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Risk factors for dementia in Parkinson's Disease — the overuse of anticholinergic drugs

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ABSTRACT

Aim of the study. To determine the risk factors for dementia in a group of patients with Parkinson's Disease (PD), especially the effect of the anticholinergic burden assessed according to the Anticholinergic Cognitive Burden scale (ACB) and the CRIDECO Anticholinergic Load Scale (CALS).

Clinical rationale for the study. To provide information about factors associated with Parkinson's Disease dementia (PDD), especially the anticholinergic burden and testing the effect of both scales in an assessment of the anticholinergic burden in this group of patients.

Material and methods. A retrospective and cross-sectional analysis of medical records of patients with Parkinson's Disease admitted to the Neurology Department of the Medical University of Silesia, Katowice, Poland between 2019 and 2021 was performed. We found 418 patients with a diagnosis of PD, but 80 were excluded due to lack of a cognitive function assessment. Based on MMSE score, the remaining 338 patients were divided into two groups of patients with, and without, PDD. Next, demographic and clinical data was collected. The anticholinergic burden was assessed using the ACB and the CALS scales. According to the authors of these scales, : if a scale score is of three or more points, this should be considered as a significant anticholinergic burden. Multiple logistic regression with backward elimination was used to assess factors significantly related to the presence of dementia, and two different models were used for both scales assessing the anticholinergic burden.

Results. 62 (18.3%) patients were diagnosed with PDD. Overall significant anticholinergic burden (≥ 3 points) was found in 31.95% of patients using CALS and in 18.93% using ACB. Anticholinergic burden was higher in patients with dementia (CALS 50 *vs.* 27.90%, p <0.001, ACB 43.5 *vs.* 13.41%, p < 0.001). According to both models, the factors significantly related to dementia were: age (ACB OR 1,114 (1.062–1.170), p < 0.001, CALS OR 1.123 (1.070–1.178), p < 0.001), significant anticholinergic burden (ACB OR 3.433 (1.746–6.750), p < 0.001, CALS OR 2.166 (1.157–4.055), p = 0.016) disease severity in the Hoehn-Yahr scale (ACB OR 1.752 (1.197–2.565), p = 0.004, CALS OR 1.831 (1.256–2.670), p = 0.002) and atrial fibrillation (ACB OR 5.593 (1.417–22.083), p = 0.014, CALS OR 5.159 (1.314–20.254), p = 0.016).

Conclusions and clinical implications. The anticholinergic burden is larger in PDD patients compared to PD patients without dementia. CALS or ACB scales are helpful in this risk assessment and might be crucial to avoid the development of PDD, especially in older PD patients with multimorbidities.

Key words: anticholinergic burden, anticholinergic drugs, Parkinson's Disease, dementia, cognitive impairment, anticholinergic burden scale, risk factors

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Introduction

Lewy body disease, including Parkinson's Disease dementia (PDD) and dementia with Lewy bodies (DLB), is one of the leading causes of cognitive impairment. The prevalence of dementia in Parkinson's Disease is c.30% and 3–4% of all patients with dementia have PDD [1]. In the course of PD, dementia usually occurs as a late, non-motor symptom. Dementia in PD is observed 2-6 times more frequently compared to the general population of the same age [1, 2]. The problem of PDD is especially important due to the fact that PD is the second most common neurodegenerative disease and that up to 80% of PD patients develop dementia [1–3]. Thus, cognitive impairment is a significant burden in this population, and significantly affects quality of life not only for patients, but also for caregivers [4].

A key aspect of developing effective preventive approaches is to identify possible strategies to modify risk factors for the development of dementia. There are many proposed risk factors of cognitive decline related to PD including: longer disease duration, older age at PD onset, male gender, disease severity, speech impairment, postural-instability-gait disorder subtype, hallucination, depression, blood pressure abnormality related to dysautonomia, REM sleep behaviour disorder, vascular risk factors, hyperhomocysteinemia, anticholinergic burden, lower level of education, low cerebrospinal fluid levels of amyloid-β42, and mutations in GBA, APOE4 or SNCA genes. However, the data from these publications is not consistent and some risk factors have been found only in single studies [5–13].

