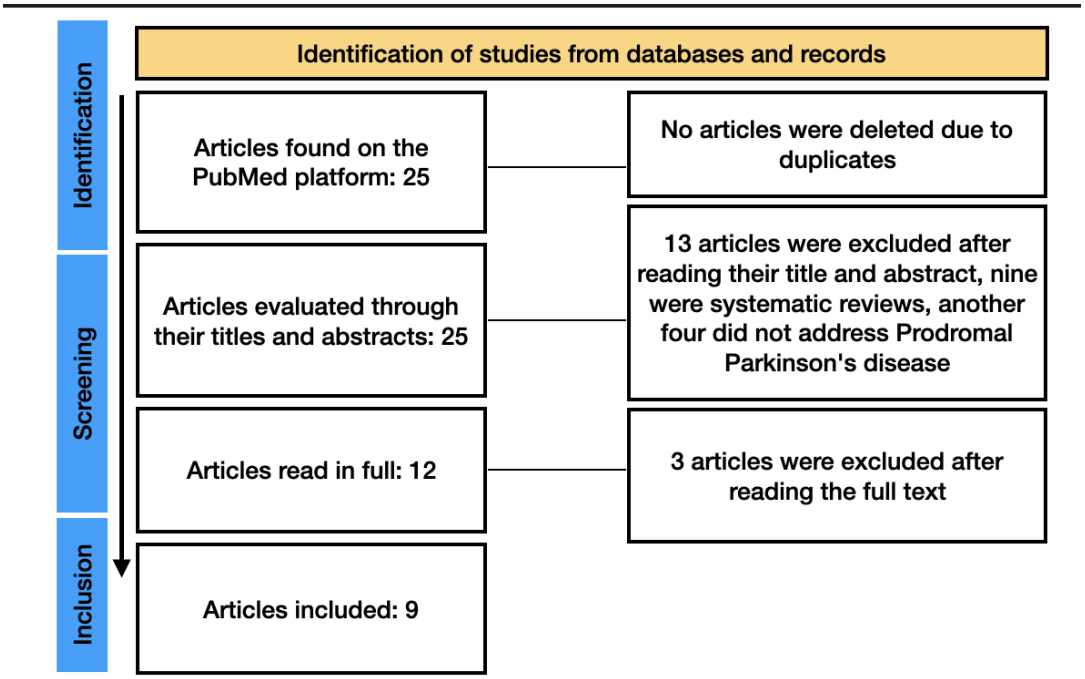

Figure 1. PRISMA 2020 flowchart of the study selection process
Source: The authors

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Frame 1. Summary of studies

	Study Design	Sample	Intruments for diagnosing depressive symptoms/ depression	Main findings
Ma et al., 2022 [33]	Prospective and cohort	423 with early PD (before age 40), 64 with prodromal PD, 196 healthy	Geriatric Depression Scale (GDS)	High predictive value of REM sleep disorders, together with depression, for the development of PD
Roos et al., 2022 [35]	Prospective and cohort	775 elderly individuals	The Center for Epidemiologi c Studies Depression Scale e Hospital Anxiety and Depression Scale	The combination of prodromal symptoms (two or more) seems to be an important finding for identifying Prodromal Parkinson's disease, surpassing any isolated symptom. Depression follows the same logic, it must be accompanied by other findings to raise diagnostic suspicion. 11% of individuals had at least two known risk factors for PD; promoting worse motor outcomes.
Schrag et al., 2015 [31]	Case-control study	8,166 individuals with PD and 46,755 without PD	Report in medical record of diagnosis of depression	5 years before PD diagnosis, the incidence of tremor, imbalance, depression, anxiety, fatigue, urinary symptoms, hypotension, dizziness, erectile dysfunction and constipation was higher among individuals who would develop PD (n=4,769) compared to controls.

	Study Design	Sample	Intruments for diagnosing depressive symptoms/ depression	Main findings
				10 years before PD diagnosis, the incidence of tremor and constipation was higher among individuals who would develop PD (n=1,680) compared to controls
Kazmi et al., 2022 [36]	Cross-sectional study	36 individuals with late-onset depression and 30 controls	DSM IV and Hospital Anxiety and Depression Scale (HADS) criteria	24% of patients with late-onset depression, compared to 4% of controls, showed changes in the dopamine transport test in the basal ganglia (^{123}I-ioflupane SPECT)
Gaenslen et al., 2014 [32]	Case-control study	698 individuals	ICD 10 or DSM IV criteria	Individuals with depression showed greater visuospatial impairment, anxiety, painful muscle tension; when compared to individuals with sleep disorders and hyposmia. Individuals with two or three of the selected prodromal symptoms were at greater risk of developing motor symptoms when compared to individuals with only one of the selected symptoms.

https://doi.org/10.25118/2763-9037.2025.v15.1507

	Study Design	Sample	Intruments for diagnosing depressive symptoms/ depression	Main findings
Gustafsson et al., 2015 [37]	Prospective and cohort study (follow-up with between 1987 and 2012)	140,688 individuals with depression and 421,943 controls	ICD 9 and ICD 10 criteria	Hospitalization was an independent risk factor for individuals with depression to develop PD (OR=1.4); depression in members of the same family was not a risk factor
Bohlken et al., 2021 [34]	Case-control study	17,702 individuals with PD and 17,702 controls	Report in medical record of diagnosis of depression	Depression, dizziness, insomnia and constipation were, in descending order, the most prevalent prodromal symptoms among individuals who developed PD. However, these symptoms were also highly prevalent among controls. Memory impairment, increased tremor and difficulty walking were, among the symptoms researched, those with the greatest impact (relative risk) for the development of PD
Liu et al., 2018 [39]	Cross-sectional study	98 individuals with PD, 210 first-degree relatives, 250 controls	Beck Depression Inventory	Siblings of patients with PD are more likely to develop depression (OR=2.438), REM sleep disorder

	Study Design	Sample	Intruments for diagnosing depressive symptoms/ depression	Main findings
				(OR=4.120) and anxiety (OR=3.434) compared to the general population
Walter et al., 2014 [42]	Prospective cohort (follow-up for 10 years)	46 individuals with major depressive disorder	Beck Depression Inventory e Hamilton Depression Rating Scale	Idiopathic hyposmia, asymmetric motor slowing and hyperechogenicity of the substantia nigra combined with at least two of the four: family history, non-smoking, constipation and non-consumption of coffee; these were predictive factors for patients with MDD to develop PD

Source: The authors
Notes: **PD** (Parkinson's disease), **DSM** (APA Diagnostic and Statistical Manual of Mental Disorders, IV Edition), **ICD** (International Classification of Diseases, 9th and 10th Editions), **MDD** (Major depressive disorder)