Antiparkinson drugs use and adherence in older adults and associated factors: an integrative review

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Abstract

Objectives: To identify factors associated with antiparkinson drugs use and adherence in older adults with Parkinson's disease (PD) through an integrative literature review. *Method:* An integrative literature review involving a search for relevant publications in Portuguese, English, and Spanish on the electronic databases LILACS, MEDLINE - via PubMed, Web of Science and Scopus, without restriction regarding date or study design, was carried out during the period August-September 2021. The selection of studies was performed independently by two reviewers and the final validation conducted by a third reviewer. *Results:* After applying the eligibility criteria, 5 of the 460 studies found were included in the review. Results showed moderate adherence rates (range 35.3-66.8%) and the main factors associated with lower adherence to antiparkinson therapy were older age, cognitive deficit, greater motor impairment, multimorbidities, change in therapy regimens, depression, polypharmacy, lower education, non-white ethnicity and male gender. Factors associated with greater adherence were younger age, white ethnicity, no change in therapy regimen, higher level of knowledge about PD, good clinical control, higher educational level, married status, higher income and greater level of awareness. *Conclusions:* Non-adherence to antiparkinsonian therapy was frequent and multifactorial., Understanding this behavior is important to help inform the scientific community and devise public policies and strategic planning in health services for improving the quality of life of the older population.

Keywords: Medication adherence. Antiparkinson Agents. Cooperation and adherence to treatment. Older adults.

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INTRODUCTION

Parkinson Disease (PD) is a progressive neurodegenerative disorder of the central nervous system (CNS) characterized by loss of dopamine neurons in the substantia nigra which causes motor deficits[1,2]. The etiology of PD is believed to involve both genetic susceptibilities and environmental factors, alone or in combination with the effects of aging[3].

With regard to prevalence, PD is the second-most-common neurodegenerative disease globally. According to the World Health Organization (WHO), the condition affects 1% of the population aged over 65 years, representing around 5 million people. The estimated prevalence of PD is 100-200 cases per 100,000 population, predominantly affecting older individuals [4].

The disease is marked by motor abnormalities, such as resting tremor, muscular rigidity, bradykinesia, postural instability, together with non-motor symptoms, including autonomic dysfunctions (hypotension, constipation), paresthesia, anxiety, depression, sleep disturbances, pain, excess fatigue, olfactory dysfunction, rapid eye movements, and both cognitive and behavioral deficits[5-8].

The diagnosis of PD is based on clinical criteria of the patient and characterized by a combination of at least 2 out of the 4 cardinal signs, i.e. resting tremor, bradykinesia, cogwheel rigidity and postural abnormalities, with the first two being the most typical symptoms[6]. The International Parkinson's and Movement Disorder Society (MDS) has developed its own core clinical diagnostic criteria which include: presence of parkinsonism (bradykinesia plus resting tremor or rigidity); absence of absolute exclusion criteria; and supportive criteria and red flags[9].

Regarding the complexity of this phenomenon, adherence to pharmacological treatment in PD may be influenced by epidemiological and clinical factors, including educational level, marital status, disease duration, polypharmacy, complex medication regimens, fear of side-effects, mood disorders, depression, anxiety, together with age-related aspects, such as physical difficulties and cognitive deficit[10,11].

Satisfactory adherence to treatment by PD patients allows physicians to make the necessary adjustments according to each individual patient´s clinical response. By contrast, non-adherence to treatment, in the form of failing to take medications and mistiming of new doses or extra doses, can lead to increased parkinsonism, with consequent worsening of motor fluctuations[12,13].

Non-adherence to therapy has negative repercussions for the individual, influencing socioeconomic factors and poses a public health problem, increasing the need for hospital admission, reducing quality of life and impacting the morbimortality of this population[14,15].

