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Anticholinergic Burden, Polypharmacy, and Cognition in Parkinson's Disease Patients with Mild Cognitive Impairment: A Cross-Sectional Observational Study

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Keywords
Parkinson's disease · Anticholinergic burden · Polypharmacy · Mild cognitive impairment · Cognition disorders

Abstract
Introduction: Anticholinergic burden may be an important risk factor for the cognitive impairment. Especially in polypharmacy, even drugs with low anticholinergic effects may contribute to a significant anticholinergic burden. The drugs with anticholinergic effects are used in treatment of motor and nonmotor symptoms of Parkinson's disease (PD). Therefore, it is important to screen for polypharmacy and anticholinergic burden in PD patients with mild cognitive impairment (MCI). ***Methods:*** This cross-sectional study was conducted with 58 patients with PD. PD-MCI was diagnosed according to MDS Level 2 Comprehensive Assessment. Cognitive performance (attention – working memory, executive functions, language, memory, and visuospatial functions) of patients was evaluated. The anticholinergic burden was scored by Anticholinergic Cognitive Burden (ACB) Scale, Anticholinergic Risk Scale (ARS), and Anticholinergic Drug Scale (ADS). ***Results:*** There was no significant difference in anticholinergic burden between PD-MCI and PD-normal cognition. A significant concordance was observed between ACB, ARS, and ADS scores ($p < 0.001$; Kendall's W = 0.653). While the variable predicting anticholinergic burden was the total number of drugs for ACB and ADS scales, it was the number of antiparkinson drugs for ARS scale. ***Conclusion:*** Patients with PD are at high risk for polypharmacy and anticholinergic burden. Anticholinergic burden should be considered in the selection of drugs, especially for comorbidities in patients with PD. No significant correlation was found between the cognition and anticholinergic burden in patients with PD-MCI. Although the risk scores of antiparkinson and other drugs were different among the 3 scales, significant concordance was observed between scales.

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Introduction

The anticholinergic effect caused by all medications of a person is referred to as anticholinergic burden [1]. Acetylcholine plays an important role in cognitive functions such as learning and memory. Therefore, high anticholinergic burden may be an important risk factor for the cognitive impairment or dementia [2, 3].

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Many anticholinergic drugs are widely prescribed, especially among older adults with multiple comorbidities such as overactive bladder, seasonal allergies, and depression [4]. The National Institute for Health and Care Excellence dementia guideline recommends considering anticholinergic burden as a factor that may contribute to cognitive impairment, screening patients with various validated tools for assessing anticholinergic burden, and minimizing anticholinergic burden-related drugs [5]. The anticholinergic burden can be assessed in a number of ways. Which anticholinergic burden measurements offer the most precise and therapeutically helpful prognostic information is a matter of debate [1]. The serum radioreceptor anticholinergic activity test (SAA) [6] and anticholinergic burden scales are the two main techniques now used. Anticholinergic risk scales are tools that classify drugs due to their anticholinergic potential and are frequently used to estimate the anticholinergic burden. The medications included in the anticholinergic scales and the ratings assigned to the medications vary. It is unknown whether these differences significantly affect the estimation of anticholinergic burden for a patient [7]. There were few studies in the literature comparing various anticholinergic scales [1].

There are studies in the literature reporting an elevated risk of cognitive impairment and dementia is linked to more cumulative anticholinergic drug use [2, 3, 8, 9]. The Cochrane review evaluating anticholinergic burden in predicting dementia and cognitive impairment noted that the evidence was of low quality, and it was unclear whether anticholinergic burden had a causal role for dementia [1]. There are limited studies investigating the relationship between cognitive impairment and anticholinergic burden in mild cognitive impairment (MCI) [10–12] and in Parkinson's disease (PD)-MCI [12, 13]. The results of MCI studies are inconsistent. Anticholinergic drugs are frequently used in the treatment of motor and nonmotor symptoms of PD, and these patients are at high risk of dementia. Therefore, the anticholinergic burden of treatment of PD and other comorbidities should be carefully evaluated.

The definition of polypharmacy in the literature ranges from two or more to 11 or more drugs, and the most widely accepted definition is the use of five or more drugs per day [14]. Polypharmacy is common in the elderly and is associated with decline in cognitive function and higher risks of MCI and dementia in several studies [15–18]. Especially in polypharmacy, even drugs with low anticholinergic effects may contribute to a significant anticholinergic burden.

The aim of this study was to examine the relationship between cognition and polypharmacy and anticholinergic burden in PD-MCI. In this study, we preferred the Anticholinergic Cognitive Burden (ACB) scale, Anticholinergic Drug Scale (ADS), and Anticholinergic Risk Scale (ARS) and aimed to compare the results of these scales in patients with PD.

Materials and Methods

Patients

This cross-sectional study was carried out using the convenience sampling method with 58 consecutive patients who applied to the Behavioral Neurology and Movement Disorders Outpatient Clinic of the Neurology Department of the Istanbul Faculty of Medicine. Inclusion criteria were a diagnosis of PD according to UK PD Society Brain Bank criteria and ≥5 years of education. Patients with a diagnosis of dementia (criteria recommended by the Movement Disorders Task Force [19]) and those receiving device-assisted therapy (deep brain stimulation, apomorphine infusion, and levodopa/carbidopa intestinal gel infusion) were excluded from the study. This study was approved by the Ethics Committee of Istanbul University, Istanbul Faculty of Medicine (December 22, 2017/21), and all participants signed informed consent.

