ORIGINAL RESEARCH

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Polypharmacy-Related Orthostatic Intolerance Syndrome in Community-Dwelling Older Adults

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Abstract

Objective: Polypharmacy (PP) is associated with various adverse outcomes in older adults. Although few studies have shown an association between PP and orthostatic blood pressure changes (OBPCs), its relationship with orthostatic intolerance syndrome (OIS), which describes a group of signs and symptoms triggered by standing up straight with or without OBPCs, is not known. Therefore, we assessed the association between PP and OIS in the geriatric population.

Materials and Methods: Ninety-nine geriatric outpatients were enrolled in the study. In addition to comprehensive geriatric assessment, frailty evaluation (Modified Fried Frailty Index), OBPC evaluations [active standing test (AST)], and OIS questioning both experienced in the last three months (self-reported OIS) and symptoms emerged during the AST were performed. PP was defined as using >4 drugs.

Results: The participants' median age was 74 and ranged from 69.5 to 79.0 years, and 66.7% (n=66) of them were female. Patients were split into non-OIS and OIS groups based on self-reported OIS, with 51 (51.5%) and 48 (48.5%) patients in each group, respectively. The frequency of PP was higher in the OIS group ($p<0.05$). In the regression analysis, OIS was significantly related to PP independent of age, sex, malnutrition, and frailty (odd ratio: 0.353, 95% confidence interval: 0.13-0.92, $p=0.033$). In addition, the number of drugs used was correlated with the total number of OIS symptoms ($r=0.204$, $p=0.042$).

Conclusion: This is the first study to show the link between PP and OIS. Further research is required to verify our results.

Keywords: Orthostatic intolerance, polypharmacy, older adults, geriatric, orthostatic blood pressure changes

Introduction

The increased multimorbidity burden in older adults leads to the prescription of multiple drugs and, ultimately, the development of polypharmacy (PP). Although no consensus on the definition of PP is available, it generally refers to the use of five or more drugs (1). Moreover, PP has been associated with many other geriatric syndromes, such as falls, disabilities, and poor physical performance (2,3).

Orthostatic blood pressure changes (OBPCs), namely orthostatic hypotension (OH), orthostatic hypertension, and orthostatic intolerance syndrome (OIS), are also prevalent issues among older adults (4). OIS is a group of symptoms caused by orthostatic position changes with or without OBPCs. These symptoms, which occur frequently, repeatedly, or persistently, are categorized primarily under seven headings: lightheadedness, exercise intolerance, tremulousness, generalized weakness, palpitations, blurred vision, and fatigue (4). Because of at least one of these symptoms, individuals with OIS have difficulty maintaining a standing position.

OIS is a cluster of symptoms resulting from transient cerebral hypoperfusion upon standing (5) and is related to various adverse outcomes such as depression, decreased quality of life, frailty, and falls (5-7). Although the underlying mechanism of OIS is still unclear, the main pathology is alterations in cerebral blood

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flow and central or peripheral cardiovascular regulation control. Various factors contributed to the development of OBPCS and OIS (8). Psychotropic medications and drugs with cardiovascular effects are one of the main factors related to OIS (8,9). Similarly, PP and specific types of drugs, such as antihypertensives and diuretics, are known to be associated with OBPCs, particularly OH (10). Although drugs and PP are considered to be one of the primary causes of OH (11,12), no studies have evaluated the link between PP and OIS.

Therefore, we assessed the association between PP and OIS in older individuals.

Materials and Methods

Study Design

This study has a cross-sectional design. Participants admitted to the geriatric outpatient clinic for three months were evaluated. After performing exclusion criteria (i.e., neurodegenerative diseases and any types of dementia, severe edema, decompensated hepatic or cardiac insufficiency, dehydration or anemia, systemic atrophies, any condition causing immobility such as amputation and stroke, demyelinating diseases, valve stenosis, delirium, and patients who were receiving any active treatment for cancer diagnosis, who were not in remission, or terminal-stage patients), 99 geriatric patients were recruited. In addition to demographic data of the individuals (age and sex), chronic diseases. Patients with a history of fall in the previous year were defined as falling in the previous year. Medications, number of drugs, and PP (defined as using ≥5 drugs) were also assessed. Hacettepe University Non-Invasive Clinical Research Ethics Committee approved the study (approval number: 2023/06-19, date: 04.04.2023). A signed informed consent form was obtained from all patients who agreed to participate in the study.