However, there is a gap in the literature on the subject, where further studies investigating the repercussions of low adherence to therapy by PD patients are needed to inform the scientific community. Therefore, the objective of the present study was to identify the factors associated with antiparkinsonian drugs use and adherence in older adults through an integrative review of the literature.

METHOD

An integrative literature review is an approach entailing a search, synthesis and critical analysis of scientific content on a given topic or question of research interest, contributing to evidence-based practices[16].

The study was conducted using a 6-stage method as outlined below: 1- identification of the topic and selection of the research question; 2- establishment of inclusion and exclusion of studies; 3- definition of information to be extracted from studies selected and categorization of this content; 4- methodological assessment of studies included; 5- interpretation of results; 6- presentation of the review and synthesis of knowledge.

In the first stage, in order to structure the search, the following guiding research question was defined: *What factors are associated with antiparkinsonian drugs use and adherence in older adults with Parkinson Disease?*

Subsequently, the articles were selected by performing a search of the *Biblioteca Virtual em Saúde* – (Virtual Health Library - BVS) site between August and September 2021. Via this site, a concomitant search of relevant studies was performed on the following scientific databases: MEDLINE (Literatura Internacional em Ciências da Saúde – International Literature on Health Science) – via Pubmed (*U.S. National Library of Medicine*), LILACS (Literatura Latino-Americana e do Caribe em Ciências da Saúde). The Web of Science and Scopus databases were also searched. These latter 2 restricted access databases were accessed free of charge via the *Comunidade Acadêmica Federada* (CAFe - Federated Academic Community) of the *Rede Nacional de Ensino e Pesquisa* (RNP - National Education and Research Network) using the Capes Journals site. Lastly, the review was complemented by handsearching the reference citations drawn from the primary studies identified.

The inclusion criteria were: primary original articles (cross-sectional, cohort or case-control studies) and unpublished literature such as congress abstracts and technical documents, addressing the factors associated with antiparkinsonian drugs use and adherence in older (>60 years) patients with Parkinson Disease, available in Portuguese, English or Spanish. There was no restriction on study design or publication date. The references/citations of articles selected were also examined for inclusion (backward reference search strategy). The search for studies, selection, extraction and analysis of data was carried out by two independent researchers. In order to reduce possible errors involving the search, assessment, analysis and interpretation of studies in the event of doubts arising from the review process, a third reviewer was consulted to resolve issues and validate the final listing.

Exclusion criteria were: articles not addressing the topic; presence of other parkinsonian syndromes; other neurological diseases; failure to report the age of study participants; duplicate studies on databases; publications unavailable in full or whose results were yet to be published; integrative or systematic reviews; letters to the Editor; and reflexive studies or experience reports.

The search for articles employed descriptors indexed on Descritores em Ciência da Saúde (DeCS) – "Adesão à medicação", "Cooperação e adesão ao tratamento" and "Antiparkinsonianos"and "Doença de Parkinson", and on Medical Subject Headings (MeSH) – "Medication Adherence" or "Treatment Adherence and Compliance" and "Antiparkinson Agents" and "Parkinson" or "Parkinson disease". These descriptors were combined using the Boolean operators AND and OR.

Chart 1. Databases consulted of articles comprising study sample. Recife, Pernambuco state, 2022.

Database	Search strategy employed to perform the search – combination of key words
LILACS MEDLINE	("Adesão à medicação" or "cooperação e adesão ao tratamento") and ("Antiparkinsonianos") and ("Doença de Parkinson")
PUBMED	("Medication Adherence" OR "Treatment Adherence and Compliance ") AND ("Antiparkinson Agents") AND ("parkinson" OR "parkinson disease")
WEB OF SCIENCE	(TS=((Medication Adherence) OR (Treatment Adherence and Compliance))) AND (TS=(Antiparkinson Agents)) AND (TS= parkinson) OR (parkinson disease)))
SCOPUS	(KEY ("Medication Adherence" OR "Treatment Adherence and Compliance") AND KEY ("Antiparkinson Agents") AND KEY ("Parkinson" OR "parkinson disease"))

Source: produced by author.

