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Is Depression a Predictive Factor for Polypharmacy in Elderly?

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ABSTRACT:

Is depression a predictive factor for polypharmacy in elderly?

Objective: Polypharmacy, quite common in elderly patients, is an important issue, resulting in increased morbidity and mortality. This study aimed to examine polypharmacy rates and drug usage characteristics in elderly patients. Second aim of this study was to compare our results with other published studies.

Methods: In a retrospective design, we reviewed hospital records of 1,205 patients (≥65 years) who presented to our geriatric clinic, which serves as a tertiary center at the University of Istanbul, Cerrahpasa School of Medicine, who were examined in detail in terms of polypharmacy between 2003 and 2012, and who had follow-up care for at least a year. Demographic characteristics, polypharmacy, drugs used at presentation and final evaluation, and comorbid conditions were recorded. The definition of ≥ 5 drugs usage for polypharmacy and ≥ 9 drugs usage for excessive polypharmacy were considered in this study. Multivariate binary logistic regression analysis was performed for independent predictive factors.

Results: Of patients, 854 were females (70%). The average age was 75.2±6.9. The number of comorbidities was 2.46±1.30. The number of drugs used at first admission and final evaluation was 3.8±2.7 and 4.3±2.8 ($p<0.001$), polypharmacy rates of 40% and 45% ($p<0.001$). Also, the rate of excessive polypharmacy was found 8% at final assessments. The rates of patients using one drug, two drugs, three drugs and four drugs were 6%, 11%, 13% and 15%, respectively. Polypharmacy rate in females was statistically significant higher than males (33% vs. 12%; $p=0.026$). The most common prescribed drugs were found as anti-platelet therapies (70%), calcium channel blockers (68%), anti-osteoporotic drugs (57%), statins (53%), and beta-blockers (49%) in all patients respectively. The most common five comorbidities were hypertension (67%), diabetes mellitus (27%), osteoporosis (27%), hyperlipidemia (25%), and depression (20%). Depression was an independent predictive factor for polypharmacy than other comorbid diseases in the regression analysis (odds ratio (OR): 4.5; 95% confidence interval (CI): 3.2–6.5; $p<0.001$).

Conclusions: The polypharmacy rate was found to be as high as 45% in elderly patients. Before starting an additional medication in elderly patients, particularly with depression, the indication should be clearly specified, and several aspects should be taken into consideration, including functional capacity of the patient, the drugs already used, and possible interactions of the new drug.

Keywords: depression, aged, polypharmacy, comorbidity

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INTRODUCTION

Polypharmacy is an important issue commonly seen in the elderly population, with a prevalence of 20% to 40%, resulting in increased morbidity and mortality[1]. In line with aging, the number of chronic diseases progressively increases in elderly patients, requiring the use of multiple drugs, especially in increasing age groups[2]. Multiple drug use inevitably leads to increases in the risks of side effects and drug interactions, treatment costs, the need for hospitalization, rates of treatment noncompliance, and related problems[3]. The most common manifestations include falls, delirium, dizziness, fragility, incontinence, syncope, and sleep disorders[1]. Drugs prescribed to elderly patients for a wide variety of medical conditions, especially sedative-hypnotics, anticholinergics, antidepressants, and antipsychotics are associated with more side effects and increased hospital admissions[4-6].

Elderly patients in Turkey and all over the world constitute the majority of patients taking drugs. Previously, the studies reported from different centers in Turkey, the rates of polypharmacy[7-9] and inappropriate medications[10] have been reported in elderly patients.

The aim of this study was to examine polypharmacy rates and drug use characteristics of geriatric patients and to emphasize the importance of polypharmacy, which is part of comprehensive geriatric assessment (CGA) in elderly patients who applied to our geriatric outpatient clinic. Second aim of this study was to compare our results with other published studies.

METHODS

Patients and Study Design

In a retrospective design, we reviewed hospital records of 1,205 patients (≥65 years) who presented to our geriatric clinic, which serves as a tertiary center at the University of Istanbul, Cerrahpasa School of Medicine, who were examined in detail in terms of polypharmacy between 2003 and 2012, and who had follow-up care for at least a year. Patients who did not meet these criteria were excluded from the study. Demographic characteristics of the patients, the presence of polypharmacy, the number of drugs used in the baseline and final evaluations (as well as the groups of the drugs), and the number of comorbid conditions were recorded. Polypharmacy diagnosis was determined only by the number of drug use. So, the use of five or more drugs was considered to be polypharmacy[2]. Also, the use of nine or more drugs was considered to be excessive polypharmacy. The study was approved by the local ethics committee (Istanbul University, Cerrahpasa School of Medicine Ethics Committee, Approval Code: A-21, Date: July 1, 2014).