Neurochemically, the most significant deficit seems to be cholinergic, which is consistent with the view that the cholinergic system is crucially involved in cognitive function, with cholinergic dysfunction playing a pivotal role in the pathophysiology of dementia [14]. Anticholinergic drugs, which impair cholinergic pathways, are commonly used in clinical practice for the management of many conditions affecting older adults [15–17].

They affect many organs, causing adverse effects such as dry mucous membranes, constipation, urinary retention, delirium, orthostatic hypotension, as well as cognitive decline, which is the major problem associated with long-term exposure to substances having anticholinergic activity. Taking more than one anticholinergic drug has a cumulative effect and the sum of exposure to these drugs is called the 'anticholinergic burden' [16, 18, 19]. Some studies have suggested an association between anticholinergic drugs use and cognitive decline in PD [8, 9].

Therefore, there was a need to develop standardised methods for assessing the exposure to anticholinergic drugs and their impact on cognitive impairment. Multiple scales have been created, although there are significant discrepancies among them with regard to anticholinergic drugs and their anticholinergic potency [16, 20, 21]. One of the most commonly used is the Anticholinergic Cognitive Burden scale (ACB), published in 2008 and updated in 2012 [22–24]. A systematic review from 2015, which compared seven anticholinergic rating scales, showed the ACB with 88 drugs as the most frequently validated scale [24]. Also, research conducted by Lisibach et al. assessed ACB as the highest rated in the following domains: rigour of development, clarity of presentation, and applicability. With the German anticholinergic burden scale, it has reached the highest overall assessment [16]. Ramos et al. in their recent study devised the CRIDECO Anticholinergic Load Scale (CALS) for assessing anticholinergic load. They found an association between anticholinergic burden measured with CALS and cognitive impairment in patients with a subjective memory complaint, which was not confirmed using the ACB scale [20].

Clinical rationale

The aim of our study was to determine the risk factors for dementia in a group of patients with PD, especially the effect of the anticholinergic burden, and to compare the anticholinergic burden assessed according to the ACB scale and the CALS. To the best of our knowledge, this is the very first study to evaluate anticholinergic burden in patients with PD with the use of CALS. Our study provides information about potential risk factors related to PDD and tests the effect of the new tool in the assessment of anticholinergic burden in this group of patients, which will be important for future research and clinical management of PD.

Material and methods

We performed a retrospective and cross-sectional analysis of all consecutive patients diagnosed with PD and admitted to the Central Clinical Hospital of the Medical University of Silesia in Katowice, Poland between January 2019 and December 2021. The diagnosis, according to the current MDS criteria [25], was confirmed by movement disorders specialists. The initial group consisted of 418 patients. 80 patients were excluded due to lack of a cognitive function assessment. Based on the results of the neuropsychological assessment, the 338-strong study group was divided into PD with a diagnosis of dementia (MMSE score < 24 and cognitive dysfunction which interferes with the activities of daily living) and PD without a diagnosis of dementia (MMSE score ≥ 24). Other tests used in the cognitive function assessment included: the Stroop test, a trail making test, and a clock drawing test. The Addenbrooke's Cognitive Examination-Revised test was also used in some patients in the analysed period. In all cases, the patients' cognitive status was assessed in the 'ON' state, i.e.: 1-2 hours after taking the usual dose of dopaminergic drugs and with activated deep brain stimulation (if applicable).

The final study group consisted of 338 patients comprising 206 (61%) males and 132 (39%) females average age of 67 (61–72), aged from 35 to 86 years. The collected clinical data comprised sex, age, body mass index (BMI), duration

