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RESEARCH ARTICLE

Influence of Drugs on Mild Cognitive Impairment in Parkinson's Disease: Evidence from the PACOS Study

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Abstract: ***Background*:** polytherapy and the anticholinergic activity of several drugs negatively influence cognition in the elderly. However, little is known on the effect on Mild Cognitive Impairment (MCI) in Parkinson's Disease (PD).

***Methods*:** patients with PD belonging to the baseline PACOS cohort with full pharmacological data have been included in this study. MCI diagnosis was made according to the MDS level II criteria. Polytherapy was defined as patients assuming ≥6 drugs. The anticholinergic burden has been calculated using the Anticholinergic Drug Scale (ADS). Molecules have been classified according to the ATC classification. Association with MCI has been assessed with a multivariate logistic regression analysis with MCI as the dependent variable.

***Results*:** pharmacological data were available for 238 patients (mean age 64.7±9.7). One hundred (42.0%) were diagnosed with MCI. No association was found in the full multivariate model (correcting for age, sex, disease duration, education, UPDRS-ME, LEDD-DAs) with either polytherapy or the ADS. Concerning drug classes, anti-hypertensive medications were positively associated with PD-MCI (OR 2.02;95%CI 1.04-3.89; p=0.035) while gastroprotective agents were negatively associated (OR 0.51; 95%CI 0.27-0.99; p=0.047).

***Conclusion*:** the magnitude of polytherapy and anticholinergic drugs burden does not appear to modulate MCI risk in PD, probably due to cautious prescription patterns. The effect of anti-hypertensive and gastroprotective agents on PD-MCI risk, while needing further confirmations, could be relevant for clinical practice.

Keywords: Parkinson's disease, mild cognitive impairment, drugs, polytherapy, polypharmacy, anticholinergic burden.

1. INTRODUCTION

Parkinson's Disease (PD) is the second most frequent neurodegenerative disease after Alzheimer's disease. It primarily affects subjects in the advanced age, with a peak incidence after 70 years [1]. Along with the classic motor symptoms, PD patients also experience a wide range of non-motor symptoms, which can significantly impact their quality of life. Mild Cognitive Impairment (MCI) represents one of the most severe, burdening PD patients with increased disability and increased risk of developing dementia [2]. Evidence supports a protective role of the level of education while increasing age and longer disease duration are one of the main risk factors [3, 4]. However, there is still uncertainty regarding the possible influence of modifiable risk factors, such as lifestyle habits, vascular risk factors, and the influence of drugs. In fact, PD patients experience a large range of comorbidities in non-motor spectrum disorders such as bowel and bladder dysfunction, orthostatic hypotension, and psychiatric conditions such as depression and anxiety [5]. The co-occurrence of the aforementioned non-motor conditions and the commonly encountered comorbidities of the advanced age, such as hypertension, account for a large amount of drugs intake by PD patients. Polytherapy is a known risk factor for falls and reduced cognitive performance in the elderly [6]. Moreover, several commonly used drugs express an anticholinergic activity varying from mild to moderate-severe [7], which can have harmful effects on cognition [8].

In PD patients, data about the effect of polytherapy on cognition is still scarce, with one study advocating for a negative effect of polytherapy [9]. On the other hand, while evidence on the anticholinergic burden generally supports an

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increased risk of cognitive impairment in PD [10, 11], a study employing the most recent MCI definition for PD [12] found no effect of an anticholinergic burden on cognition [13].

In order to study the effect of medications on cognition in PD, we sought to investigate the association between cognitive impairment and both polytherapy and anticholinergic burden in a cross-sectional sample from the PACOS cohort. As a secondary analysis, we examined the association between selected drug classes and PD-MCI.

2. MATERIALS AND METHODS

2.1. Study Population

From the PACOS baseline cohort, we have selected patients for whom there was an available full list of total drug intake. All the patients underwent an extensive neuropsychological examination and were diagnosed as PD-MCI according to modified MDS level II criteria, according to the protocol extensively described elsewhere [4]. Cognitive domains were considered impaired if at least one of the cognitive tests in the relative domain was altered. [4]. Patients were classified in amnestic MCI(aMCI) or non-amnestic MCI (naMCI) on the basis of at least one impaired test in the memory function domain. Patients' motor condition was recorded using the Unified Parkinson's Disease Rating Scale- Motor Examination (UPDRS-ME) and the Hoehn and Yahr scale. All the patients provided informed consent before being included in the study. The research has been approved by the local ethical committee (approval number: 14:03/2018) and was conducted in accordance with the Declaration of Helsinki.