Neuropsychological Tests, MCI Diagnosis, and Clinical Evaluation

Global cognitive function was assessed by the Montreal Cognitive Assessment (MoCA). PD-MCI was diagnosed according to MDS Level 2 Comprehensive Assessment [20]. Neuropsychological tests including at least two tests for each of the five cognitive domains were used in the comprehensive assessment (Digit span and Trail Making Test for attention and working memory, Verbal Fluency Test and Stroop Test for executive function, Wechsler Memory Scale-Logical Memory subtest and 15-word Verbal Memory Test-Oktem Verbal Learning Test version for memory, Boston Naming Test and Responsive Naming Test for language, Benton Judgment of Line Orientation Test and Benton Facial Recognition Test for visuospatial functions). The tests were performed on the participants in Turkish, and tests with validation and norm studies were selected. In neuropsychological tests, performance below 1.5 standard deviations (SDs) according to age, education, gender, and culturally appropriate norms was evaluated as impairment. For the diagnosis of PD-MCI, impairment in at least two tests must be present, either in a single cognitive domain or in different cognitive domains. The clinical assessment comes out of a neurological examination and the application of The MDS-Unified Parkinson's Disease Rating Scale (MDS-UPDRS) [part I (nonmotor symptoms), part II (motor symptoms), part III (motor examination), and part IV (motor complications)], Hamilton depression and anxiety scales, Modified Hoehn-Yahr scale, Schwab-England Activities of Daily Living Scale.

Anticholinergic Burden and Polypharmacy Evaluation

All drugs used by the patients for PD and other comorbidities were listed. The levodopa equivalent dose (LEDD) of antiparkinson drugs was calculated with the Levodopa Equivalent Dose Cal-

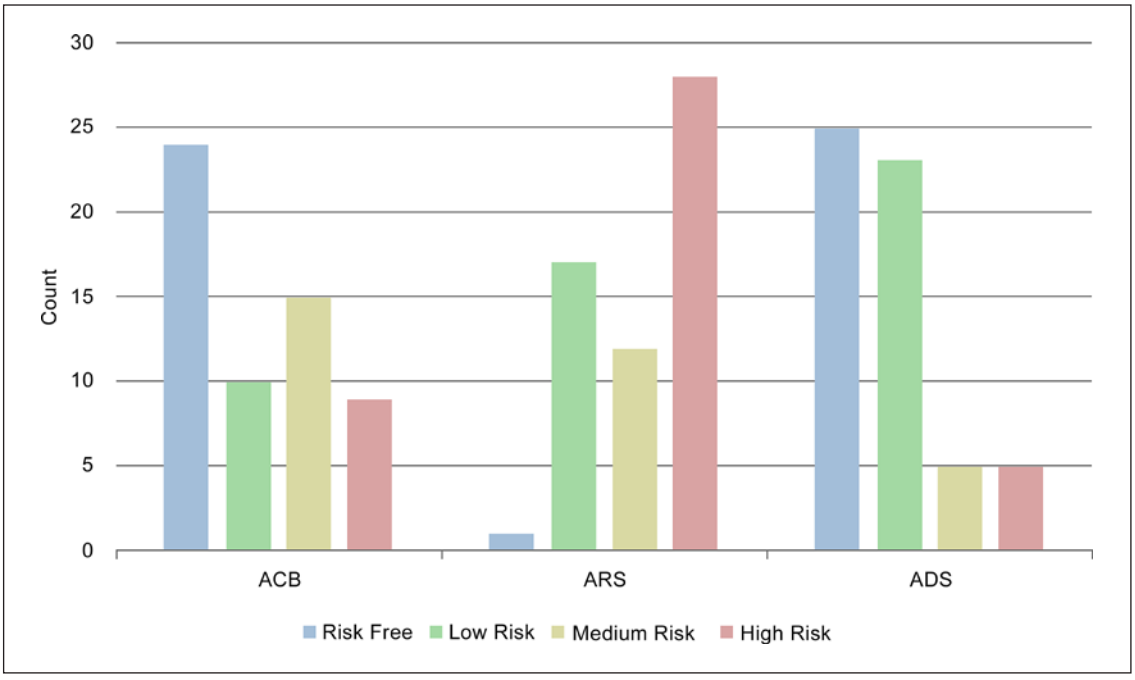


Fig. 1. Comparison of anticholinergic burden levels of patients with PD according to ACB, ARS, and ADS scales.

culator (https://www.parkinsonsmeasurement.org/toolBox/levodopaEquivalentDose.htm). The use of 5 or more total drugs per day was considered polypharmacy in this study.

Anticholinergic burden scales are drug lists that classify drugs according to their anticholinergic effects. The scales used in the literature are different in that they include drugs in their lists and give scores to the drugs. In this study, "Anticholinergic Cognitive Burden (ACB) Scale" [21], "Anticholinergic Risk Scale (ARS)" [22], and "Anticholinergic Drug Scale (ADS)" [23] were used to evaluate the anticholinergic burden of drugs. These best validated instruments are widely applied among older adults and are user-friendly in clinical practice [24, 25]. In these scales, drugs are categorized according to their anticholinergic properties by scoring from 0 to 3 (0; none or limited, 1; possible/moderate, 2; strong, 3; very strong). The anticholinergic effect in several investigations, ranging from in vitro studies to clinical studies, was taken into consideration while developing these scales. In vitro, receptor binding, or serum anticholinergic activity studies provide evidence for a possible impact (1 point), whereas clinical effects are the basis for strong scores (2 and 3 points). Calculations were made according to 3 different scales specified with a web portal software called "Anticholinergic Burden Calculator" (www.anticholinergicscales.es/).