The present integrative review was registered on the OSF Registries system under protocol 10.17605/OSF.IO/SK3RE. For data extraction, a second full reading of the 5 articles selected was done. The data were compiled into tables under the headings study title and publication year, authors, name of journal, objective, study/method type, results and level of evidence.

The methodological analysis of the studies reviewed was performed by applying an instrument which allowed appraisal of different study design adapted from the Critical Appraisal Skill Programme (CASP). The original CASP comprised 8 specific assessment tools for different study designs such as reviews, cohort studies, cross-sectional studies, clinical trials etc. In the present review, an instrument adapted from CASP containing 10 scored items was employed: 1) clear and justified aims; 2) methodology appropriate; 3) presentation and discussion of theoretical and methodological procedures; 4) adequate selection of sample; 5) detailed data collection; 6) relationship between researchers and participants; 7) ethical issues maintained; 8) robust rigorous data analysis; 9) presentation and discussion of findings; and 10) contributions, limitations and identification of new areas for research. A value of 0 (zero) or 1 (one) was assigned to each item, where the final result was the sum of scores (maximum 10 points). The articles selected were rated according to score range: level A – 6 to 10 points (good methodological quality and low bias) or Level B – ≥ 5 points (satisfactory methodological quality, but high risk of bias)[17].

The studies were rated according to the level of evidence based on the classification of the Oxford Centre for Evidence-Based Medicine (2009)[18], comprising 5 hierarchical levels of evidence per study type, as outlined below: 1a. Systematic review (with homogeneity) of randomized clinically controlled trials (RCTs). 1b. RCTs with narrow confidence interval (CI), 1c. Therapeutic results of "all or none" type. 2a. Systematic review (with homogeneity) of cohort studies. 2b. Individual cohort study (including low quality RCT, e.g., <80% follow-up). 2c. Outcomes research (observation of therapeutic results or clinical evolution); Ecological studies. 3a. Systematic review (with homogeneity) of case-control studies. 3b. Individual case-control study. 4. Case-series (and poor-quality cohort and case-control studies) 5. Expert opinion without explicit critical appraisal, based on physiology, bench research or "first principles". For summarizing of associated factors, the percentage of studies whose intergroup analysis, association or correlation was significant for the expected outcome was considered.

RESULTS

A total of 460 studies were identified in the databases searched which, after removal of duplicates (n=11), gave 449 studies for screening. After analysis of titles and abstracts of each study, a further 418 were excluded for being off-topic or not matching the objective and inclusion criteria. Subsequently, another 8 studies were excluded because the texts were not available in full. Thus, 23 studies were selected for full reading, 18 of which were later dropped for not meeting the eligibility criteria, giving a final sample of 5 studies for inclusion in the review (Figure 1).