2.2. Drugs and Cholinergic Burden Assessment

Total drug intake was computed by gathering data from the clinical records. Active drugs were considered those taken without interruption in the three months preceding the assessment or, for antibiotics, if patients were taking therapy at the time of the neuropsychological examination. According to the ATC classification system, molecules have been classified into major categories, considering only drug classes used by at least 10 participants. For each molecule, the total anticholinergic load was calculated using the Anticholinergic Drug Scale [7], which assigns to each molecule a score ranging from 0 (no anticholinergic activity), 1 (mild anticholinergic activity), 2 (moderate anticholinergic activity), and 3 (high anticholinergic activity). The dopaminergic burden has been evaluated using the Levodopa Equivalent Daily Dose (LEDD) [14]. Finally, LEDD has been calculated only for the dopamine agonist molecules (LED Dopamine Agonists; LEDD-DAs).

2.3. Statistical Analysis

Data were analyzed using STATA 16 software packages. The association between PD-MCI and polytherapy was analyzed both by considering polytherapy a continuous variable and as a dichotomized variable according to the definition of polytherapy (number of drugs ≥6 [9]). The association with the anticholinergic burden was studied considering the total anticholinergic score and after dichotomizing the patients in those without anticholinergic burden (ADS=0) and with any anticholinergic drug (ADS≥1). Association with drug classes has been analyzed by including in the different classes patients using at least one of the molecules belonging to the specific drug class. In order to test the association between either predictor variables and the dependent variable (MCI), multivariate logistic regression analysis was conducted by adjusting for known PD-MCI modifiers such as age, sex, disease duration, UPDRS-ME score, and education. Additional demographic variables associated with PD-MCI at the univariate analysis with a $p<0.1$ have been included in the multivariate models. A separate analysis has been conducted on the association between LEDD and LEDD-DAs with PD-MCI. Moreover, to assess the confounding role of antiparkinsonian agents, the association with polytherapy has been analyzed after the removal of antiparkinsonian drugs (levodopa, dopamine agonists, MAO inhibitors, COMT inhibitors, amantadine, anticholinergic drugs). Main analyses have also been stratified by sex.

3. RESULTS

From the original PACOS cohort of 659 patients, pharmacological data were available for 238 patients (36.1%) with a mean (±Standard Deviation, SD) age of 64.7±9.7 and a mean disease duration of 5.6±5.3. MCI was diagnosed in 100 subjects (42.0%). Concerning impaired domains, 104 (43.7%) patients had an impaired attention, 72 (30.3%) impaired executive functions, 39 (16.4%) memory function and 63 (26.5%) impaired visuospatial function. According to subtype classification, 36(36%) MCI patients were diagnosed as aMCI and 64 (64%) as naMCI. Demographic and clinical characteristics are displayed in Table **1.**

At the univariate analysis, a significant association with MCI was found for age, disease duration, education, UPDRS-ME, LEDD-DAs, and polytherapy both as a continuous variable and as a dichotomized variable (Table **1**).

At the multivariate analysis, adjusting for age, sex, disease duration, education, UPDRS-ME, and LEDD-DAs, no association was found for the presence of polytherapy and PD-MCI as well as between polytherapy and MCI subtypes (aMCI and naMCI) or with the different cognitive domains (Table **2** and Supplementary Table **1**). The analysis of polytherapy after removing antiparkinsonian agents yielded overlapping results in the multivariate analysis.

Concerning the ADS score, we found a borderline positive association with MCI at the univariate analysis, both as a continuous variable and as a dichotomized variable (Table **1**). However, in the fully adjusted model, the association was not confirmed. Of note, only 19 patients out of 238 (7.9%) were taking an anticholinergic drug for the treatment of tremor in PD. Furthermore, we did not find any significant association between aMCI subtypes and ADS score as well as between the different cognitive domains and the ADS score (Supplementary Table **1**).

In multivariate logistic regression analysis (adjusting for age, sex, disease duration, education, and UPDRS-ME), LEDD was not significantly associated with PD-MCI, while we found a borderline positive association between PD-MCI and LEDD-DAs (OR 1.002;95%CI 0.99-1.005;p=0.06). Considering the MCI subtypes, although there was no significant association between LEDD-DAs and aMCI (OR 1.001; 95%CI 0.99-1.004; p-value 0.529), in the analysis of the

Table 1. Demographic characteristics and univariate analysis.