Statistical Analysis

The descriptive statistics of the qualitative variables in the study are given as numbers and percentages, and the descriptive statistics of the quantitative variables are given as mean, median, SD, minimum, and maximum. Normal distribution assumption was examined using the Shapiro-Wilk test. Relationships between quantitative variables were analyzed using the Spearman correlation coefficient. Multiple linear regression analysis was used to examine the factors affecting the ACB, ARS, and ADS scores. Variables with p value up to 0.10 in univariate analysis results were included in the model with the enter method for multiple linear regression; variables that were significant in univariate analyses. The independent sample t test was used for the mean comparison of two independent groups, and the Mann-Whitney U test was used for the median comparison of two independent groups. To determine the factors that are effective in predicting the presence of polypharmacy, binary logistic regression analysis was performed, and estimated risk values and confidence intervals were given. Model explanatory was examined with the Nagelkerke R square value, and the fit of the model was examined with the Hosmer and Lemeshow test. The concordances between the scores were examined with Kendall's W test. The statistical significance level was taken as 0.05, and the SPSS (version 28) package program was used.

Results

Fifty-eight patients (41 male, 70%) with PD participated in our study. According to the MDS PD-MCI level 2 criteria, 26 (44.8%) patients were diagnosed with PD-MCI, and the cognition of 32 (55.2%) patients with PD was normal. The mean age of PD patients with normal cognition was 61.19 years (SD 9.05), while that of the MCI group was 65.65 years (SD 10.29). There were no significant difference between the age (p: 0.084) and gender (p:

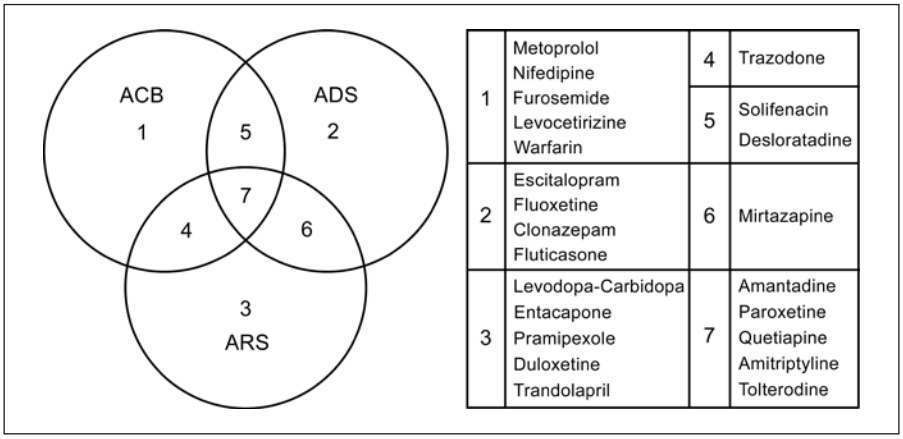


Fig. 2. Drugs with anticholinergic burden risk used by the patients with PD in ACB, ADS, ARS scales.

0.34) of the groups. The median education years of the PD-NC and PD-MCI groups were 5 years; there was no significant difference between the education levels of the groups (p: 0.23). Disease duration of PD-NC and PD-MCI patients was 6.5 and 6 years, and total UPDRS scores were 30 and 50, respectively. There was no significant difference between the disease duration (p: 0.41) and UPDRS scores of the groups (p: 0.18). The mean MoCA score of the PD-NC group was 25.30 (SD 2.5), while the mean score of the PD-MCI group was 20.04 (SD 3.24), and there was a significant difference between them ($p < 0.001$). All cognitive domain scores of the PD-MCI group were significantly impaired compared to PD patients with normal cognition (for attention and working memory, $p = 0.00$; for memory, executive functions, and language, $p < 0.001$; for visual-spatial functions, $p = 0.003$).

Patients were classified as risk free, low, moderate, and high risk according to ACB, ARS, and ADS scales. Risk groups of patients according to different scales are shown in the figure (Fig. 1). A statistically significant correlation was found between the scales for anticholinergic burden (ACB and ARS: $p < 0.001$, $r = 0.752$; ACB and ADS: $p < 0.001$, $r = 749$; ARS and ADS $p < 0.001$, $r = 0.595$). A significant concordance was observed between ACB, ARS, and ADS scores ($p < 0.001$; Kendall's W = 0.653). Antiparkinson, antidepressant, antihistaminic, antihypertensive, and drugs used in urinary diseases were found to be associated with anticholinergic burden. The drugs with anticholinergic burden risk used by the patients are shown in Figure 2 according to different scales.

Anticholinergic burden levels were compared between cognitive groups according to the ACB, ARS, and ADS scales (Fig. 3). There was no significant difference in anticholinergic burden between PD-MCI and PD-normal cognition patients ($p > 0.05$).The relationship between risk scores on the ACB, ARS, and ADS scales and various variables (age, disease duration, education, MoCA score, cognitive domain z-scores [attention, visuospatial functions, language, executive functions, memory], depression and anxiety score, MDS-UPDRS total and subscores, Hoehn-Yahr stage, levodopa equivalent dose, number of antiparkinsonian tablets and drugs daily, total number of drugs used daily, Schwab England score) in our study was investigated. Variables associated with anticholinergic burden in patients with PD according to the ACB, ARS, and ADS scales are presented in the table (Table 1).