CGA is a multidisciplinary approach that aims to evaluate medical status, neuropsychological condition, functional capacity, and social circumstances of the patient so that management and long-term follow-up of the geriatric patient can be planned effectively[11,12]. Elderly patients presenting to our geriatric clinic undergo a multidimensional geriatric assessment that includes a re-evaluation of polypharmacy at each visit, an inquiry into the medications that the patient has been taking, and in turn, discontinuation of unnecessary and inappropriate medications.

Statistical Analysis

Data were processed and analyzed using the SPSS software, version 15.0 for Windows (SPSS Inc, Chicago, IL). Continuous variables were expressed as mean±SD. Rates of polypharmacy on presentation and final evaluation were compared using the Mc Nemar's test. Polypharmacy rates based on gender and age distribution and evaluation of drug groups in terms of the presence of polypharmacy were analyzed using the Chi-square test. Continuous variables (age and number of comorbidities) were analyzed using the Student's t-test or ANOVA test. The association between polypharmacy and comorbid diseases was analyzed by Chi-square test. And then,

Multivariate Binary logistic regression analysis was performed for independent predictive factors using available parameters. A p value <0.05 was considered to be statistically significant.

RESULTS

A total of 1,509 patient files were examined retrospectively. Of these, 1,205 patients (80%) were found eligible for the study. Demographic characteristics of the patients, the number of drugs used, and polypharmacy rates are shown in Table 1. There were 854 females (70%). The average age of males was higher, but this was not statistically significant (p=0.08).

At first, the average number of drugs used was 3.80; this showed a significant rise to 4.36 after final evaluation (p<0.001). Similarly, compared to the baseline visits, the rate of polypharmacy was statistically significantly higher at final assessments, increasing from 40% to 45% (p<0.001). Also, the rate of excessive polypharmacy was found 8% (n=90) at final assessments. According to gender, initial number of drugs and initial polypharmacy rate in females were higher than males but it was not statistically significant (p=0.06, p=0.06, respectively). Polypharmacy rate in females was statistically significantly higher than males (33% vs. 12%; p=0.03). Additionally, excessive polypharmacy statistically significantly higher in females (7% vs. 1%; p=0.01). When the drug use of patients analyzed according to comorbid diseases, the average number of drugs for dementia patients (6.32±2.72), depression (6.19±2.73), osteoporosis (5.82±2.69), diabetes mellitus (5.45±3.03), and hypertension (4.81±2.76) were statistically significantly higher at the final visit (p<0.001).

The number of drugs used in the final evaluation of patients ranged from 0 to 17. The rates of patients using one drug, two drugs, three drugs and four drugs were 6%, 11%, 13%, and 15%, respectively. According to age groups (65–74, 75–84 and over 85 years), the average number of drugs was found 4.26±2.74, 4.60±2.90 and 3.90±2.99, respectively. In post-hoc analysis, the average number of drugs in the 75–84 years was statistically significant higher than over 85 years age group (p=0.05).

Table 2 shows the demographic characteristics of the polypharmacy patients. The rates of drugs acting on the central nervous system (sedative-hypnotics, antidepressants and antipsychotics), anticholinergics, diuretic drugs, calcium channel blockers and beta blockers were statistically significant higher (p<0.001) in polypharmacy group than non-polypharmacy group. The mean age did not differ statistically significant between patients with and without polypharmacy (p=0.47) (Table 2). In our study, the most common prescribed drugs were found as anti-platelet therapies (70%), calcium channel blockers (68%), anti-osteoporotic drugs (57%), statins (53%), and beta-blockers (49%) in all patients respectively (Table 2).