of PD, the assessment of motor status with part III of the MDS-UPDRS scale (Movement Disorder Society — Unified Parkinson's Disease Rating Scale) [26] performed without dopamine replacement therapy (DRT) and after the administration of a dose of levodopa, a rating on the Hoehn-Yahr scale, an assessment of cognitive function using the Mini Mental State Examination scale (MMSE), and the presence of depression (Beck Depression Inventory ≥ 14 pts). Data about daily levodopa equivalent dose (LEDD) was also collected [27]. An analysis of the laboratory results regarding thyroid function, lipid profile, homocysteine, vitamin D3, vitamin B12 and folate was conducted, and data on current treatment and comorbidities was collected. Anticholinergic burden was assessed using the CALS scale and the updated version of the ACB scale, with cut-off points as recommended by the authors [20, 22, 23]. ACB classifies drugs according to their serum anticholinergic activity or *in vitro* binding affinity with muscarinic receptors and clinically established anticholinergic adverse effects, and scores each drug from 0 to 3 points. A score from summation ≥3 is considered clinically relevant [20–24]. CALS is a scale based on a synthesis of the other scales found in a systematic review of the literature and includes 217 anticholinergic drugs each scoring 1-3 points according to their anticholinergic potency where 1 = low, 2 = medium, and 3 = high. A score from summation ≥ 3 is considered clinically relevant [20].

Statistical analysis was performed using STATISTICA 13 PL software (Tibico Software Inc.). Quantitative variables were presented as an arithmetic mean and a standard deviation (normally distributed variables) or a median and the interquartile range (variables of not normal/skewed distribution). The normality of distribution was assessed with the Shapiro–Wilk test. Qualitative variables were presented as absolute values and percentages. Intergroup differences for the quantitative variable were assessed using the U-Mann–Whitney or t-Student test, respectively. For qualitative variables, a chi-square test (Chi^2), or a chi square test with Yates correction (Chi^2YC) were used. Due to multiple comparisons, the Bonferroni correction was applied and a p-value of 0.002 was considered as significant, however the traditional cut-off point of 0.05 was also taken into account. Next, selected variables with p-value < 0.05 were analysed using a backward stepwise logistic regression model to evaluate risk factors associated with the occurrence of PDD, and two alternative models were built for ACB and CALS. The results of logistic regression were presented as odds ratios (OR) with 95% confidence intervals (CI) and Nagelkerke's R^2. The Hosmer–Lemeshow test was also performed to assess goodness of fit of final logistic regression models; its insignificant value ($p > 0.05$) suggests that the model was well-fitted. McNemar's and Cohen's kappa coefficients were used to compare scales. Agreement in Cohen's kappa was interpreted in the following way: < 0.00: poor; 0.00–0.20: slight; 0.21–0.40: fair; 0.41–0.60: moderate; 0.61–0.80: substantial; and 0.81–1: almost perfect.

Due to the retrospective character of this work and data anonymisation, the Ethics Committee of the Medical University of Silesia waived the requirement to obtain ethical approval for this study.

Results

In the study group, 62 (18.3%) patients with PD were diagnosed with dementia. The group with dementia was older (72 (68–75) *vs.* 66 (57.5–71.5) years, $p < 0.001$) and presented a longer PD duration (11 (7.5–14) *vs.* 7 (3–12) years, $p = 0.001$) than patients without dementia. Demented patients displayed higher MDS-UPDRS part III scores both with (24.5 (18–32) vs. 16 (9–25), $p < 0.001$) and without dopamine replacement therapy (44 (40–58) *vs.* 36 (24.5–48), $p < 0.001$) and a higher Hoehn-Yahr score (3 (3–4) *vs.* 3 (2–3), $p < 0.001$), as well as LEDD (1,110 (605–1,500) *vs.* 720 (350–1,335) mg, $p = 0.008$).

Patients with PDD were characterised by a statistically higher occurrence of hypertension (58.06 *vs.* 42.91%, $p = 0.030$), atrial fibrillation (AF) (8.06 *vs.* 1.81%, $p = 0.027$), and the presence of two or more of the listed vascular risk factors [stroke/transient ischaemic attack (TIA), insert abbreviation (IHD), AF, arterial hypertension, and diabetes mellitus] (30.65 *vs.* 18.48%, $p = 0.033$) than the group of PD patients without dementia, although after the application of Bonferroni correction the differences did not reach statistical significance. They also displayed a higher frequency of anticholinergic burden defined by results ≥ 3 of the CALS (50 *vs.* 27.90%, $p < 0.001$) and ACB (43.5 *vs.* 13.41%, $p < 0.001$) scales. Overall, 108 (31.95%) patients had a significant anticholinergic burden according to CALS and 18.93% according to ACB. There was 81.7% agreement between the scales in terms of an assessment of a significant burden (Cohen's kappa = 0.53, moderate agreement). The difference between the numbers of patients who were found to have ≥ 3 points in both scales was significant in McNemar's test $p < 0.001$. 51.5% and 43.5% of patients took at least one anticholinergic drug according to CALS and ACB, respectively. All anticholinergic drugs according to CALS and ACB are set out in Supplementary Table 3.