In the regression analysis performed with the variables with significant correlation, the variables that most affected the anticholinergic burden were determined according to different scales. The total drug effect was statistically significant for the ACB and ADS variables ($p < 0.001$ for each). For ARS, the antiparkinson drug effect was found to be statistically significant ($p = 0.001$). Each increase in the total number of drugs increases the anticholinergic burden 0.293 times for ACB and 0.215 times for ADS. According to ARS, each increase in the number of antiparkinson drugs increases the anticholinergic burden by 0.617 times (Table 2).

In our study, polypharmacy was determined in 35 (60.3%) patients with PD. No correlation was found between the diagnosis of MCI and polypharmacy in PD ($\chi^2 = 0.02$, $p = 0.86$). The scores of the anticholinergic burden scales, cognitive and various clinical variables in patient groups with and without polypharmacy are compared. Anticholinergic burden score (for ACB $p < 0.001$, for ADS $p = 0.004$, for ARS $p < 0.001$), disease duration ($p = 0.02$), and the number of antiparkinson drugs ($p = 0.047$) were significantly different between patients with and without polypharmacy. In our study, according to the ACB and ADS scales, 44% and 60% of the patients, re-

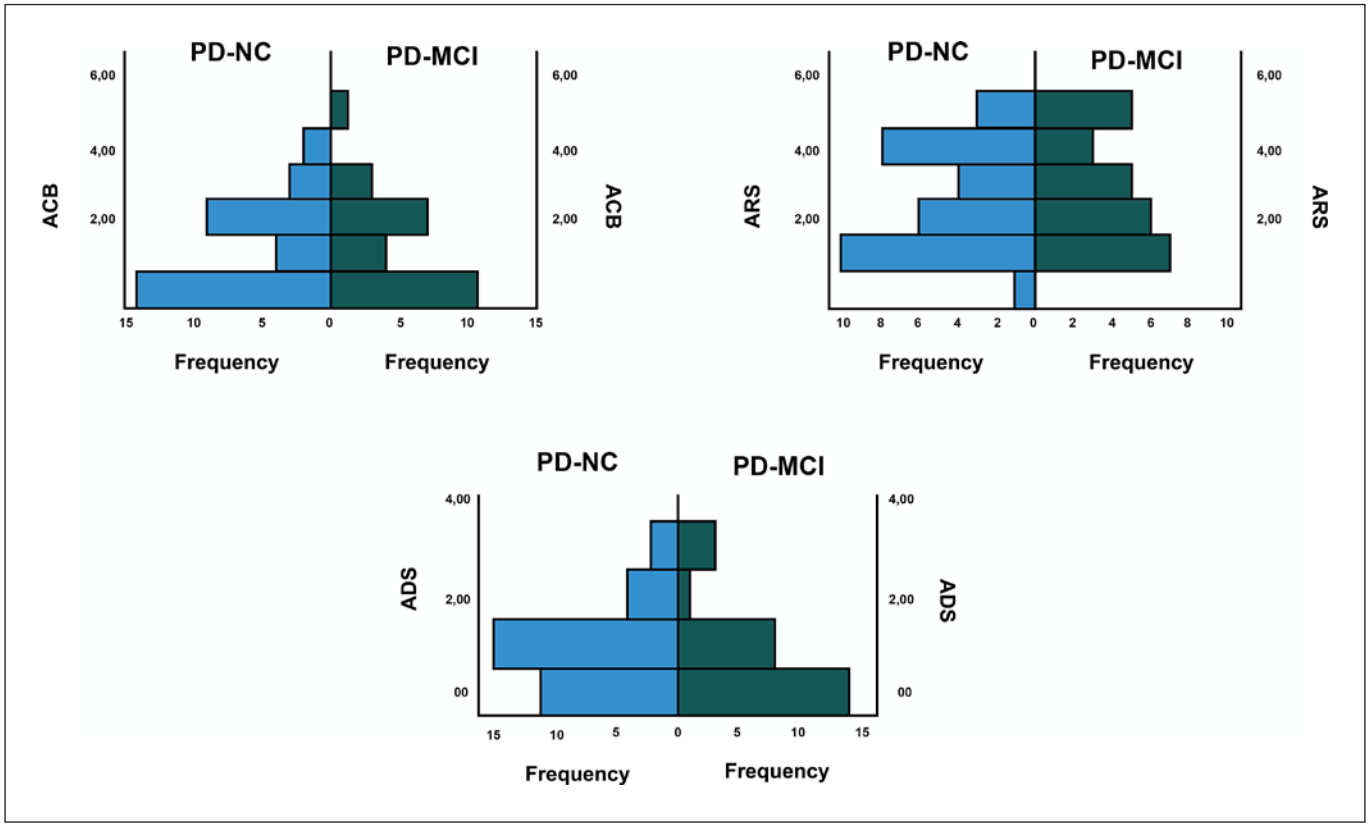


Fig. 3. Comparison of anticholinergic burdens of PD-MCI and PD-NC groups. ACB, Anticholinergic Cognitive Burden scale; ADS, Anticholinergic Drug Scale; ARS, Anticholinergic Risk Scale; PD-MCI, Parkinson's disease-mild cognitive impairment; PD-NC, Parkinson's disease-normal cognition.