When the patients' drug use was analyzed according to age groups, the use of statins, metformin, and oral antidiabetic drugs (at least

Table 1: Demographic characteristics of the patients, the number of drugs used and polypharmacy rates

	All patients	Females	Males	P value¶
Patients, n (%)	1205 (100)	854 (71)	351 (29)	
Average age±SD (years)	75±6.90	74.9±6.90	75.7±6.60	0.08
Age groups n (%)				
65-74 years	576 (48)	421 (35)	155 (13)	0.23
75-84 years	502 (42)	343 (29)	159 (13)	
≥85 years	126 (11)	90 (8)	37 (3)	
Comorbidities	2.46±1.30	2.52±1.35	2.31±1.25	0.01
Initial number of drugs	3.80±2.70*	3.87±2.73	3.55±2.62	0.06
Final number of drugs	4.36±2.84*	4.56±2.90	3.87±2.62	<0.001
Initial polypharmacy rate, n (%)	483 (40)**	357 (30)	126 (11)	0.06
Final polypharmacy rate, n (%)	544 (45)**	403 (33)	141 (12)	0.03

Table 2: Demographic characteristics of patients and drugs used based on the presence and absence of polypharmacy

	Polypharmacy (+)	Polypharmacy (-)	P value
Gender, n (F/M)	544 (403/141)	661 (451/210)	0.03
Age (years)	75.30±6.50	75±7.10	0.47
Number of comorbidities	3.00±1.25	2.03±1.22	<0.001
Drugs used, n (%)			
ACE inhibitors	158 (29)	93 (14)	<0.001
ARB	91 (16.7)	48 (7.3)	<0.001
ACE inhibitors + diuretics	27 (5)	28 (4.2)	0.60
ARB + diuretics	85 (16)	49 (7)	<0.001
Diuretics	84 (15)	37 (6)	<0.001
Calcium channel blockers	184 (34)	96 (34)	<0.001
Beta-blockers	199 (37)	80 (12)	<0.001
Alpha-blockers	22 (4)	16 (2)	0.10
Anti-arrhythmic drugs (digoxin, propafenone)	34 (6)	10 (2)	<0.001
Anti-platelet therapies (ASA, clopidogrel)	266 (49)	141 (21)	<0.001
Anti-coagulants (Warfarin)	30 (6)	3 (0.5)	<0.001
Statins	199 (37)	106 (16)	<0.001
Fibrates	10 (2)	2 (0.3)	0.01
Metformin	115 (21)	55 (8)	<0.001
Sulfonylureas	73 (13)	41 (6)	<0.001
OAD	149 (27)	67 (10)	0.001
Insulin	42 (8)	15 (2)	<0.001
Proton pump inhibitors	184 (34)	66 (10)	<0.001
Antidepressants (SSRI, TCA)	176 (32)	64 (10)	<0.001
Antidementia drugs	95 (18)	37 (6)	<0.001
Antiparkinsonian drugs	23 (4)	12 (2)	0.03
CNS acting other drugs (antipsychotics, benzodiazepines, antiepileptics, etc.)	63 (12)	5 (1)	<0.001
Anticholinergic / muscarinic drugs (urinary incontinence medications, amitriptyline, etc.)	16 (3)	2 (0.3)	<0.001
Antiosteoporotic drugs	218 (40)	111 (17)	<0.001
NSAI drugs	13 (2)	18 (3)	0.85

F: Female, M: Male; SD: Standard deviation; ACE: Angiotensin converting enzyme; ARB: Angiotensin receptor blockers; CNS: Central nervous system; ASA: Acetylsalicylic acid; OAD: Oral antidiabetic drugs; SSRI: Selective serotonin reuptake inhibitors; TCA: Tricyclic antidepressants; NSAI: nonstreoidal anti-inflammatory.

Table 3: The most common comorbid diseases that predict the polypharmacy in elderly patients followed at the geriatrics outpatient clinic

Comorbid diseases	Phi coefficient	p value*	Odds Ratio	95% Confidence Interval	p value**
Depression	0.282	< 0.001	4.5	3.2 – 6.5	< 0.001
Osteoporosis	0.260	< 0.001	4.1	3.0 – 5.6	< 0.001
Heart diseases	0.201	< 0.001	3.8	2.6 – 5.3	< 0.001
Dementia	0.189	< 0.001	3.3	2.1 – 5.3	< 0.001
Diabetes mellitus	0.189	< 0.001	2.5	1.8 – 3.3	< 0.001
Hypertension	0.192	< 0.001	2.1	1.5 – 2.8	< 0.001
Hyperlipidemia	0.108	< 0.001	1.5	1.1 – 2.0	0.007

*Chi-square test analysis, **Multivariate Binary Logistic regression analysis (forward stepwise), Malignancy and thyroid diseases is not associated with polypharmacy, data not shown.

one drug) were statistically significantly higher in the 65–74 age group (60%, 60%, 50%, p<0.001, p=0.01, p=0.01, respectively). However, the use of warfarin, antiarrhythmic drugs, and anti-dementia drugs were statistically significant higher in the 75–84 age group (60%, 60%, 60%, p=0.05, p=0.01, p<0.001, respectively).