Comprehensive Geriatric Assessment

In line with an objective comprehensive geriatric assessment (CGA), Katz basic and Lawton Brody Instrumental Activity of Daily Living (IADL) activities scales, Yesevage Geriatric Depression Scale (YGDS), Mini-Mental State Examination (MMSE) and Mini-nutritional assessment short form (MNA-SF) and were used. The Katz ADL scale (for basic ADL) and Lawton Brody scale (for IADL) were used to evaluate the participants' functional status, with the score decreasing as dependence increased (13-15). Nutritional screening was performed via MNA-SF. Scores ≤7 points refer to malnutrition (16,17). In addition, scores of more than 5 points in YGDS have been defined as positive for depression screening. Clinical assessments were performed to confirm the diagnosis of depression (18). The modified Fried Frailty Index (FFI), which consisted of five criteria (i.e., weight loss, burnout, loss of strength, limitation in physical activity, and slow gait speed), was used to evaluate frailty status. Patients were defined as non-frail (0 points), prefrail (1-2 points), and frail (3-5 points) according to FFI scores (19,20).

Since questioning self-reported OIS depends on normal remembering function, we performed a detailed cognitive assessment. We excluded patients with dementia. According to current recommendations from the National Institute of Neurological and Communicative Diseases and Stroke/Alzheimer's Disease and Related Disorders Association and the fifth edition of the Diagnostic and Statistical Manual of Mental Disorders criteria, patients were evaluated via cognitive assessment with a detailed history, cognitive tests, and neuroimaging when needed (21,22). For dementia screening and as a part of the CGA, we used the MMSE test, which also has Turkish validation (23,24). Although a study conducted in older Turkish adults suggested that an MMSE score <22 distinguishes dementia from mild cognitive impairment (25), we evaluated patients with a clinical suspicion of dementia according to clinical assessment, even if the MMSE score was not <22. In summary, after performing the assessments above, patients with no suspicion regarding cognitive functions were defined as having normal cognition and were included in the study.

Orthostatic Status Evaluation

To assess OBPCs, the active standing test (AST) was used. The initial blood pressure reading was acquired using a digital automatic blood pressure measurement instrument (CONTEC ABPM 50®) after the patient lay still on the examination bed for 20 min. The patients were then lifted into an upright position, and measurements were taken from the same arm at the first, third, fifth, and tenth minutes. Symptoms throughout the test were noted, and for OBPC assessment, the data gained from each minute of measurement were assessed. OH is described as a systolic blood pressure drop of at least 20 mmHg or a diastolic blood pressure drop of at least 10 mmHg. Orthostatic hypertension was defined as an increase in systolic or diastolic blood pressure of at least 20 mmHg.

Regarding the presence of OIS, the patients were questioned. We followed the 2017 American College of Cardiology/American Heart Association/Heart Rhythm Society Guidelines to define OIS (4). OIS was described in this recommendation as a group of symptoms that appear in response to a change in the orthostatic position. Patients were questioned with the following questions to assess OIS: "Have you ever experienced one of the following symptoms when you stood up from a sitting or lying position during the last three months?"

1- Lightheadedness

2- Palpitations (tachycardia)

3- Tremulousness

4- Generalized weakness

5- Blurred vision

6- Exercise intolerance (having trouble when exercising)

7- Fatigue

One or more symptoms were required for OIS diagnosis. Patients were also evaluated for the aforementioned symptoms that occurred during AST, and this data is also presented in the results and tables.

Statistics

Version 22.0 of SPSS was used for analysis. The normality of the distribution of the variables was tested using both graphical (histogram, probability graph) and statistical approaches. The number of cases and percentages were reported for nominal variables, whereas the mean and standard deviation were used to define continuous variables with a normal distribution (ND). Variables without ND are given as median [interquartile range (IQR)]. To compare median values across groups, we used the Mann-Whitney U test. Chi-square or Fisher exact tests were used to compare the data for categorical variables, with Bonferroni correction applied where appropriate. Independent factors linked with OIS were analyzed using a multivariate logistic regression model with the enter method. Before performing a multivariate logistic regression analysis, univariate analysis was performed, and confounders with a p-value of <0.05 in the univariate analysis [i.e., age, sex, malnutrition (MNA-SF scores), frailty (FFI score), and PP] were included in the multivariate logistic regression model. Using the Hosmer-Lemeshow goodness-of-fit statistic, the model fit was evaluated. For each predictor, we calculated odd ratios (OR) and 95% confidence intervals (CI). In addition, the Spearman correlation test was used to determine the relationship between each measurement and the total number of OIS symptoms. A p-value of 0.05 was considered statistically significant.