Table 1. Variables with significant correlation with ACB, ARS, and ADS risk scores

	LEDD	AP tablet	AP drug	Total drug	Disease duration	Hoehn-Yahr stage
ACB						
r	0.411	0.421	0.402	0.525	0.371	0.323
p value	**0.001**	**0.001**	**0.002**	**<0.001**	**0.004**	**0.013**
ARS						
r	0.499	0.567	0.600	0.353	0.398	0.165
p value	**<0.001**	**<0.001**	**<0.001**	**0.006**	**0.002**	0.215
ADS						
r	0.187	0.260	0.275	0.504	0.228	0.161
p value	0.159	**0.048**	**0.036**	**<0.001**	0.086	0.226

ACB, Anticholinergic Cognitive Burden scale; ADS, Anticholinergic Drug Scale; ARS, Anticholinergic Risk Scale; LEDD, levodopa equivalent dose.

Table 2. Linear regression analysis of variables associated with ACB, ARS, and ADS risk score

	Unstandardized B	*p* value	95% confidence interval for B	
			lower bound	upper bound
ACB				
Disease duration	0.036	0.301	–0.033	0.106
Hoehn-Yahr stage	0.370	0.071	–0.032	0.773
AP drug	0.141	0.409	–0.199	0.481
Total drug	0.293	**<0.001**	0.142	0.444
LEDD	0.000	0.251	0.000	0.001
ARS				
Disease duration	0.059	0.117	–0.015	0.133
AP drug	0.617	**0.001**	0.252	0.983
Total drug	0.141	0.092	–0.023	0.303
LEDD	0.389	0.322	–3.91	0.011
ADS				
Disease duration	0.008	0.751	–0.045	0.062
AP drug	–0.009	0.934	–0.245	0.0225
Total drug	0.215	**<0.001**	0.009	0.336

For ACB scale, adjusted $R^2 = 0.364$, ANOVA $p < 0.005$, $F = 7.516$; for ARS scale, adjusted $R^2 = 0.417$, ANOVA $p < 0.001$, $F = 14.6$; for ADS scale, adjusted $R^2 = 0.170$, ANOVA $p = 0.004$, $F = 4.90$. ACB, Anticholinergic Cognitive Burden scale; ADS, Anticholinergic Drug Scale; ARS, Anticholinergic Risk Scale; LEDD, levodopa equivalent dose; AP, antiparkinson.

Table 3. Anticholinergic burden scales in predicting the presence of polypharmacy

	p value	OR	95% CI for EXP (B)	
			lower	upper
Model 1				
Disease duration	0.201	1.112	0.945	1.307
AP drug	0.797	1.091	0.562	2.117
ACB	**0.008**	2.408	1.252	4.630
Model 2				
Disease duration	0.129	1.131	0.965	1.325
AP drug	0.999	1.000	0.488	2.047
ARS	**0.050**	1.700	0.998	2.894
Model 3				
Disease duration	0.068	1.158	0.989	1.357
AP drug	0.380	1.322	0.709	2.466
ADS	**0.017**	2.733	1.194	6.253

Nagelkerke *R* square for model 1, 0.345; Hosmer and Lemeshow test $p = 0.475$. Nagelkerke *R* square for model 2, 0.254; Hosmer and Lemeshow test $p = 0.293$. Nagelkerke *R* square for model 3, 0.319; Hosmer and Lemeshow test $p = 0.506$. ACB, Anticholinergic Cognitive Burden scale; ADS, Anticholinergic Drug Scale; ARS, Anticholinergic Risk Scale; AP, antiparkinson.

spectively, were at high risk due to the use of a single drug with a high anticholinergic score (score of 3). According to the ARS scale, all patients at high risk are due to multiple drug use. Concomitant use of low anticholinergics is also an important problem in terms of anticholinergic burden.

Binary logistic regression analysis was performed in three different models for different anticholinergic burden scores for variables that were found to be significant between patients with and without polypharmacy. The anticholinergic burden is predictive of polypharmacy risk according to all anticholinergic burden scales. The strongest

association with polypharmacy was observed between the ADS and ACB scales, with each increase in ADS and ACB increasing the risk of polypharmacy by 2.7 and 2.4 times, respectively. It has been determined that the binary logistics models have good fit (Hosmer and Lemeshow $p = 0.944$). The explanatory percentages of the models were obtained as 0.345, 0.254, and 0.319, respectively. The model with the highest explanatory rate is model 1 (Table 3).

Discussion

In this cross-sectional study, anticholinergic burden and polypharmacy were investigated in patients with PD-MCI. Although the risk scores of antiparkinson and other drugs were different among the 3 scales, significant concordance was observed for total anticholinergic burden. No significant correlation was found between the cognition and anticholinergic burden in patients with PD-MCI.