-	PD-NC (n=138)	PD-MCI (n=100)	Total (n=238)	OR	95%CI	*P* Value
Age (years)	63.5±10.4	66.4±8.4	64.7±9.7	1.03	1.00-1.06	**0.027**
Sex (Men)	67 (48.5)	59 (59.0)	126 (52.9)	1.52	0.90-2.56	0.11
Disease duration, years	4.9±4.7	6.5±5.9	5.6±5.3	1.06	1.01-1.11	**0.019**
Years of education	10.4±4.4	7.9±4.6	9.3±4.7	0.88	0.83-0.94	**<0.001**
UPDRS-ME	31.1±11.7	34.5±12.3	32.5±12.1	1.02	1.00-1.04	**0.036**
Hoehn and Yahr	2.2±0.6	2.4±0.8	2.3±0.7	1.55	1.03-2.31	**0.032**
Hypertension	46 (33.3)	35 (35)	81 (34.0)	1.07	0.62-1.85	0.789
LEDD (mg)	333.5±413.4	433.0±475.1	375.3±442.1	1	0.99-1	0.088
LEDD-DAs (mg)	39.3±84.8	73.0±125.9	53.5±105.2	1	1-1.01	0.017
ADS score	1.1±1.6	1.6±2.2	1.3±1.9	1.12	0.98-1.28	0.086
ADS≥1	62 (44.9)	57 (57.0)	119 (50.0)	1.62	0.96-2.73	0.067
Number of drugs	4.4±3.1	5.7±3.1	4.9±3.1	1.13	1.04-1.24	**0.003**
Number of drugs ≥6	48 (34.8)	50 (50)	98 (41.2)	1.87	1.1-3.17	**0.019**
Number of drugs without antiparkinsonian agents	3.2±2.6	4.2±2.8	3.6±2.8	1.13	1.03-1.25	**0.009**
Number of drugs ≥6 without antiparkinsonian agents	26 (18.8)	27 (27)	53 (22.3)	1.59	0.82-2.94	0.137

Legend: continuous variables are displayed as means ± standard deviations; Qualitative variables are displayed as a number (percentage).; PD-NC: PD Normal cognition; PD-MCI: PD with Mild Cognitive Impairment; CI: confidence intervals; UPDRS-ME: Unified Parkinson's Disease Rating Scale-Motor examination; ADS: Anticholinergic Drug Scale; LEDD: Levodopa Equivalent Daily Dose; LEDD-DAs: Levodopa Equivalent Daily Dose-Dopamine Agonists; OR: Odds Ratio. In bold significant p values at the univariate analysis.

Table 2. Association with anticholinergic burden and polytherapy after adjusting for significant variables (age, sex, disease duration, education, UPDRS-ME, LEDD-DAs).

-	adjOR	95%CI	*P* Value
ADS score	1.12	0.94-1.33	0.184
ADS≥1	1.29	0.69-2.42	0.417
Number of drugs	1.03	0.92-1.15	0.530
Number of drugs ≥6	0.92	0.48-1.79	0.826

Legend: ADS, Anticholinergic Drug Scale; adjOR, adjusted Odds Ratio; CI, Confidence intervals.

different cognitive domains, we found a significant association only with the memory domain impairment in the fully adjusted model (OR 1.003; 95%CI 1.001-1.01;p=0.046) (Supplementary Table **1**). Details on dopamine agonist use in the sampled population are reported in Supplementary Table **2**.

When conducting the secondary analysis on the major drug classes, at the multivariate analysis, the use of antihypertensive medications was positively associated with PD-MCI (OR 2.02;95%CI 1.04-3.89; p=0.035), along with urologic drugs (OR 3.7;95%CI 1.1-12.6; p=0.036). The use of gastroprotective agents was negatively associated with PD-MCI (OR 0.51; 95%CI 0.27-0.99; p=0.047), as shown in Table **3**.

In a supplementary analysis for anti-hypertensive medications classified according to the mechanisms of action, a significant positive association with MCI has been found for calcium channel blockers (OR 3.05; 95%CI 1.09-8.54; p=0.033), and a borderline positive significant association with the use of diuretics (OR 2.10; 95%CI 0.94-4.53; p=0.058) (Supplementary Table **3**).

When analyses have been stratified according to sex, overlapping results for polytherapy, ADS score, and the drug classes have been found with the exception of a lack of association with either men or women for both antihypertensive and gastroprotective agents, and the lack of association between women and urologic drugs (Supplementary Tables **4** and **5**).

Table 3. Main drug classes across PD-NC and PD-MCI patients.

