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ORIGINAL ARTICLE

Association of anticholinergic burden with Parkinson's disease severity and stage

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ABSTRACT

Objectives: The study aimed to investigate the association of anticholinergic burden with polypharmacy, the Movement Disorders Society Unified Parkinson's Disease Rating Scale (MDS-UPDRS), and the modified Hoehn and Yahr (HY) staging system in Parkinson's disease (PD).

Patients and methods: The cross-sectional study included 75 patients (38 males, 37 females; mean age: 65.7±9.6 years; range, 32 to 86 years) who were admitted between January 2023 and January 2024. Demographic characteristics, systemic diseases, medications, MDS-UPDRS, and modified HY were recorded. Polypharmacy was defined as the use of five or more medications at the same time. The anticholinergic burden was calculated using the Anticholinergic Cognitive Burden (ACB) scale. Patients were divided into two groups: those with an ACB risk score ≥3 (high risk) and those with a risk score <3 (low risk).

Results: When analyzed according to ACB scale risk status, 41 patients with PD were found to be at high risk for anticholinergic burden (score ≥3). The presence of at least one comorbid disease was more common in the high-risk group than in the low-risk group ($p<0.05$). The presence of unipolar depression was higher in the high-risk group ($p=0.001$). Frequency of polypharmacy was higher in the high-risk group (73.2% *vs.* 32.4%; $p=0.001$). In regression analysis, a high ACB score was statistically associated with modified HY Stage 4 when confounding factors were excluded (odds ratio=12.80; $p=0.030$).

Conclusion: Patients with polypharmacy in PD had higher ACB scores (>3) and depression as a comorbidity in these patients. A high ACB risk score was associated with modified HY Stage 4 when adjusted for confounding factors. The anticholinergic risk might be highest in the advanced stage of PD. Therefore, patients diagnosed with PD should be questioned about their drug history and evaluated for anticholinergic drug use at every visit.

Keywords: Anticholinergic burden, Parkinson disease, polypharmacy.

Parkinson's disease (PD) is a neurodegenerative disease whose frequency is increasing day by day with the increasing elderly population globally, and the number of these patients is expected to double by 2040.[1] Although the exact pathogenesis is unknown, dopamine denervation due to Lewy body accumulation and cell death in the substantia nigra appear to be the primary neuropathology, but nondopaminergic or extranigral involvement is more prominent for nonmotor symptoms. The diagnosis of PD is clinical and includes bradykinesia, resting tremor, rigidity, and postural instability, with an absence of red flags.[2] Following a prodromal phase with nonmotor symptoms such as anosmia, constipation, and rapid eye movement sleep behavior disorder that may last for years, the disease progresses to include motor symptoms.

The Movement Disorders Society Unified Parkinson's Disease Rating Scale (MDS-UPDRS) is the most preferred scale for the evaluation of PD. The MDS-UPDRS is the most widely used tool in PD follow-up. It was developed by Fahn et al.[3] in 1987, and the Movement Disorders Society revised

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it in 2009.[4] The scale has different clinical features, including motor and nonmotor symptoms in four subsections, and consists of 50 items. Each item is given a score between 0 and 4, with a maximum range of 0 to 200.[5]

Clinical symptom progression in PD is defined using the Hoehn and Yahr (HY) staging system that Hoehn and Yahr[6] developed in 1967. The modified HY system is a descriptive staging scale used to assess disability and impairment due to clinical disease progression from 0 to 5.

Currently, there is no proven disease-modifying or neuroprotective treatment for PD, and symptomatic treatment based mainly on dopaminergic replacement or modulation is widely used.[1] Levodopa, dopamine agonists, and monoamine oxidase B inhibitors are commonly used in the initial treatment of PD, whereas apomorphine, levodopa gel, and deep brain stimulation are options in the advanced stages. Anticholinergics are no longer preferred in PD due to the risk of cognitive decompensation.[7]

Polypharmacy is defined as the consumption of five or more medications, and polypharmacy has been rapidly increasing in recent years due to developments in the pharmaceutical industry, easier access to health institutions, and advances in diagnosis and treatment. According to research, polypharmacy is linked to more drug interactions, more adverse drug reactions, less adherence to treatment, more frailty, more hip fractures, more falls, and more hospitalizations. Researchers are also more interested in the adverse effects of more anticholinergic use on these patients.[8] Studies demonstrated that, in parallel with the increase in the number of drugs in the elderly receiving outpatient treatment, there were increased side effects and approximately 10% of hospitalizations due to drug side effects, particularly in the geriatric age group.[9,10]