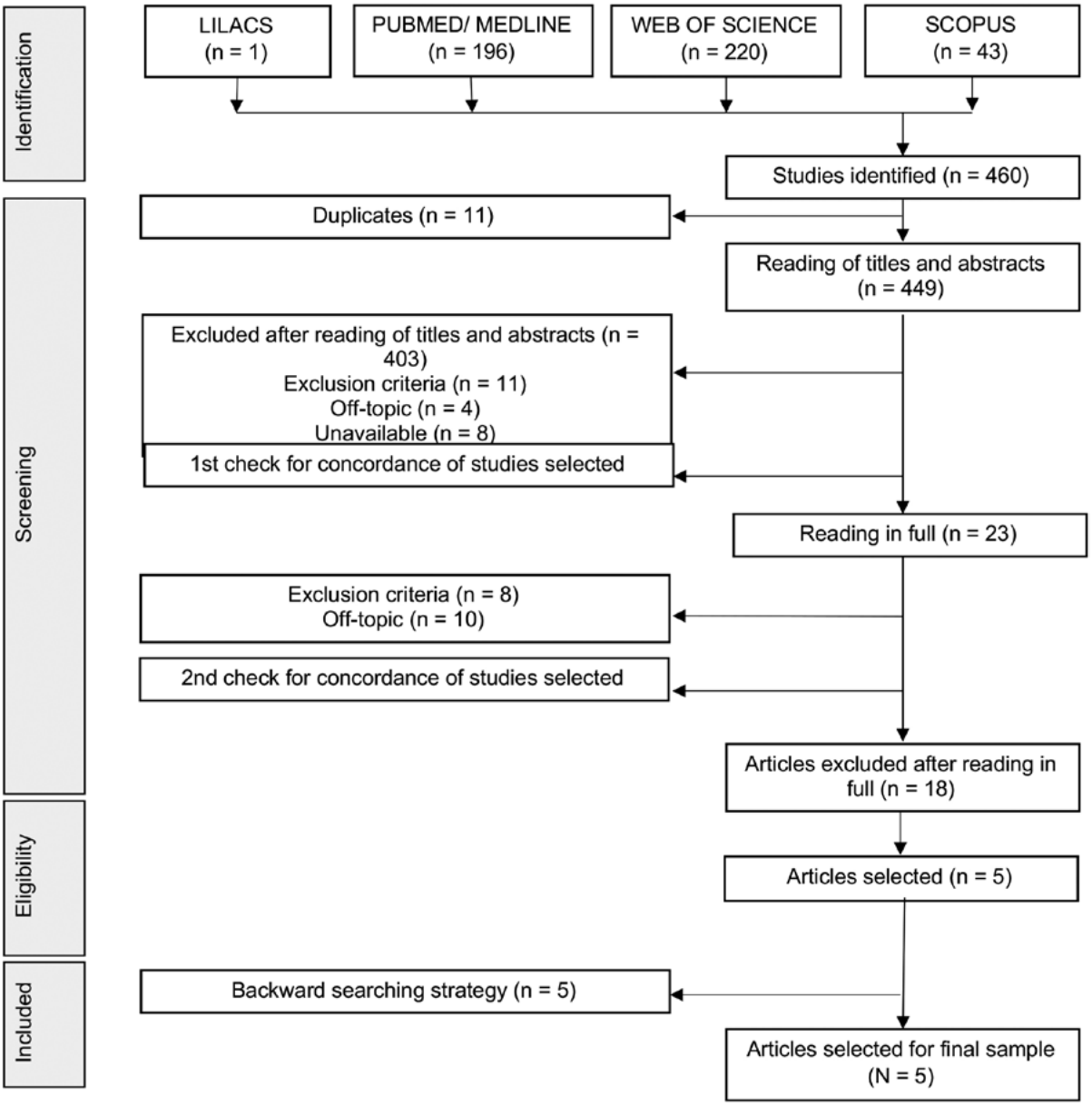

Figure 1. Flow diagram of search process, selection stages and reasons for exclusion of studies selected for integrative review. Recife, Pernambuco, 2022.

In the present integrative review, 5 studies that met the pre-defined selection criteria were selected for inclusion in the final sample. All articles were published in English in international journals between 2011 and 2020. Of the studies reviewed, 4 (80%) were conducted in European countries (Spain, Germany and Slovakia) and 1 (20%) in the USA. The objectives of the articles addressed the research question and the methodologies entailed a quantitative approach.

All studies were rated as Level A in methodological quality by the adapted CASP instrument. The articles addressed the following main topics: a)

level of adherence to antiparkinson agents; and b) factors associated with good adherence and poor adherence in patients with PD. The main elements reported were: age, cognition, non-motor symptoms, polypharmacy, and sociodemographic data (sex, income, marital status, education, color and ethnicity).

An overview of the characteristics of the studies included in the review are given in Table 1. The following parameters are included: study author, year of publication, place, journal, objective, study design, sample, and level of adherence.