Results

Ninety-nine community-dwelling older adults were enrolled in the study. The median (IQR) age of participants was 74 (69.5-79.0) years, and 66.7% (n=66) were female. According to self-reported OIS, patients were divided into non-OIS and OIS groups, with 51 (51.5%) and 48 (48.5%) patients in each group, respectively. Although no significant difference was observed between groups according to OH and hypertension in the AST, the frequency of OIS that occurred during the test was also higher in the OIS group (p=0.004). In the OIS group, the MNA-SF scores were lower, and the number of drugs and the frequencies of frailty and falling in the previous year were significantly higher. In addition, the frequency of PP in the whole group was 58.6% (n=58) and was significantly higher in the OIS group (p=0.016). There were no significant differences between the groups regarding age, sex, chronic diseases, and other CGA parameters (p>0.05) (Table 1).

Table 1. Demographical characteristics and comprehensive geriatric assessment according to the presence of orthostatic intolerance

	Non-OIS group n= 51 (51.5%)	OIS group n=48 (48.5%)	p-value
Age, median (IQR)	72 (68-79)	74 (70-79)	0.219
Female sex, n (%)	30 (58.8)	36 (75.0)	0.088
BMI, median (IQR)	30.1 (27.1-32.9)	30.5 (26.6-35.6)	0.701
Hypertension, n (%)	31 (60.8)	33 (68.8)	0.694
Diabetes mellitus, n (%)	21 (41.2)	17 (35.4)	0.556
Cancer, n (%)	2 (3.9)	7 (14.6)	0.065
Depression, n (%)	5 (9.8)	9 (18.8)	0.202
Cardiovascular diseases, n (%)	7 (13.7)	11 (22.9)	0.236
Cerebrovascular disease, n (%)	5 (10.0)	4 (8.3)	0.775
Renal diseases, n (%)	2 (3.9)	2 (4.2)	0.951
Falling in the previous year, n (%)	10 (20.0)	19 (36.9)	0.034
Basic ADLs, median (IQR)	6 (5.0-6.0)	6 (5.0-6.0)	0.063
Instrumental ADLs, median (IQR)	8 (7.0-8.0)	7 (5.0-8.0)	0.094
MMSE, median (IQR)	26 (23.0-29.0)	25 (21.0-28.0)	0.339
Yesevage scores, median (IQR)	2 (0.0-3.0)	3 (1.0-9.0)	0.059
MNA-SF scores, median (IQR)	13 (10.0-14.0)	10 (8.0-13.0)	0.004
Number of drugs, median (IQR)	4 (2.0-6.0)	6 (4.0-7.0)	0.005
Polypharmacy, n (%)	24 (47.1)	34 (70.8)	0.016
Frailty via FFI, n (%)	34 (66.7)	47 (96.9)	<0.001
Orthostatic hypotension, n (%)	11 (21.6)	13 (27.1)	0.522
Orthostatic hypertension, n (%)	10 (19.6)	8 (16.7)	0.705
Symptoms occurred during the test, n (%)	3 (5.9)	13 (27.1)	0.004

BMI: Body mass index, ADL: Activity of daily living, MMSE: Mini-mental state examination, MNA-SF: Mini-nutiritional assessment short form, FFI: Fried frailty index

After univariate analysis, which was performed to determine the confounders related to OIS with a p-value of <0.05, age, sex, malnutrition (MNA-SF scores), frailty (FFI score), and PP were included in the multivariate logistic regression model. Regression analysis was used to assess the independent factors related to OIS. According to the multivariate logistic regression analysis, OIS was significantly related to PP regardless of age, sex, malnutrition, and frailty (OR:0.353, 95%CI: 0.13-0.92, p=0.033) (Table 2).