The cumulative effect of anticholinergic drugs in the body is called the anticholinergic load.[11] Anticholinergic drugs are drugs that block the binding of acetylcholine to muscarinic receptors, and their side effects develop depending on the properties of anticholinergic drugs that block the muscarinic receptor. They most commonly manifest peripherally as dry mouth, dry eyes, constipation, blurred vision, and increased heart rate, while in the central nervous system, they manifest as dizziness, sedation, confusion, delirium, and even cognitive disorders.[11,12] Muscarinic receptors come in different subtypes, from M1 to M5. The most common type in the brain and the spinal cord are M1 receptors. These receptors are important for executive functions and episodic memory in the hippocampus and prefrontal cortex.[8]

Currently, there are many anticholinergic risk scales that are used in studies shown to be effective in clinical practice.[8,13] These scales provide practicality for healthcare professionals in predicting anticholinergic-related adverse effects, particularly in the elderly population, increasing awareness, and preventing side effects before they develop through close follow-up.[12,13]

Anticholinergic drugs are a heterogeneous group of drugs, and there appears to be little awareness among healthcare professionals about their effects and interactions with other drugs.[14] More research is being conducted on the effects and side effects of anticholinergics, cholinergic burden, the higher risk of dementia, and the increased brain atrophy, dysfunction, and cognitive decline, which were linked to loss of cognitive performance, as well as dementia.[13-15] In addition to cognitive effects, anticholinergic load was also associated with falls, fractures, and mortality.[16-18] These effects of anticholinergic drugs, which are used more often in older patients, also change depending on how quickly the drug is eliminated or the dose given to the elderly. However, more research is needed to fully confirm this as a good clinical outcome when the anticholinergic load is reduced.[19] The following scales are used in research: the Anticholinergic Drug Scale, the Anticholinergic Cognitive Burden (ACB) scale, the Anticholinergic Risk Scale, the Duran Scale, the Salahudeen Scale, and the new CRIDECO Anticholinergic Load Scale (CALS). Country-specific scales such as the German Anticholinergic Burden Scale (GABS) and the Korean Anticholinergic Burden Scale are also becoming more common. It appears that new scales will be developed in the future as awareness of this subject increases.[8]

Currently, the evaluation of anticholinergic load uses serum radioreceptor anticholinergic activity assays and anticholinergic load scales evaluated by expert-based drug lists.[20] The ACB scale determines the impact of anticholinergic medications. It was introduced in 2008 and is widely used to estimate anticholinergic burden and its relationship with cognitive impairment.[21] Furthermore, it is the most easily accessible and most frequently used

scale in practice.[20] Scores range from 0 to 9 according to the affinity of the drugs to muscarinic receptors and their effects on cognition, with 0 indicating no burden and 3 or above indicating high risk. The anticholinergic burden of 88 drugs is calculated in the ACB scale. The CALS, one of the new scales developed, includes 217 drugs.[8] A study comparing the scales rated the ACB and GABS scales as having the highest quality rating. However, studies demonstrated that no anticholinergic burden scale can be considered the gold standard.[20,22] Patients with PD are more likely to experience polypharmacy since comorbidities are frequently present.

This study aimed to investigate the relationship between the total anticholinergic burden of patients with PD measured by using the ACB scale and the severity, progression and functional disability of the patients with PD measured by using MDS-UPDRS and modified HY scale. In addition, this study aimed to increase the awareness of healthcare professionals about the effects of polypharmacy and cholinergic burden in PD.

PATIENTS AND METHODS

This cross-sectional study was conducted with 75 patients (38 males, 37 females; mean age: 65.7±9.6 years; range, 32 to 86 years) with PD diagnosed according to the criteria of the Movement Disorders Association[2] at the Balıkesir University Hospital between January 2023 and January 2024. Age, sex, disease duration, creatine, and albumin values and all regular medications in the last six months were documented by interviewing the patient or querying the system. The MDS-UPDRS scores and modified HY stages were assessed by a physician experienced in movement disorders for newly admitted PD patients, and patients whose MDS-UPDRS scores and modified HY stages were fully recorded in the last 1 year were included in the study. The modified HY staging system was used for clinical staging of PD. The study protocol was approved by the Balıkesir University Faculty of Medicine Clinical Research Ethics Committee (date: 21.02.2024, no: 2024/18). Written informed consent was obtained from all participants. The study was conducted in accordance with the principles of the Declaration of Helsinki.