Details on study author, year of publication, method of assessing adherence of PD patients and factors associated with adherence or non-adherence to antiparkinson drugs therapy are given in Table 2. The factors associated with non-adherence to treatment in more than one study were male gender, presence of non-motor symptoms, polypharmacy and cognitive impairment.

Table 1. Main characteristics of studies included in integrative review. Recife, Pernambuco state, 2022.

Author, year, place and journal	Objective	Study design, sample	Instruments used to assess medication adherence	Main results on adherence
1) Valldeoriola et al.[15], 2011, Barcelona (Spain), *European Journal of Neurology*	To determine demographic, social and clinical aspects modifying therapy adherence.	Cross-sectional study, N= 418 patients	Neurologist Opinion Morisky-Green Test (MGT).	According to physician´s opinion 93.6%, and on the MGT 60.4%, of patients adhered to parkinsonian therapy.
2) W.J. Yu et al.[19], 2013, Baltimore (Maryland), *Clinical Therapeutics*	To provide updated, comprehensive population-based data on antiparkinson drugs (APD) use and adherence and to examine characteristics associated with adherence behaviors.	Cross-sectional study N= 7,583; 65 years (93.6%); female (59.9%); White (89.3%)	Medication possession ratio (MPR).	Good adherence rate: 72.7% of sample.
3) Straka et al.[20], 2019, Slovakia, Journal Frontiers in Neurology	To detect the extent of adherence to pharmacotherapy in PD patients who take a minimum of three daily doses of drugs and to identify factors associated with lower levels of adherence.	Cross-sectional study, 124 individuals Male (58%)	Morisky Medication Adherence Scale (MMAS). .	The MMAS identified a high level of adherence in 33.9% of sample; medium level in 29.8% and 36.3% reported low level of adherence
4) Mendorf et al.[21], 2020, Germany, Frontiers in Medicine	To describe common self-reported reasons for nonadherence. replicate the associations between different degrees of nonadherence and PD-specific clinical parameters explore the impact of PD-specific clinical parameters on distinct clusters/reasons of nonadherence.	Cross-sectional study, N=226 patients, Male (58.7%)	Self-reported German Stendal Adherence to Medication Score (SAMS).	Fully adherent: 14.2% of patients; Moderately non-adherent: 66.8%, and non-adherent: 19%.
5) Zipprich et al.[22], 2021, Germany, Brain Sci	To provide additional data to determine whether self-reported non-adherence is associated with HRQOL in PD	Cross-sectional, N=164 patients, Male (61%)	Self-reported German Stendal Adherence to Medication Score (SAMS).	10.4% of patients were fully adherent, 66.4% moderately nonadherent and 23.2% nonadherent.

*Source: produced by author.

Table 2. Categorization of studies, author, publication year, assessment instruments and factors associated with adherence and non-adherence to antiparkinson therapy in older adults. Recife, Pernambuco, 2022.

Author, year	Assessment Instruments	Factors associated with adherence	Factors associated with non-adherence	Measures of statistical association/Level of evidence
1) Valldeoriola et al,[15] 2011	Physician´s subjective perception and Morisky–Green Test (MGT).	High level of knowledge about the disease, good clinical control, spouse or life partner, and higher income.	Psychiatric symptoms	95% CI/2b
2) W.J. Yu et al.[19], 2013	1. Medicare records; 2. Chronic Condition Data Warehouse 2006–2007	Younger age, white ethnicity, receipt of financial support, early enrollment, intact cognitive function, fewer comorbidities, no change in drugs regimen, and longer long-term care stay.	Older age, non-white race, cognitive impairment, high comorbidity, and patients switching therapy and/or augmentation.	Prevalence ratio and 95% CI/ 2b
3) Straka et al.[20], 2019	8-Item Morisky Medication Adherence Scale (MMAS-8)	Factors associated with adherence not assessed.	Male gender, longer PD duration, worse quality of life, frequency and severity of non-motor symptoms and more severe motor and non-motor symptom fluctuations.	Spearman's rank correlation coefficient (r_s) and correlation ratio eta (η)/ 2b)
4) Mendorf et al.[21], 2020	German Stendal Adherence with Medication Score (SAMS)	Factors associated with adherence not assessed.	Lower educational level, higher rate of motor impairment in activities of daily living, higher number of medications per day and higher rate of motor complications of PD	Regression coefficient for cluster/ 2b
5) Zipprich et al.[22], 2021	Self-reported German Stendal Adherence with Medication Score (SAMS).	Factors associated with adherence not assessed.	Male gender, lower Montreal Cognitive Assessment (MoCA) score, higher non-motor symptoms questionnaire (NMS-Quest) score, greater number of medications per day (indicator of comorbidity), and higher Beck Depression Inventory (BDI) score	Correlation/ 2b