In addition, in the correlation analysis of the total number of OIS symptoms experienced in the last three months and other parameters, besides the MNA-SF and FFI scores, the number of drugs used was also correlated to the total number of OIS symptoms (r=0.204, p=0.042) (Table 3).

To evaluate the diagnostic accuracy of the number of drugs for predicting OI, the receiver operating characteristic curves were analyzed. Using more than four drugs daily was the cutoff for OIS prediction (area under the curve: 0.665, 95% CI: 0.558-0.771, p=0.005) (Figure 1).

Discussion

This study, which was designed to investigate whether PP is related to OIS regardless of the medication type, revealed that PP is related to OIS regardless of confounders with well-established relationships with OIS (i.e., age, sex, frailty, and malnutrition). Furthermore, our results revealed that using more than four drugs daily may accurately predict OIS.

The prevalence of PP and OIS varies in the geriatric population. The prevalence of PP changes according to the cut-off drug numbers used and the environment where the study was conducted. In a study on Turkish geriatric female patients, PP was defined as using ≥5 drugs, and the prevalence of PP was 47.6% (26). Furthermore, a large sampled study that included

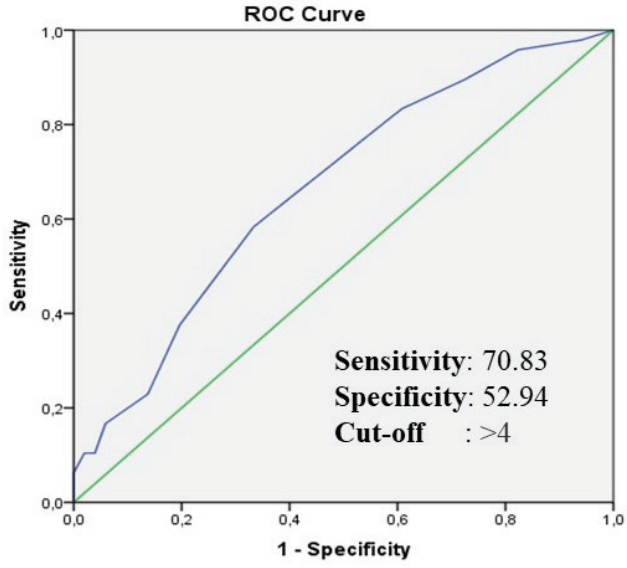

Figure 1. ROC curves demonstrating the accuracy of the predictive value of number of drugs used in determining orthostatic intolerance

AUC: 0.665, 95% CI: 0.558-0.771, p=0.005

ROC: Receiver operating characteristic, AUC: Area under the curve

Table 2. Logistic regression analysis of independent factors associated with orthostatic intolerance

	Presence of orthostatic intolerance*	
	OR (95% CI)	p-value
Polypharmacy	0.353 (0.13-0.92)	0.033
Frailty	1.590 (1.09-2.31)	0.015

*Variables included in the multivariate logistic regression analysis: age, sex, malnutrition (Mini-nutiritional assessment short form scores), frailty (Fried Frailty Index score) and polypharmacy
OR: Odd ratio, CI: Confidence interval

Table 3. Correlation analysis of the total number of orthostatic intolerance symptoms experienced in the last three months and other parameters

	Total number of orthostatic intolerance symptoms	
	r	p-value
Age	0.083	0.414
Basic ADLs	-0.189	0.066
Instrumental ADLs	-0.154	0.126
MMSE	-0.124	0.245
Yesevage score	0.130	0.220
MNA-SF score	-0.345	0.001
Fried frailty index score	0.462	<0.001
Number of drugs	0.204	0.042

ADL: Activity of daily living, MMSE: Mini-mental state examination, MNA-SF: Mini-nutiritional assessment short form

17 European countries revealed that 32.1% of older adults take five or more medications daily (27). Studies in higher-income countries have reported higher PP prevalence (28). Our results demonstrated that the frequency of PP was 58.6%. Because our main aim was not to evaluate the prevalence and the sample size was relatively limited, the prevalence may be slightly higher than that reported in the literature. Unlike the many studies on PP prevalence, there are limited data on OIS prevalence in geriatric patients. Studies on OIS prevalence were often evaluated depending on OH occurrence, ranging between 24-100% (29). We evaluated self-reported OIS and OIS during the AST, and the prevalences were 48.5% and %16.2, respectively. Because there are scant and conflicting data on the link between OH and OI in the geriatric population (29), the prevalence of OIS defined solely based on symptoms during the OH evaluation may have overlooked the actual OIS prevalence. The higher prevalence of self-reported OIS than the symptoms in the test in our results may also support that hypothesis.