The MDS-UPDRS consists of nonmotor features of daily life experiences (maximum of 52 points), motor features of daily life experiences (maximum of 52 points), motor examination (maximum of 132 points), and motor complications (maximum of 24 points), which are scored between 0 and 4 according to the severity of the findings. The scale consists of four subsections and 55 items.

The scale includes stages from 0 to 5. Stage 0 indicates no symptoms of the disease, and Stage 5 defines patients who are bedridden or wheelchair-bound without assistance.

Anticholinergic burden was defined as the cumulative effect on an individual taking one or more drugs with anticholinergic activity. The total anticholinergic burden for each patient was calculated by entering all medications used by the patients into the ACB scale at https://www.acbcalc.com. Each drug was scored between 0 and 3 according to the affinity of the drug to muscarinic receptors and the effects on cognition, with a total score of 3 points or more being considered high risk.[23] All patients were divided into two groups according to ACB risk: those with an ACB risk score ≥3 (high risk) and those with a risk score <3 (low risk).

Statistical analysis

Data were analyzed using IBM SPSS version 22.0 (IBM Corp., Armonk, NY, USA). Categorical variables were expressed as frequency and percentage, and continuous data were expressed as mean ± standard deviation (SD). Continuous variables were evaluated by the Kolmogorov-Smirnov test for normal distribution. All of the variables except for age were not normally distributed. Therefore, age was evaluated using the independent sample t-test, and other continuous variables were evaluated using the Mann-Whitney U test. Differences between categorical variables were evaluated using the chi-square test and Fisher's exact test. Correlation between ACB risk and other continuous data was performed using Spearman's correlation analysis. Multinomial logistic regression analysis was performed to evaluate the effects of polypharmacy with ACB high-risk category on the HY stage. Model 1 was adjusted for demographic features including age and sex. Model 2 was adjusted for Model 1 plus comorbidities. The odds ratio (OR) and 95% confidence intervals (CIs) were calculated for the association between HY stages and high-risk ACB scores with polypharmacy. A p-value <0.05 was considered statistically significant.

TABLE 1
The comparison of demographic features, including age, sex, duration and severity of PD, presence of comorbidities, and laboratory findings between high-risk (≥3) and low-risk (<3) groups

	ACB >3 (n=41)		ACB <3 (n=34)		
	%	Mean±SD	%	Mean±SD	*p*
Age (year)		66.5±7.8		64.9±11.5	0.467
Sex					
Female	51.2		47.1		0.720
Education year (>8 year)	34.1		38.1		0.403
Parkinson duration (year)		4.97±3.79		4.79±4.91	0.366
UPDRS (motor)		39.60±32.67		27.50±22.57	0.139
UPDRS (non-motor)		9.07±6.42		7.55±7.35	0.168
Hoen and Yahr Scale		2.04±1.16		1.58±0.85	0.079
Comorbid disease (>1)	82.9		55.9		0.010
Hypertension	43.9		35.3		0.449
Diabetes mellitus	29.3		11.8		0.065
Cardiovascular disease	7.3		17.6		0.171
Hyperlipidemia	14.6		17.6		0.723
Depression	41.5		8.8		0.001
Osteoporosis	14.6		2.9		0.083
Polypharmacy (>5 medicine use)	73.2		32.4		<0.001
Serum creatinine level (mg/dL)		0.90±0.21		0.90±0.24	0.903
Albumin level (g/L)		40.58±3.05		41.88±3.40	0.064

PD: Parkinson's disease; ACB: Anticholinergic burden scale; SD: Standard deviation; UPDRS: Unified Parkinson disease rating scale.

RESULTS

When examined according to ACB scale, 41 patients with PD were found to be at high risk (score ≥3). Demographic characteristics, including age and sex, and laboratory findings, including serum creatinine and albumin levels, were statistically similar between the high- and low-risk groups (p<0.05). The presence of at least one comorbid disease was observed more frequently in the high-risk group than in the low-risk group (p<0.05).

TABLE 2
The correlation between ACB risk scores and age, number of medications, the duration and severity scores of PD, and serum creatinine and albumin levels

	Rho value	*p*
Age	0.046	0.698
Duration of Parkinson's disease	0.128	0.273
UPDRS motor findings	0.161	0.167
UPDRS non-motor findings	0.244	0.035
Hoehn and Yahr Scale	0.192	0.100
Medication number	0.650	<0.001
Creatinine level	−0.016	0.894
Albumin level	−0.182	0.119

ACB: Anticholinergic burden scale; UPDRS: Unified Parkinson disease rating scale.