Source: produced by the author.

DISCUSSION

The present integrative review identified a higher rate of good adherence to therapy in 2 studies[1,5,19], whereas 3 studies[20-22] found predominantly moderate adherence, followed by low adherence. Rates reported ranged from 10-93% for higher adherence, 36.3%-66.4% for moderate adherence, and 6.3-36% for lower adherence. In the PD patients assessed, sociodemographic, clinical and mental aspects were associated with treatment adherence.

Publications on this topic in Brazil proved scarce, while most studies were published by European

researchers. This lack of local publications highlights the need for more studies in the Brazilian population.

Adherence to therapy is influenced by multiple factors both in the older population in general and patients with Parkinson disease[23,24]. The pharmacotherapy in PD patients is often less than ideal and non-adherence is influenced by a number of aspects, such as disease stage, motor complications, complexity of timing and the presence of clinical depression[25]. A study of 27 individuals in a geriatric and gerontological referral service found low medication adherence in 79% of older patients[23]. Another study (n=80 older participants) found that 16% of patients were fully adherent and 25.9% non-adherent[24].

Lower adherence was associated with male gender[20,22], corroborating the findings of Weyn et al.[26] showing that men represented 34% of the group of potential non-adherents to medication and that males, besides making lower use of health services, do not exhibit care in taking medications correctly, behavior regarded as a risk factor.

Concerning age, one of the studies reviewed[19] showed that more advanced age was associated with lower adherence. Tavares et al.[27] demonstrated in their findings that younger old had lower treatment adherence and there was no significant difference between males and females. Similar results were reported by another study in which men aged 60-79 years and black individuals had lower adherence to treatment[28]. This correlation can be explained by the fact that younger old individuals have less family support and lower presence of caregivers involved in administering medication therapy compared to older old individuals with greater cognitive deficit[29].

However, cognitive deficit and older age are considered risk factors for non-adherence to treatment because of a greater number of age-related comorbidities, such as impaired memory, attention and concentration inherent to cognitive decline[30].

Regarding medication treatment non-adherence associated with skin color, a higher prevalence of treatment abandonment was reported in non-whites. This finding might be related to the socioeconomic characteristics of low family income, low educational level and less access to health services in this group[31].

Muniz et al.[32] noted that non-adherence to drug therapy is associated with cognitive deficit, reduced independence, low education, presence of comorbidities and polypharmacy, increasing the risk of adverse events and drug-drug interactions.

With regard to educational level, lower education was found to be associated with poorer adherence[21]. This result is consistent with the findings of Mendorf et al.[33,] confirming that lower educational level was mainly associated with modification of medication and poorer knowledge about prescribed medication, but not with forgetting to take medication.

The sociodemographic variable of greater income correlated positively with adherence to antiparkinson therapy[19], whereas low-income individuals were less likely to adhere to drug therapy[34]. The economic aspect is an important predictor of treatment adherence and of reduction in signs and symptoms. PD leads to physical and cognitive limitations that can force these individuals to give up their jobs, resulting in a loss of income for both the individual and family members. Moreover, expenses with medical visits, hospital admissions, medications and food also tend to increase, directly impacting treatment and disease evolution[35].