OIS is associated with many factors, such as long-term bed rest, chronic diseases (diabetes mellitus, Parkinson's disease, multiple sclerosis, etc.), and drugs, particularly diuretics and those with psychotropic effects (8,30-32). In addition to the well-known relationship between OIS and drugs, drugs also have a well-established relationship with OBPCs. A meta-analysis of 27.079 individuals from 69 studies, compared with placebo, beta-blockers, tricyclic antidepressants, alpha-blockers, antipsychotics, and SGLT-2 inhibitors, showed a higher risk of OH. Although the above study was not designed to assess the link between OH and PP, the authors revealed that patients with PP may be at the greatest risk of drug-induced OH (10). In the study conducted by Samajdar et al. (33), geriatric patients were evaluated in terms of cardiac autonomic dysfunction via the Valsalva ratio, the presence of OH, the rise in diastolic blood pressure following an isometric hand-grip exercise, and heart rate variability, and the results showed that PP was significantly related to cardiac autonomic neuropathy. Cardiovascular autonomic dysfunction is also strongly associated with OIS (34,35). The underpinning pathway of the relationship between OIS and PP shown in our study may be cardiovascular autonomic dysfunction associated with both OIS and PP.

In previous studies, OIS and PP were related to various geriatric syndromes. Although OH is a major risk factor for falls in older adults, limited data have shown that OIS is associated with falls (36,37). Similar to OH, PP is strongly related to fall risk in the geriatric population (38). Moreover, interventions on PP and OH are recommended to prevent falls in older adults (37). Malnutrition and frailty are other common geriatric syndromes associated with PP and OBPCs, including OIS (7,39-41). In line with the current evidence, our results revealed that falls, frailty, and malnutrition are more likely in patients with OIS, and the number of OIS symptoms experienced in the last three months correlated with malnutrition and frailty. Moreover, when adjusted for independent factors that are both related to PP and OIS (i.e., age, sex, frailty, and malnutrition), a significant relationship between OIS and PP remained. This finding may indicate that there may be a strong and distinct pathway, such as exaggerated autonomic dysfunction, in the underlying mechanism for the independent relationship between these two entities. In addition to reviewing the drug groups for the prevention/treatment of OIS, reviewing the number of drugs may also work in geriatric patients.

Study Limitations

There are also some limitations in this study. The relatively small sample size was the major limitation. In addition, the small sample size may also make it unable to evaluate the effect of individual drug groups on the relationship between PP and OIS. Because FFI primarily assesses the physical domain of frailty, using only FFI for frailty assessment may be a limitation.

Conclusion

In conclusion, to the best of our knowledge, this is the first study showing that the number of drugs and multiple drug usage, namely PP, is associated with a higher frequency of OIS in the geriatric population. Larger sampled studies, including multidimensional frailty assessment and more detailed drug group analysis, are warranted to support our findings.

Ethics

Ethics Committee Approval: Hacettepe University Non-Invasive Clinical Research Ethics Committee approved the study (approval number: 2023/06-19, date: 04.04.2023).

Informed Consent: Informed consent was obtained.

Authorship Contributions

Surgical and Medical Practices: A.O.B., M.G.O., S.C., Z.K., S.Ç., M.C., M.G.H., Concept: A.O.B., Y.Ö., M.G.O., S.C., S.Ç., C.B., B.B.D., M.G.H., Design: A.O.B., Y.Ö., B.B.D., M.G.H., Data Collection or Processing: A.O.B., M.G.O., S.C., Z.K., S.Ç., M.K., M.G.H., Analysis or Interpretation: A.O.B., Y.Ö., M.G.O., S.C., M.K., M.E., C.B., B.B.D., M.C., M.G.H., Literature Search: A.O.B., Y.Ö., M.K., M.E., C.B., B.B.D., M.G.H., Writing: A.O.B., M.E., C.B., M.G.H.

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