The presence of unipolar depression was higher in the high-risk group (p=0.001). The frequency of polypharmacy (≥5 medication use) was statictically higher in the high-risk group (73.2% *vs.* 32.4%; p<0.001). Additionally, PD duration, MDS-UPDRS, and modified HY stage were similar in both groups (p>0.05; Table 1).

In Spearman's correlation analysis, ACB risk score was observed to be statistically correlated with the number of medications (rho: 0.650; p<0.001) and MDS-UPDRS nonmotor findings (rho: 0.244; p=0.035). The other continuous variables were not correlated with the ACB score (p<0.05; Table 2). When modified HY Stage 1 was taken as a reference category in terms of PD staging, it was observed that Stages 2 and 3 were not significant in terms of high-risk ACB scores and polypharmacy (p<0.05), while in Stage 4, high-risk ACB scores were found to be statistically significant, independent of age, sex,

TABLE 3
Evaluation of the effects of polypharmacy and high-risk ACB scores according to HY stages

	ACB risk score (>3)			Polypharmacy (>5 medication use)		
Hoehn and Yahr Scale	OR	95% CI	*p*	OR	95% CI	*p*
2						
Unadjusted	1.83	0.58-5.71	0.296	1.31	0.42-4.04	0.632
Model 1*	1.83	0.58-5.78	0.299	1.22	0.37-3.96	0.734
Model 2**	2.44	0.69-8.54	0.102	2.41	0.49-11.79	0.275
3						
Unadjusted	0.93	0.21-4.01	0.926	3.68	0.67-20.01	0.131
Model 1*	0.92	0.21-4.00	0.920	3.70	0.64-21.39	0.143
Model 2**	0.85	0.18-3.99	0.845	6.93	0.60-79.90	0.121
4						
Unadjusted	9.33	1.06-81.91	**0.044**	1.31	0.30-5.64	0.712
Model 1*	9.78	1.06-81.75	**0.044**	1.09	0.24-5.02	0.904
Model 2**	12.80	1.27-128.80	**0.030**	1.44	0.24-8.43	0.684

ACB: Anticholinergic burden scale; HY: Hoehn and Yahr; CI: Confidence interval; OR: Odds ratio; * Model 1: Adjusted for age and sex; ** Model 2: Adjusted for age, sex, and comorbidity.

and comorbidities (OR=12.80, 95% CI: 1.27-128.80, p=0.030; Table 3).

DISCUSSION

The present study underlined that anticholinergic burden might be related to the severity of PD. This association of between anticholinergic burden and modified HY Stage 4 existed independently of confounding factors.

Anticholinergic drugs are widely used among older adults to treat bladder dysfunction, psychotic disorders, and pain that increases with advanced age, and they have easy access to these drugs.[24] Since 1867, the antiparkinsonian effect of anticholinergics was recognized, and they were used as the sole treatment for a long time.[25] Today, anticholinergic side effects of commonly used drugs are frequently encountered. Polypharmacy and the accompanying increased cholinergic load bring new problems, such as increased cognitive problems, particularly in elderly patients.[8] In a study conducted in elderly patients, a relationship was found between ACB scores, polypharmacy, and nutritional status.[26] Similarly, patients with polypharmacy were approximately 2.5 times more likely to have high-risk ACB scores in our study.

Studies on anticholinergic burden have focused on impairments in cognitive function. These studies have been associated with increased brain atrophy, dysfunction, and cognitive decline, as well as an increased risk of dementia.[8,27,28] In contrast to anticholinergic drugs, acetylcholinesterase inhibitors (donepezil hydrochloride, rivastigmine tartrate, and galantamine hydrobromide), which increase cholinergic activity, are widely used in patients with dementia and were shown to improve cognitive features.[29] However, drugs with anticholinergic activity are widely used together with drugs that increase cholinergic activity, particularly in patients with dementia of advanced age. Individuals with PD may be more likely to be negatively affected by these types of anticholinergic drugs since their brains are losing cholinergic pathways and connections.[30]