-	PD-NC (n=138)	PD-MCI (n=100)	Total (n=238)	Univariate Analysis			Multivariate Analysis*		
				OR	95%CI	P value	OR	95%CI	*P* Value
Anti-parkinsonian agents (N04)	87 (63.0)	70 (70)	157 (66)	0.264	0.78-2.37	0.264	0.76	0.37-1.57	0.468
Anti-hypertensives (C02; C03; C07; C08; C09)	57 (41.3)	62 (62)	119 (50)	**2.31**	**1.36-3.92**	**0.002**	**2.02**	**1.04-3.89**	**0.035**
Gastroprotective agents (A02B)	51 (37.0)	36 (36)	87 (36.6)	0.95	0.56-1.63	0.880	**0.51**	**0.27-0.99**	**0.047**
Benzodiazepines (N05C)	41 (29.7)	37 (37)	78 (32.8)	1.38	0.80-2.39	0.238	1.35	0.69-2.64	0.375
Antiplatelet/anticoagulants (B01)	41 (29.7)	37 (37)	78 (32.8)	1.38	0.80-2.39	0.238	0.90	0.47-1.75	0.774
Psychoanaleptics (N06)	43 (31.2)	32(32)	75 (31.5)	1.03	0.59-1.80	0.890	0.92	0.47-1.81	0.824
Lipid modifying agents (C10)	23 (16.7)	23 (23)	46 (19.3)	1.49	0.78-2.84	0.224	0.87	0.40-1.87	0.732
Antidiabetic agents (A10)	13 (9.4)	16(16)	29 (12.2)	1.83	0.83-4.00	0.130	1.48	0.58-3.75	0.413
Anti-infectives (J)	14 (10.1)	8 (8)	22 (9.2)	0.77	0.31-1.91	0.574	0.68	0.23-1.95	0.474
Antipsychotics (N05A)	11 (8.0)	10 (10)	21 (8.8)	1.28	0.52-3.14	0.587	1.11	0.36-3.40	0.846
Thyroid agents (H03)	12 (8.7)	9 (9)	21 (8.8)	1.03	0.41-2.56	0.935	1.11	0.40-3.1	0.828
Urologic drugs (G04)	6 (4.4)	15 (15)	21 (8.8)	**3.88**	**1.44-10.39**	**0.007**	**3.7**	**1.1-12.6**	**0.036**
Anti-seizure medications (N03)	11 (8.0)	4 (4)	15 (6.3)	0.48	0.14-1.55	0.222	0.62	0.17-2.29	0.480

* Adjusting for significant variables (age, sex, disease duration, education, UPDRS-ME, LEDD-DAs).
Legend:PD-NC: PD Normal cognition; PD-MCI: PD with Mild Cognitive Impairment;OR: Odds Ratio; CI: confidence intervals. Qualitative variables are displayed as number (percentage).

4. DISCUSSION

In our sample, we tested the association between polytherapy and ADS scores, both measuring the impact of drugs on cognition in PD, and found no association with either of them, after adjusting for other factors commonly associated with PD-MCI [4].

The negative effects of polytherapy on elderly subjects have been extensively documented [6]. However, studies analyzing the relation of polytherapy on cognition in PD patients, a group of patients with an increased drug intake compared to the general population [5], are lacking. In fact, only one study has effectively evaluated this association, finding that polytherapy was a risk factor for worse cognitive performances [9]. We found a significant association between MCI and polytherapy both as a continuous variable and dichotomized at the univariate analysis, even if such association was not significant at the multivariate analysis. The different results might be due to our stricter definition of MCI, requiring a full neuropsychological evaluation rather than the use of the Mini-Mental State Examination [15] as done by Ishii and coll. [9].

Concerning the anticholinergic burden, despite several pieces of evidence pointing out a significant role of drugs with anticholinergic properties on cognition in the general population [8,16], data regarding PD patients is still inconsistent [10, 11, 13]. Our results are in line with a prospective study conducted in a British cohort that found no impact of the use of drugs with anticholinergic properties on cognition at an 18 months follow-up [13]. A possible explanation might be related to the increased awareness of movement disorder specialists on the side effects of several drugs with anticholinergic properties that have progressively improved the drug prescription on PD patients. Indeed, in our sample that has been recruited from a third-level neurological service, only 7% of patients were treated with anticholinergic drugs for the treatment of tremor.