PD patients with dementia showed lower BMI (24.15 (21.47–25.71) *vs.* 25.96 (24.02–29.05) kg/m^2, $p = 0.01$), lower total cholesterol (187.14 ± 47.37 *vs.* 204.49 ± 48.24 mg/dl, $p = 0.013$), lower LDL-cholesterol (LDL) (109.64 ± 39.16 *vs.* 123.42 ± 41.34 mg/dl, $p < 0.028$), and higher homocysteine level (16.22 (13.46–20.71) *vs.* 13.77 (11.2–17.1) µmol/l, $p = 0.009$), but statistical significance after the application of Bonferroni correction was not reached. There were no significant differences in terms of the sex of patients in any performed laboratory tests. No statistical difference was obtained in comorbidities such as diabetes mellitus, depression, past acute cerebrovascular conditions (stroke, TIA, SAH), ischaemic heart disease, valvular defect, cancer (past or current) or respiratory system diseases (asthma, chronic obstructive pulmonary disease, pneumoconiosis). A detailed comparison of both groups is set out in Table 1.

Table 1. Characteristics of quantitative and qualitative demographic and clinical variables comparing non-demented PD with PDD

	Non-dementia PD	PDD	P-value
Age, years	66 (57.5–71,5)	72 (68–75)	< 0.001
Duration of disease, years	7 (3–12)	11 (7.5–14)	0.001
BMI, kg/m^2	25.96 (24.02–29.05)	24.15 (21.47–25.71)	0.01
Hoehn-Yahr scale	3 (2–3)	3 (3–4)	< 0.001
MDS-UPDRS part III 'OFF'	36 (24.5–48)	44 (40–58)	< 0.001
MDS-UPDRS part III 'ON'	16 (9–25)	24.5 (18–32)	< 0.001
LEDD, mg	720 (350–1,335)	1,110 (605–1,500)	0.008
Total cholesterol, mg/dL	204.49 ± 48.24	187.14 ± 47.37	0.013
HDL cholesterol, mg/dL	59.05 (51.0–70.6)	56.05 (44.2–67.9)	0.118
LDL-C cholesterol, mg/dL	123.42 ± 41.34	109.64 ± 39.16	0.028
Triglycerides, mg/dL	85.6 (65–115)	79.8 (64.0–96.1)	0.117
TSH, µIU/mL	1.47 (1.03–2.13)	1.21 (0.93–1.80)	0.066
Vitamin B_{12}, pg/mL	344 (252–449.5)	367 (264.8–476.5)	0.405
Vitamin D_3, ng/mL	25.7 (17–33)	22.0 (14–37)	0.354
Folic acid, ng/mL	6.66 (4.84–8.96)	6.63 (4.72–10.50)	> 0.5
Homocysteine, µmol/L	13.77 (11.2–17.1)	16.22 (13.46–20.71)	0.009
Sex, % male	61.96	56.45	0.422
DBS, %	8.33	6.45	> 0.5
Depression, %	13.41	19.35	0.244
Diabetes, %	12.32	19.67	0.146
CALS ≥ 3, %	27.90	50	< 0.001
ACB ≥ 3, %	13.41	43.5	< 0.001
HT, %	42.91	58.06	0.030
Stroke/TIA/SAH, %	4.56	4.84	> 0.5
IHD, %	14.49	17.74	> 0.5
Cancer (active or in history), %	3.76	9.68	0.09
AF/AFl, %	1.81	8.06	0.027
Heart valves defect, %	3.76	8.06	0.233
Asthma/COPD/pneumoconiosis, %	3.63	4.84	> 0.5
> 1 RF of dementia (without LDL), %	18.48	30.65	0.033