The use of antipsychotic 3% (n=31), antiepileptic 1% (n=11), benzodiazepine 0.8% (n=10), tricyclic antidepressant 0.7% (n=8), and anticholinergic/ antimuscarinic 1% (n=11) were found in all patients. By age groups, 48% of antipsychotic use in the 75–84 age group, 36% in the 65–74 age group, and 16% in the over 85 age

group (p=0.30); 46% of antiepileptic use in the 65–74 age group, 36% in the 75–84 age group, and 18% in the over 85 age group (p=0.70); 60% of benzodiazepine use in the 65–74 age group, 30% in the 75–84 age group, and 10% in the over 85 age group (p=0.70); 63% of tricyclic antidepressants use in the 75–84 age group and 37% in the 65–74 age group (p=0.40); 36% of anticholinergic/ antimuscarinic use in the 65–74 age group, 36% in the 75–84 age group, and 28% in the over 85 age group (p=0.20) were shown.

The number of comorbidities ranged from 0 to 6, with 577 patients (48%) having more than three comorbidities. Comorbid diseases included hypertension (67%), osteoporosis (27%), diabetes mellitus (27%), hyperlipidemia (25%), depression (20%), heart diseases (18%), thyroid diseases (12%), dementia (11%), malignancy (5%), and others (26%). As expected, the presence of polypharmacy was associated with the number of comorbidities (3.00±1.25 and 2.03±1.22, p<0.001) (Table 2). Also, depression was found to be a better independent predictor of polypharmacy than other comorbid diseases in the regression analysis (odds ratio (OR): 4.5; 95% confidence interval (CI): 3.2–6.5; p<0.001) (Table 3).

DISCUSSION

Likewise in the world, elderly patients in Turkey account for the majority of patients using prescribed medications. In the literature, there are many definitions for polypharmacy. The most appropriate definition of polypharmacy involves several circumstances, including the simultaneous use of five or more drugs, the use of at least one unnecessary drug or the use of more drugs than clinically necessary[2,13]. The prevalence of polypharmacy has been reported to be between 20% and 40%[1]. In our study, although patients were examined in detail in terms of polypharmacy, it was found to be as high as 45%. The average number of drugs was 3.80 at first and 4.36 at final evaluation. Qato et al. examined 3,005 patients between 57 and 85 years of age and found that the highest rate of using five or more drugs (35%–40%) was in the age bracket of 75–85 years; they also reported a higher rate of polypharmacy in males (37% vs. 36%)[14]. Similarly, in the current study, polypharmacy rate was statistically significant higher (33%) in females at final evaluation (p=0.03). In a multicenter study from Turkey, Kutsal et al. also found that the average number of drugs was higher in females[8]. Similarly, several previous studies reported that females used more drugs than males in all age groups of ≥65 years[15,16]. In another study reported from Turkey, ≥4 chronic drug usage and ≥10 chronic drug usage in male outpatients were shown 55%, 8%, respectively[9]. Kara et al. In this study, ≥5 drug usage was found as 63%[10]. Differences in polypharmacy rates in terms of gender and age groups can be explained by the cross-sectional design of the studies and by the heterogeneity of the study groups. In our study, the polypharmacy and excessive polypharmacy rate after the final evaluation were 45%, 8%, respectively. Also, the rates of patients using one drug, two drugs, three drugs and four drugs were 6%, 11%, 13%, and 15%, respectively. According to comorbid diseases, the average number of drugs for dementia patients 6.3, depression 6.2, osteoporosis 5.8, and diabetes mellitus 5.4 were very high.