In our sample, LEDD-DAs, which represents the total dopaminergic effect of dopamine agonists only, was positively associated with PD-MCI. This finding confirms the possible effect of dopamine agonists on cognition. In particular, literature data suggest a possible detrimental effect on memory function by pramipexole, a D2/D3 agonist [17, 18], and it should be noted that in our sample, almost two-thirds (59%) of patients on dopamine agonist medications were taking pramipexole. Discontinuation of dopamine agonists, on the other hand, is often associated with cognitive impairment and confusion; as such higher LEDD-DAs should be expected in PD-NC patients. Nonetheless, literature data suggests that the main predictor for dopamine agonists discontinuation is related to high levodopa dosage (>750 mg) [19]. Even if we cannot exclude that chance alone can explain this result, the low mean LEDD in our sample (375.3 mg) has possibly reduced dopamine agonists discontinuation.

When analyzing the different drug classes, we found a positive association of PD-MCI with antihypertensive medications and urologic drugs.

For antihypertensive drugs, contrary to our results, literature evidence supports a weak protective role of different

medications belonging to this class on the risk of cognitive impairment[20]. It is possible that the association represents a proxy of underlying hypertension, which is a risk factor for the development of PD-MCI, as demonstrated in other studies [21, 22]. However, in our sample, there was no significant difference in the prevalence of hypertension between PD-NC and PD-MCI patients. Furthermore, in a supplementary analysis, the positive association was significant only for calcium channel blockers and borderline significant for diuretics. While the results of this supplementary analysis should be taken with caution due to the reduced sample size, a possible explanation of the overall positive association of anti-hypertension medications lies in the increased risk of orthostatic hypotension described with the use of these medication classes [23], that represents a known risk factor for the development of cognitive impairment in PD [24].

Considering that anticholinergic molecules belong to this class, the risk of cognitive impairment associated with urologic drugs was expected. Nevertheless, other urologic drugs such as alpha-blockers and 5-alpha reductase inhibitors have been shown to negatively affect cognitive functions [25].

Interestingly, we have found that gastric protectors seem to protect from MCI. This category encompasses both proton pump inhibitors (PPI) and H2 receptor antagonists (H2RA). Previous evidence has shown that the use of PPI was associated with an increased risk of cognitive impairment [26]. However, in accordance with our results, more recent evidence has suggested a protective rather than a detrimental effect on cognitive impairment [27]. A possible mechanism of action lies in the anti-neurotoxic properties of PPI on astrocytes and microglia [28].

Concerning the analysis stratified according to sex, the lack of association with antihypertensive and gastroprotective agents is probably due to the low statistical power of the subgroup analysis.

Our results are limited by the cross-sectional nature of the sample, not allowing the evaluation of the risk of future development of dementia. We also included patients with different disease durations. However, we kept this limitation into account by forcing disease duration in the multivariate model. Finally, we used slightly modified level II criteria for the diagnosis of PD-MCI since not all the enrolled patients had an available language assessment. Nevertheless, this should not impact the significance of our results since only a very small percentage of patients (up to 6.5%) in the published literature on PD-MCI showed any impairment in the language domain [4]. At any rate, we think that our sample more reliably represents a "real life" setting of a PD center, mirroring the drug dispensary habits used in the chronic management of these patients. Another limitation is the lack of both the dosage and total exposure time for each drug. In fact, data for this study comes from the clinical record of patients regularly followed in both the inpatient and the outpatient services, where drug intake is regularly assessed as part of the scheduled examinations but not investigated in the past.

Our study has also several strengths. It is one of the few cohorts assessing the association with anticholinergic burden and MCI using MDS criteria level II and is the only study that analyzed the association with polytherapy and with specific drug classes.

CONCLUSION

In conclusion, while our cross-sectional analysis found no association with polytherapy, anticholinergic burden, and PD-MCI, we found a significant protective effect of gastroprotective agents on the risk of MCI. Since drugs are a modifiable risk factor, to validate these pieces of evidence, there is an urgent need for larger studies with a prospective design and animal model studies elucidating the role of gastroprotective agents on cognitive impairment.

ETHICS APPROVAL AND CONSENT TO PARTICIPATE

The research has been approved by the local ethical committee University Hospital P. Giaccone, Palermo, Italy (approval number: 14:03/2018).

HUMAN AND ANIMAL RIGHTS

No animals were used for studies that are the basis of this research. The study on humans was conducted in accordance with the Declaration of Helsinki.

CONSENT FOR PUBLICATION

All the patients provided informed consent before being included in the study.

STANDARDS OF REPORTING

STROBE checklist were followed for the study.

AVAILABILITY OF DATA AND MATERIALS

Not applicable.

FUNDING

None.

CONFLICT OF INTEREST

The authors declare no conflict of interest, financial or otherwise.

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Declared none.

SUPPLEMENTARY MATERIAL

Supplementary material and STROBE checklist are available on the publisher's website along with the published article.

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