BMI — body mass index; LEDD — daily levodopa equivalent dose; DBS — deep brain stimulation; ACB — Anticholinergic Cognitive Burden scale; AF — atrial fibrillation; AFI — atrial flutter; CALS — CRIDECO Anticholinergic Load Scale; IHD — ischemic heart disease, COPD — Chronic Obstructive Pulmonary Disease; RF — risk factors

Variables including age, disease duration, assessment of disease severity in the Hoehn-Yahr scale, LEDD, presence of arterial hypertension, AF, and the presence of more than one vascular risk factor (stroke/TIA, ischaemic heart disease, AF, arterial hypertension, and diabetes mellitus) were included in the stepwise logistic regression analysis to assess their association with the occurrence of PDD in two alternative models for ACB and CALS scales. The Hoehn-Yahr scale and MDS-UPDRS are measures of disease severity and we decided to use the Hoehn-Yahr scale in regression analysis due to its simplicity. BMI and homocysteine were not included due to data incompleteness. Total cholesterol and LDL were not included due to lack of data in some cases and a possible association with malnutrition that can occur in advanced PD and can coexist with dementia and older age [28–30].

The influences of age, anticholinergic burden, higher Hoehn-Yahr stage, and AF were confirmed in both models as set out in Table 2. The Hosmer–Lemeshow test revealed that both models were well-fitted (CALS p = 0.23, ACB 0 = 0.49). Nagelkerke's R^2 were 0.265 and 0.293, respectively. OR for assessment of anticholinergic burden in CALS ≥ 3 was lower than for ACB ≥ 3 [2.166 (1.157–4.055) *vs.* 3.433 (1.746–6.750)].

Table 2. Results of logistic regression with risk factors of PDD with ACB and CALS

ACB (Nagelkerke's R^2 = 0.293)				
	OR	**95% CI**		**P-value**
Age, years	1.114	1.062	1.170	< 0.001
ACB > 2	3.433	1.746	6.750	< 0.001
Hoehn-Yahr scale	1.752	1.197	2.565	0.004
AF/AFI	5.593	1.417	22.083	0.0140
CALS (Nagelkerke's R^2 = 0.265)				
	OR	**95% CI**		**P-value**
Age, years	1.123	1.070	1.178	< 0.001
CALS > 2	2.166	1.157	4.055	0.016
Hoehn-Yahr scale	1.831	1.256	2.670	0.002
AF/AFI	5.159	1.314	20.254	0.019

OR — odds ratio; CI — confidence interval; ACB —Anticholinergic Cognitive Burden scale; AF — atrial fibrillation; AFI — atrial flutter; CALS — CRIDECO Anticholinergic Load Scale

Discussion

It is well established that age, sex and genetic predispositions are non-modifiable risk factors of dementia development, not only in Alzheimer's Disease, but also in PD. Age is the primary risk factor for developing dementia including PDD, and it was significantly associated with the presence of cognitive impairment in our study [5, 7, 31]. There has beendata suggesting that sex is an important risk factor for dementia. However, this was not found in our study. Unlike Alzheimer's Disease, male gender is a risk factor for PDD and it is associated with its faster progression [31]. Lack of association between male sex and dementia might be potentially interplayed with the chosen method of cognitive function assessment. A meta-analysis of risk factors for PDD by Xu et al. indicated that advancement of motor symptoms measured with MDS-UPDRS part III scale correlates with the occurrence of PDD. However, that research presented no association with higher score in the Hoehn-Yahr scale. Other studies, like the one performed by Guo, have found it to be a predictor of cognitive impairment in PD besides MDS-UPDRS part III [7, 32]. In line with this result, Marinus et al. have described a higher severity of motor symptoms in both scales as being independently associated with the occurrence of non-motor symptoms, with PDD and cognitive impairment among these [2]. AF is a condition frequently mentioned as contributing to dementia development in the general population, in post-stroke patients, in patients with Alzheimer's Disease, and in patients with vascular dementia [33]. It is also one of the most common comorbidities in PD patients, and some research considers AF to be even more frequent in PD patients than in the general population [34, 35]. However, data confirming its potential association with PDD is scarce [36]. Our study suggests that AF might be a potential risk factor for PDD, something which should be considered in future studies, but there is also a possibility that the relation of AF and cognitive functions could be related to some potential risk factors not assessed in our study.