Besides the number of drugs, the properties of drugs used are also very important in elderly patients. In a meta-analysis, the adverse effects of anticholinergic drugs on cognition and physical function have been shown[17]. In our study, anticholinergic/ antimuscarinic drug use was 1%. That was not different by age group. There was not tricyclic antidepressant use in the over 85 age group. Its rate was 0.7% of all patients in other age groups. Drugs acting on the central nervous system can lead to negative consequences such as falls and delirium related polypharmacy[18,19]. Antipsychotic use was highest in the 75–84 age group and 3%. Benzodiazepine use was 0.8% and was used more frequently by the 65–74 age group. According to age groups, the use of statins and oral antidiabetic drugs (at least one drug) were higher in the 65–74 age group. However, the use of warfarin, antiarrhythmic drugs, and anti-dementia

drugs were higher in the 75–84 age group. In this study of Kara et al. (average age, 74), the most prescribed drugs have been found as calcium-vitamin D supplement, statin, and antiplatelet therapy in patients[10]. In the literature, the most common prescribed drugs have been shown as calcium-vitamin D supplement, metformin, statin, aspirin, angiotensin converting enzyme inhibitors, and antiplatelet therapies in elderly patients[20-22]. Compared with these studies, in our study, the most common prescribed drugs were as anti-platelet therapies, calcium channel blockers, anti-osteoporotic drugs, statins, and beta-blockers in all patients respectively.

The prevalence of chronic diseases increases with aging, often necessitating the use of multiple drugs. Therefore, the presence of multiple comorbidities constitutes an important risk factor for the development of polypharmacy. In our study, the average number of comorbidities in elderly patients was 2.46, with 48% of patients having more than three comorbidities. In a study of 515 elderly women (average age 73 years) from Turkey, Bahat et al. found the average number of comorbidities was 2.8, and 61% of the participants had more than three diseases, the most frequent of the three being hypertension (75%), depression (45%) and dementia (39%)[7]. In another study reported from our country, the average number of comorbid diseases was 4, the most frequent diseases were found hypertension (83%), ischemic heart disease (51%), diabetes mellitus (43%), hyperlipidemia (43%), and osteoporosis (33%)[10]. In our study, the most five common comorbid diseases were hypertension (67%), osteoporosis (27%), diabetes mellitus (27%), hyperlipidemia (25%) and depression (20%).

In addition, we showed that depression was a better independent predictor of polypharmacy than other comorbid diseases. This concurs with another study that showed that respondents' increased depressive symptoms were associated with using more than four medications[23]. Treatment in elderly depression has several challenges: a) diagnosis in elderly may be difficult because of some common symptoms in comorbid conditions or considering depressive symptoms as a part of normal aging, b) polypharmacy and possible drug interactions in elderly may cause depression and/or treatment resistance, c) depressive patients more than 60 years old were less likely to receive adequate treatment and d) thus, it is important to improve the knowledge of non-mental health physicians[24].

It has been demonstrated that CGA reduces the morbidity and mortality of elderly patients, as well as the rates of nursing home admissions, and has a favorable impact on functional status. Polypharmacy is an important geriatric syndrome included in the CGA of elderly patients[12]. In our study, even after detailed examination, the rate of polypharmacy was high (45%). This emphasizes the fact that the number of drugs, drug interactions, and both the necessity and inaptitude of medications should be reviewed at each visit to reduce the adverse effects of polypharmacy. This will significantly reduce the negative consequences of polypharmacy.

A major limitation to our study is its retrospective design that only allowed us to examine the polypharmacy rates and drug use characteristics of elderly patients. Though there are various definitions of polypharmacy, we only considered the number of drugs used, namely ≥5 drugs. We were unable to report data on inappropriate drug use, discontinued drugs (due to adverse effects), and related complications due to the lack of sufficient patient information. More comprehensive, prospective studies are needed to clarify these issues.

Being relatively common in the elderly, polypharmacy is an important geriatric syndrome that impairs the quality of life, brings economic burden, and increases mortality and morbidity. Physiological changes that occur with aging and a large number of comorbid diseases in elderly individuals have a significant impact on the pharmacokinetics and pharmacodynamics of drugs. These issues not only require special attention to be paid to the treatment of diseases of the elderly but also make it difficult to plan and implement their treatment. Considering these problems in the

elderly, several guides to appropriate drug usage have been developed to reduce inappropriate drug usage and adverse effects, such as The Drug Burden Index, The Beers Criteria, STOPP (Screening Tool of Older Persons' potentially inappropriate Prescriptions), START (Screening Tool to Alert doctors to Right Treatment) and IPET (Improved Prescribing in the. Elderly Tool)[25-29]. These guides should be utilized for rational drug usage, which is one of the ultimate goals of CGA.

In conclusion, before prescribing a new medication to geriatric patients, indications should be clearly specified, and several aspects should be taken into consideration, including the functional capacity of the patient, the drugs already used, and possible interactions of the new drug, especially in depressed elderly patients.

Conflict of Interest: The authors declare that they have no conflicts of interest.

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