Anticholinergic drugs can be used for the treatment of motor and nonmotor symptoms of PD. The 2018 Update of International Parkinson and Movement Disorder Society Evidence-Based Medicine Review indicated that anticholinergics are "likely efficacious" treatments of motor symptoms, for symptomatic monotherapy or as a symptomatic adjunct therapy in early or stable PD patients [26]. For treatment of nonmotor symptoms, "insufficient evidence" for urinary antispasmodics has been reported [27]. In our study, the risks associated with anticholinergic burden in patients ranged from 58.6% to 98.3% according to the ACB, ARS, and ADS scales. In the literature, the anticholinergic burden was reported as 53.6% [28] and 58.2% [29] according to Duran scale, 42.6% [12] according to ADS, and 84.9% [30] according to ARS in Parkinson's patients. The reason why the rate of patients at risk is higher in the ARS scale compared to the other two scales is the different evaluation of the anticholinergic burden of the antiparkinson drugs. While only amantadine was associated with anticholinergic burden on the ACB and ADS scales, additionally, levodopa-carbidopa/benserazide, entacapone, and pramipexole were scored as low risk on the ARS scale. Similar to the literature, patients with PD had a high risk of anticholinergic burden. Anticholinergic burden increase has been found to be associated with adverse outcomes among patients with PD [30, 31]. Anticholinergic burden should be considered in the selection of drugs, especially for comorbid conditions in patients with PD.

In our study, no significant relationship was found between cognition and anticholinergic burden and polypharmacy in PD-MCI. Anticholinergic medications' adverse effects have been examined in cross-sectional and longitudinal investigations including healthy people, patients with MCI and dementia. Ehrt et al. [32] reported that Mini-Mental State Examination (MMSE) scores of patients who used anticholinergic drugs decreased significantly more in the 8-year follow-up of Parkinson's patients. It has been reported in the literature that the use of anticholinergics and exposure of heavy anticholinergics were associated with an increased risk of dementia [2, 3, 8, 33]. However, there is conflicting information about the effects of anticholinergic medications on cognition and whether or not these effects are reversible [34]. In the Cochrane review, it was stated that there is low-certainty evidence that the use of anticholinergic drugs in the elderly without cognitive impairment will lead to cognitive impairment [1]. According to a review, ten studies showed statistically significant associations between high anticholinergic burden and worse cognitive outcomes, while nine studies found no significant association [35]. Heterogeneity of the results could be due to the use of the MMSE, which is a limited neuropsychological test to identify subtle changes induced by drugs [25] and heterogeneity of the cholinergic reserves of the participants [36]. Studies investigating the relationship between PD-MCI and anticholinergic burden are limited in the literature [12, 13], and no relationship was found between them. A detailed neuropsychological evaluation was performed in our study. In this respect, it was more sensitive to detecting cognitive dysfunction than studies using screening tests such as MMSE. However MCI is a heterogeneous group; not all patients with MCI progress to dementia, and some return to normal cognition [37]. Therefore, longitudinal studies considering the heterogeneity of MCI patients may observe the relation between cognition and anticholinergic burden more clearly. In addition, the cognitive impairment due to anticholinergic burden could not be detected in present study, perhaps due to the fact that the age and duration of the disease were not advanced and the number of patients was small.

There is no gold standard scale to evaluate anticholinergic burden, and there are differences in scoring between frequently used scales [25]. The literature on concordance of scales is inconsistent. While Naples et al. [38] reported moderate agreement (moderate concordance) between the scales we used, good agreement was reported between ACB and ADS and weaker agreement with the others in another research [39]. Lozana-Ortega et al. [24] also compared the six anticholinergic scales and determined that the ACB and ADS scales were well suited for observation-

al studies as they included the largest number of drugs and were confirmed by adverse clinical outcomes. No matter whatever anticholinergic scale was employed in a population cohort, it was observed that anticholinergic burden was highly associated with poor future health outcomes [40]. Anticholinergic burdens of antiparkinson drugs are scored differently on scales. Therefore, we wanted to compare the scales in patients with PD. Although the ACB, ARS, and ADS scales scored antiparkinson drugs differently, we observed a significant concordance in their cumulative scores. In addition, the relationships of these scales with cognition and polypharmacy were similar. However, the ACB scale was more powerful in describing polypharmacy, while the ARS scale was more sensitive in detecting the effect of antiparkinson drugs.

In our study, the total number of drugs was determined as a predictive variable for anticholinergic burden for all scales. Clinically significant anticholinergic burden may result from the concomitant use of several low-risk drugs [29]. Our findings support this situation. Therefore, polypharmacy is an important risk for anticholinergic burden. Polypharmacy was seen in 60% of our patients, and there was a significant relationship between anticholinergic burden and polypharmacy. In addition to the use of drugs with high anticholinergic scores, the concomitant use of drugs with low scores was also an important problem for anticholinergic burden.

This study has a number of important limitations that should be noted when interpreting the results. Our sample size was small, and there were no patients with anticholinergic burden scores higher than 6. A clinically significant relationship between anticholinergic burden and cognition may not be detected due to the reason that highly effective drugs were not used frequently in our patients. In addition, we did not evaluate the over-the-counter drug use of the patients, and patients may have anticholinergic burden due to their nonprescribed drug use.

Conclusion

Patients with PD have a high risk of anticholinergic burden and polypharmacy. The increase in the number of drugs was determined as a variable predicting anticholinergic burden. So, care should be exercised while selecting medications for comorbidities, since antiparkinson treatment poses a risk of anticholinergic burden in patients with PD. Concurrent use of medications with limited/low anticholinergic potential can result in clinically considerable anticholinergic burden. Clinical use of anticholinergic risk scales is practical and beneficial. Although the drugs received different scores, there was consistency between the scales' predictions of the overall anticholinergic burden in patients with PD.