Vascular risk factors, other than AF/AFI, have also been considered as risk factors for PDD, but the significance for the development of PDD differs between studies [6, 7, 37]. However, our study did not display any significant difference in vascular risk factors between PD patients with and without dementia, which seems to be in agreement with a large Swedish study which revealed that PDD is less associated with diabetes mellitus and ischaemic heart disease compared to Alzheimer's Disease [37].

Literature data suggests that an increased blood level of homocysteine, frequently present in PD patients, is related to levodopa therapy [11] and is associated with cognitive decline. However there was no significant difference in homocysteine level between the groups in our study [11].

It is known that patients with PD show poorer cognitive performance if they are assessed in the 'OFF' state. Data from the literature suggests that dopaminergic treatment does not have any negative effects on cognitive function, but also might reduce the risk of cognitive decline in PD patients [38, 39]. However, there were no statistically significant negative or positive effects of LEDD in our study.

In 1996, Pondal et al. in a small sample of patients identified long-term anticholinergic therapy as a risk factor for dementia in PD [40]. In 2009, Ehrt et al. published a prospective study which displayed a larger decline in MMSE for patients taking anticholinergics [8]. Also, a large retrospective study from Taiwan revealed that patients with a high cumulative dose of anticholinergics had a higher risk of developing dementia [9]. On the other hand, some studies have not found any association between anticholinergics and cognitive decline in PD patients. However, their authors did suggest that this could be related to factors such as a low anticholinergic burden in the analysed group or a short follow-up [41–43].

Our study is in agreement with parts of the previously acquired data, and suggests that the anticholinergic burden is related to worsening of cognitive function in this group of patients. However, it is not possible to conclude that the anticholinergic burden is related to long-term cognitive decline. The differences between studies might be explained by various ways of assessing the anticholinergic burden and cognitive function, as well as differences in the assessed populations and study designs.

In two studies using ACB, 15.5-18.5% of patients had more than 2 points and 41.5–46.3% took at least one anticholinergic drug; these seem to be similar results to those in our study [42–44]. Geriatric patients from the same area of Poland hospitalised in a geriatric ward had a lower anticholinergic burden (ACB ≥ 3 13.98%, ACB ≥ 1 40.73%) than PD patients from our study, which might suggest that the topic is especially relevant for PD patients [45]. In the study population, 15 patients had used biperiden, known to be a medication having a strong anticholinergic effect, which is marked by the highest score in CALS, but however was not included in the ACB scale [22, 23]. According to the 2017 National Institute for Health and Care Excellence (NICE) guidelines for the diagnosis and management of Parkinson's Disease in adults, there is no indication to use anticholinergic medications in the treatment of motor symptoms in PD [19, 46]. Among medicaments presenting a medium anticholinergic potency in CALS and ACB, the greatest importance was attached to amantadine with 76 cases [20]. Amantadine is not only an antagonist of the N-Methyl-d-aspartate (NMDA) receptor, but also improves striatal dopaminergic signalling owing to the inhibition of dopamine reuptake [47]. It is widely used as a second-line drug in PD treatment in spite of the (often anticholinergic) adverse effects [35]. The NICE guidelines note no evidence of improvement of motor symptoms or activities of daily living when applying amantadine to treatment, but suggests considering amantadine if "dyskinesia is not adequately managed by modifying existing therapy" [19].

Other anticholinergics with high or medium potency include psychiatric drugs, medications for urinary incontinence, which poses a significant problem in PD, and tramadol, which is a common analgesic drug.

The basis of pharmacological treatment of motor symptoms in PD remains levodopa, which revolutionised opportunities to fight this incurable disease. Additional drugs used in this indication belong to dopamine agonists, monoamine oxidase B inhibitors (MAO-B inhibitors), or catechol-O-methyltransferase inhibitors (COMT inhibitors) which ensures an extension of an effective treatment and L-dopa sensitivity in patients. Both Levodopa-carbidopa and alternative medications such as entacapone belonging to COMT inhibitors, selegiline as a representive of MAO-B inhibitors, or rotigotine and pramipexole which belong to dopamine agonists, are assigned to the group with low anticholinergic potency according to CALS, but not according to ACB [20]. In the conducted research, the above-mentioned drugs have been used by the vast majority of patients. Though low scores are attributed to these drugs (1 point in CALS) their frequent usage in many combinations causes a considerable increase in the anticholinergic burden measured by CALS in patients with PD.