Parkinson's disease is a neurodegenerative disorder in which cognitive deficits are common in addition to widespread motor symptoms. While motor manifestations of PD are associated with loss of dopamine in the substantia nigra, degeneration of the basal nucleus of Meynert, and the connections of the pedunculopontine nucleus with the subcortical structure can cause severe deficits in a range of functions, including cognition, attention, gait, and postural stability, due to decreased cholinergic activity. At the same time, disease disability, prolonged hospitalization, and length of stay were also associated with anticholinergic drugs.[31] While objective cognitive impairment is present in one out of four patients

at the time of diagnosis in PD, the detection of dementia reaches 80 to 90% 12 years after diagnosis.[29,32] It is now more clearly known that these losses become more pronounced with the use of anticholinesterase, in addition to the degeneration that occurs in the course of the disease. Studies revealed that visual hallucinations, falls, and gait might be supported by acetylcholine.[24] In our study, the association of PD with dementia did not reach statistical significance. We believe that this association could increase with an increase in the number of patients with PD and the longitudinal follow-up of these patients. In a study conducted on Medicare in the USA in patients with PD, the concurrent prescription of a highly effective anticholinergic drug and an acetylcholinesterase inhibitor was 17.4% and 72.4%, respectively, and 45% of prescribers assumed that this concomitant use would not lead to cognitive deterioration.[29]

Depression is a common nonmotor symptom in PD, and approximately 25% of patients with PD use an antidepressant, most commonly selective serotonin reuptake inhibitors, at any stage.[33] In our study, patients with PD with high-risk ACB scores had at least one comorbid disease, and the prevalence of depression as a comorbid condition was statistically significantly higher in these patients compared to other comorbid conditions. Anticholinergic drugs were shown to improve all motor symptoms, particularly tremor, by balancing the levels of dopamine and acetylcholine in the striatum and blocking muscarinic receptors at the postsynaptic level in PD.[34] In a neuropathologic study, the use of antimuscarinic drugs in PD for more than two years was associated with twice as much cortical plaques or tangle formation compared to those who used them for less than two years and compared to those who never used them.[35]

Since its development in 2008, the ACB scale has been the most frequently studied scale due to its ease of access and use.[20] However, the ACB scale scores fewer drugs according to their anticholinergic properties compared to other scales. The score obtained may help identify patients with a high risk of adverse events and provide guidance on interventions for these patients. Therefore, many drugs with varying amounts of anticholinergic activity are not evaluated on these scales. The correlation of ACB risk score with UPDRS motor findings and HY Scale was evaluated, but no significance was found. The MDS-UPDRS nonmotor scores of the patients were found to be weakly correlated with ACB scores. In the regression analysis of our study, high-risk ACB scores was statistically associated with modified HR Stage 4 when independent variables were excluded. While this association could not be demonstrated with polypharmacy, the finding of an association with ACB scores suggests that the effect of ACB scores on the prognosis and severity of PD is more prominent. Longitudinal studies involving more patients are needed in this regard.

Although studies on the effects of PD and anticholinergic drugs were found in the literature, no studies were found to examine the correlation with clinical and staging scales. Thus, there is a need for studies that more clearly reveal drug interactions and the worsening of symptoms related to the disease. It is important to increase the awareness of physicians about the characteristics of neurodegenerative diseases, prescription habits, and the issues that arise in patients with these habits in Türkiye. This awareness will enable more efficient management of drug-related issues. Additionally, there is a need for country-specific scales and prescriptions that measure anticholinergic load, contain more anticholinergic drugs, are easily accessible, and can increase the awareness of all physicians.

The study had some limitations. First, it was a retrospective and cross-sectional study. Second, the sample size was small. Third, other effects of the drugs including adverse peripheral effects, effects on gait and balance, hospitalisation were not evaluated. The study had several strengths. First, this was the first study to show the relationship between PD severity and anticholinergic load. Second, this relationship was partially independent of confounding factors, specifically age.

In conclusion, the anticholinergic burden of medications in patients with PD who are at high risk for anticholinergic side effects is undeniable. Drug history is important in patients with PD and anticholinergic risk may increase as the disease progresses. In our study, the adverse effects of increased anticholinergic burden in PD, such as cognitive and autonomic symptoms, fracture risk, hospitalization, and length of hospital stay, were not studied. Large-scale longitudinal studies with larger samples are needed to support these findings.

Data Sharing Statement: The data that support the findings of this study are available from the corresponding author upon reasonable request.

Author Contributions: Idea/concept, design, analysis and/or interpretation, critical review, data collection and/or processing, literature review, writing the article, materials: Ü.S.S., S.E.K.; Control/supervision, references: Ü.S.S.

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