Akin to the present study, previous investigations found that a higher number of drugs was associated with lower adherence[19,21,22]. Similarly, Grosset et al.[36] found that total adherence and timing adherence were significantly better for once daily drugs compared with drugs prescribed more frequently. Assessment of prescription of dopamine agonists once daily versus thrice daily revealed that patients taking more medications had poorer adherence for both antiparkinson drugs alone (P=0.007) and all medications combined (P=0.01).

The same factors found to be positively associated with adherence[15] were also documented by Almeida et al.[37] and Nunes et al.[38], noting that patients who had a partner exhibited greater treatment adherence compared to individuals who lived alone or were widowed. According to the literature, the presence of a partner and being part of an active support network is fundamental for resolving the problems which arise during the process of living with PD. The partner is often also the caregiver, serving to

assist in the administration of medications and in accompanying the patient during health service visits.

With regard to the variable depression, this is also considered a factor impacting therapy adherence by patients, particularly for being directly involved in the progression of physical symptoms of PD, cognitive decline, reduced self-care ability and worse quality of life[38]. However, no association between patient adherence to treatment and presence of depressive symptoms was found ($p>0.05$) when correlating results of the Morisky-Green Test and the IAAFTR instrument with scores on the GDS-15 used in the cited study[39].

As highlighted in the present review[15,20-22], the Morisky-Green Test and German Stendal Adherence with Medication Score (SAMS) were the most used measures for assessing adherence. According to the literature, the most commonly employed methods include interview, pill count, drug dispensing control, treatment monitoring, semi-structured questionnaires and self-reporting. This heterogeneity hampered comparison of results found[40].

There are a range of consequences of non-adherence to medication therapy, including poor disease control, greater risk of hospital admission and increase in mortality, leading to clinical, social and economic repercussions[40].

The synthesis of the studies reviewed showed that adherence to antiparkinson therapy is multifactorial. Thus, identifying and understanding the factors outlined above is important given they are amenable to intervention through the devising of public policies and targeted strategic planning. This approach involves the implementation of health service interventions with the formulation of public policies optimizing therapy management for this patient group to reduce complications, promote adherence and improve quality of life in older individuals, thereby ensuring active healthy aging.

This integrative review has some limitations including the dearth of longitudinal studies addressing PD in older Brazilians and investigating the factors that influence adherence. Also, the lack of standardization of instruments assessing the factors associated with adherence may influence the interpretation of results. In addition, the inclusion of self-reports as a tool for assessing adherence introduces the risk of overestimation of results owing to memory problems in this older population[42]. It should be noted, however, that the measures used in the studies investigating adherence were internationally validated instruments. Future studies should include interventions on adherence in older adults with Parkinson Disease.

CONCLUSION

The analysis of the results of this integrative review identified the factors which contribute to higher or lower adherence to antiparkinson therapy in older patients. The reasons for poor adherence were determined, namely: low educational level, concurrent use of several medications, comorbidities, older age, cognitive deficit, presence of depression and non-motor symptoms. The main factors associated with good medication adherence were younger age, higher level of knowledge about the disease, good clinical control of PD, no changes in treatment regimen, white ethnicity, higher income, and presence of family or a partner. Patients with higher educational level were more likely to practice behaviors favorable for positive adherence. Although the studies reviewed differ for level adherence of the population studied, a considerable proportion of studies (3 out of 5) reported low-to-moderate adherence to drug treatment, with rates of 36.3-66.4% for moderate adherence and 6.3-36% for low adherence.

Lastly, the evidence gathered in this study can help inform the scientific community on which factors favor and detract from antiparkinson drug treatment adherence, contributing to debates and furthering understanding of this process in older patients with Parkinson Disease.

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