As many as 92% of geriatric patients with PD are characterised by multimorbidities [35]. It has been shown that more than half of them struggle with polypharmacy i.e. taking 5+ drugs [48]. The common practice is that geriatric PD patients have on average more than eight drugs prescribed [49]. To avoid the deterioration of cognitive function, it seems to be necessary to apply the treatment with a low anticholinergic potential in PD patients who are already at increased risk of dementia development. ARS like CALS or ACB may provide a valuable tool in avoiding harmful side effects of anticholinergics in PD patients. Another tool, which may increase drug safety in PD patients and reduce the anticholinergic burden, could be lists of inappropriate drugs for geriatric patients like the Fit fOR The Aged (FORTA) Classification, Beer's Criteria, the START/STOPP list, or the PRISCUS list [35, 49].

In terms of the anticholinergic burden, the most relevant seems to be the conversion of medications with high or medium potency to equivalents with low or no anticholinergic potency where possible. This concerns all of the above PD--specific drugs, including biperiden (displaying high potency) and amantadine (presenting medium anticholinergic potency) which, due to their negligible action, should be replaced with dopamine agonists or a levodopa therapy. Similarly, other medications should be considered for conversion for fear of an increased risk of cognitive deterioration.

Some drugs having medium to high anticholinergic potency in CALS (amitriptyline, clozapine, olanzapine or amantadine) are in group D ('avoid') in the FORTA Classification. Considering that, it seems reasonable to follow the current guidelines concerning diagnosis and treatment combined with the use of an ARS like CALS. This will allow effective treatment of PD patients and, despite multimorbidities and polypharmacy, will permit many of them to avoid dementia.

Our study has some limitations. The first is its retrospective and cross-sectional design, meaning that it is impossible to conclude that anticholinergics are related to dementia or only worsening cognitive function which could be reversed after discontinuation of the the anticholinergic drugs.

Secondly, due to data incompleteness, it was impossible to take into account the following potential risk factors: gene mutations, hallucinations, white matter lesions or increased homocysteine.

The next major limitation of this study was the method of statistical analysis, where the cognitive function assessment was based on total MMSE score with a cut-off of 24 points. However, the diagnosis of PDD was based on a neuropsychologist's opinion and DSM-IV criteria where all demented patients had been confirmed by a caregiver as having a significant interference of cognitive dysfunction with their activities of

daily living. This is not a precise method to assess cognitive function in PD, although it is included in the Level 1 MDS Task Force Criteria for PD dementia diagnosis [1, 50]. Other scales for cognitive function assessment were also used for clinical purposes during psychological assessment. However, due to their high heterogeneity in the analysed period and the better accessibility of the MMSE results, we decided not to include them in our analysis. All PD patients with a cut-off of 24 points had dementia, but the number of patients with a diagnosis of mild PDD might have been underestimated in our study.

Clinical implications/future directions

Older age, greater severity of disease, AF, and anticholinergic burden were all significantly associated with the presence of of PDD in our study. Our study results suggest that both the ACB and the CALS scales are valid for the assessment of anticholinergic burden, although CALS contains a wider list of medications.

The results of our study have clinical implications because they suggest that anticholinergics, which are commonly used in the PD population, are associated with cognitive dysfunction, which is one of the most important non-motor symptoms related to increased mortality and significantly affects the quality of patients' lives and those of their caregivers [4]. However, we could not conclude that anticholinergics cause PDD, due to the cross-sectional design of our study and the potential reversibility of their effect after proper drug adjustments.

This implies that proper drug management using tools such as CALS or ACB might be crucial to avoid the development of cognitive decline, especially in older patients with multimorbidities and advanced PD. Avoiding anticholinergics might also prove beneficial in the context of other non-motor symptoms such as orthostatic hypotension, delirium or constipation, which they can exaggerate [18, 19]. There is an overwhelming need for in-depth studies of the anticholinergic burden in the context of PPD, and especially large prospective studies.

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