Statement of Ethics

This study was performed in accordance with the ethical standards of the Declaration of Helsinki. Ethics approval was obtained from the Ethics Committee of Istanbul Faculty of Medicine, Istanbul University (December 22, 2017/21). After the study was explained, written informed consent was obtained from all the participants before the study began.

Conflict of Interest Statement

The authors have no conflicts of interest to declare.

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Author Contributions

Betul Sumbul Sekerci: conception and design, acquisition of data, analysis and interpretation of data, drafting of the manuscript, final approval of the version to be published, and agreement to be accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved. Basar Bilgic: conception and design, analysis and interpretation of data, final approval of the version to be published, and agreement to be accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved. Ozge Pasin: analysis and interpretation of data, drafting of the manuscript, final approval of the version to be published, and agreement to be accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved. Murat Emre and Hasmet A. Hanagası: critical revision of the manuscript for important intellectual content, final approval of the version to be published, and agreement to be accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved.

Data Availability Statement

The data in this study are available upon written request to the corresponding author.

References

1 Taylor-Rowan M, Edwards S, Noel-Storr AH, McCleery J, Myint PK, Soiza R, et al. Anticholinergic burden (prognostic factor) for prediction of dementia or cognitive decline in older adults with no known cognitive syndrome. Cochrane Database Syst Rev. 2021;5(5):Cd013540.

2 Gray SL, Anderson ML, Dublin S, Hanlon JT, Hubbard R, Walker R, et al. Cumulative use of strong anticholinergics and incident dementia: a prospective cohort study. JAMA Intern Med. 2015;175(3):401–7.

3 Coupland CAC, Hill T, Dening T, Morriss R, Moore M, Hippisley-Cox J. Anticholinergic drug exposure and the risk of dementia: a nested case-control study. JAMA Intern Med. 2019;179(8):1084–93.

4 Myint PK, Fox C, Kwok CS, Luben RN, Wareham NJ, Khaw KT. Total anticholinergic burden and risk of mortality and cardiovascular disease over 10 years in 21,636 middle-aged and older men and women of EPIC-Norfolk prospective population study. Age Ageing. 2015;44(2):219–25.

5 National Institute for Health and Care Excellence. Guidelines. Dementia: Assessment, management and support for people living with dementia and their carers. London: National Institute for Health and Care Excellence (NICE); 2018.

6 Carnahan RM, Lund BC, Perry PJ, Pollock BG. A critical appraisal of the utility of the serum anticholinergic activity assay in research and clinical practice. Psychopharmacol Bull. 2002;36(2):24–39.

7 Lertxundi U, Domingo-Echaburu S, Hernandez R, Peral J, Medrano J. Expert-based drug lists to measure anticholinergic burden: similar names, different results. Psychogeriatrics. 2013;13(1):17–24.

8 Grossi CM, Richardson K, Fox C, Maidment I, Steel N, Loke YK, et al. Anticholinergic and benzodiazepine medication use and risk of incident dementia: a UK cohort study. BMC Geriatr. 2019;19(1):276.

9 Hafdi M, Hoevenaar-Blom MP, Beishuizen CRL, Moll van Charante EP, Richard E, van Gool WA. Association of benzodiazepine and anticholinergic drug usage with incident dementia: a prospective cohort study of community-dwelling older adults. J Am Med Dir Assoc. 2020;21(2):188–93.e3.

10 Chuang YF, Elango P, Gonzalez CE, Thambisetty M. Midlife anticholinergic drug use, risk of Alzheimer's disease, and brain atrophy in community-dwelling older adults. Alzheimers Dement. 2017;3(3):471–9.

11 Risacher SL, McDonald BC, Tallman EF, West JD, Farlow MR, Unverzagt FW, et al. Association between anticholinergic medication use and cognition, brain metabolism, and brain atrophy in cognitively normal older adults. JAMA Neurol. 2016;73(6):721–32.

12 Yarnall AJ, Lawson RA, Duncan GW, Breen DP, Khoo TK, Brooks D, et al. Anticholinergic load: is there a cognitive cost in early Parkinson's disease? J Parkinsons Dis. 2015;5(4):743–7.

13 Cicero CE, Monastero R, Terravecchia C, Donzuso G, Luca A, Baschi R, et al. Influence of drugs on mild cognitive impairment in Parkinson's disease: evidence from the PACOS study. Curr Neuropharmacol. 2022;20(5):998–1003.

14 Masnoon N, Shakib S, Kalisch-Ellett L, Caughey GE. What is polypharmacy? A systematic review of definitions. BMC Geriatr. 2017;17(1):230.

15 Bektay MY, Gökçe M, Selvitop R, Bolat E, Yildiz GB. Investigation of the effects of polypharmacy on cognitive functions: cohort study. Cohort Study. 2021;55(1s):s312–7.

16 Cheng CM, Chang WH, Chiu YC, Sun Y, Lee HJ, Tang LY, et al. Association of polypharmacy with mild cognitive impairment and cognitive ability: a nationwide survey in Taiwan. J Clin Psychiatr. 2018;79(6):17m12043.

17 Niikawa H, Okamura T, Ito K, Ura C, Miyamae F, Sakuma N, et al. Association between polypharmacy and cognitive impairment in an elderly Japanese population residing in an urban community. Geriatr Gerontol Int. 2017;17(9):1286–93.

18 Khezrian M, McNeil CJ, Myint PK, Murray AD. The association between polypharmacy and late life deficits in cognitive, physical and emotional capability: a cohort study. Int J Clin Pharm. 2019;41(1):251–7.

19 Emre M, Aarsland D, Brown R, Burn DJ, Duyckaerts C, Mizuno Y, et al. Clinical diagnostic criteria for dementia associated with Parkinson's disease. Mov Disord. 2007;22(12):1689–707; quiz 1837.

20 Litvan I, Goldman JG, Tröster AI, Schmand BA, Weintraub D, Petersen RC, et al. Diagnostic criteria for mild cognitive impairment in Parkinson's disease: movement disorder society task force guidelines. Mov Disord. 2012;27(3):349–56.

21 Boustani M, Campbell N, Munger S, Maidment I, Fox C. Impact of anticholinergics on the aging brain: a review and practical application. Impact Antich Aging Brain Rev Pract Appl. 2008;4(3):311–20.

22 Rudolph JL, Salow MJ, Angelini MC, McGlinchey RE. The anticholinergic risk scale and anticholinergic adverse effects in older persons. Arch Intern Med. 2008;168(5):508–13.

23 Carnahan RM, Lund BC, Perry PJ, Pollock BG, Culp KR. The anticholinergic drug scale as a measure of drug-related anticholinergic burden: associations with serum anticholinergic activity. J Clin Pharmacol. 2006;46(12):1481–6.

24 Lozano-Ortega G, Johnston KM, Cheung A, Wagg A, Campbell NL, Dmochowski RR, et al. A review of published anticholinergic scales and measures and their applicability in database analyses. Arch Gerontol Geriatr. 2020;87:103885.

25 Salahudeen MS, Hilmer SN, Nishtala PS. Comparison of anticholinergic risk scales and associations with adverse health outcomes in older people. J Am Geriatr Soc. 2015;63(1):85–90.

26 Fox SH, Katzenschlager R, Lim S-Y, Barton B, de Bie RMA, Seppi K, et al. International Parkinson and movement disorder society evidence-based medicine review: update on treatments for the motor symptoms of Parkinson's disease. Mov Disord. 2018;33(8):1248–66.

27 Seppi K, Ray Chaudhuri K, Coelho M, Fox SH, Katzenschlager R, Perez Lloret S, et al. Update on treatments for nonmotor symptoms of Parkinson's disease-an evidence-based medicine review. Mov Disord. 2019;34(2):180–98.

28 Lertxundi U, Isla A, Solinis MA, Domingo-Echaburu S, Hernandez R, Peral-Aguirregoitia J, et al. Anticholinergic burden in Parkinson's disease inpatients. Eur J Clin Pharmacol. 2015;71(10):1271–7.

29 De Germay S, Montastruc JL, Rousseau V, Chebane L, Bondon-Guitton E, Moulis F, et al. Atropinic (anticholinergic) burden in Parkinson's disease. Mov Disord. 2016;31(5):632–6.

30 Crispo JAG, Willis AW, Thibault DP, Fortin Y, Hays HD, McNair DS, et al. Associations between anticholinergic burden and adverse health outcomes in Parkinson disease. PLoS One. 2016;11(3):e0150621.

31 Rajan R, Saini A, Verma B, Choudhary N, Gupta A, Vishnu VY, et al. Anticholinergics may carry significant cognitive and gait Burden in Parkinson's disease. Mov Disord Clin Pract. 2020;7(7):803–9.

32 Ehrt U, Broich K, Larsen JP, Ballard C, Aarsland D. Use of drugs with anticholinergic effect and impact on cognition in Parkinson's disease: a cohort study. J Neurol Neurosurg Psychiatr. 2010;81(2):160–5.

33 Sheu JJ, Tsai MT, Erickson SR, Wu CH. Association between anticholinergic medication use and risk of dementia among patients with Parkinson's disease. Pharmacotherapy. 2019;39(8):798–808.

34 López-Álvarez J, Sevilla-Llewellyn-Jones J, Agüera-Ortiz L. Anticholinergic drugs in geriatric psychopharmacology. Front Neurosci. 2019;13:1309.

35 Kersten H, Wyller TB. Anticholinergic drug burden in older people's brain – how well is it measured? Basic Clin Pharmacol Toxicol. 2014;114(2):151–9.

36 Collamati A, Martone AM, Poscia A, Brandi V, Celi M, Marzetti E, et al. Anticholinergic drugs and negative outcomes in the older population: from biological plausibility to clinical evidence. Aging Clin Exp Res. 2016; 28(1):25–35.
37 Malek-Ahmadi M. Reversion from mild cognitive impairment to normal cognition: a meta-analysis. Alzheimer Dis Assoc Disord. 2016;30(4):324–30.
38 Naples JG, Marcum ZA, Perera S, Gray SL, Newman AB, Simonsick EM, et al. Concordance between anticholinergic burden scales. J Am Geriatr Soc. 2015;63(10):2120–4.
39 Pont LG, Nielen JTH, McLachlan AJ, Gnjidic D, Chan L, Cumming RG, et al. Measuring anticholinergic drug exposure in older community-dwelling Australian men: a comparison of four different measures. Br J Clin Pharmacol. 2015;80(5):1169–75.
40 Hanlon P, Quinn TJ, Gallacher KI, Myint PK, Jani BD, Nicholl BI, et al. Assessing risks of polypharmacy involving medications with anticholinergic properties. Ann Fam Med. 2020;18(2):148–55.