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Original article

POLYPHARMACY IN ADULTS WITH CHRONIC DISEASE – CHARACTERISTICS AND ASSOCIATION WITH COGNITIVE DISORDERS

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Abstract

Polypharmacy in the elderly with multimorbidity in particular results in drug interactions and manifestation of cognitive impairments and functional deficits.

To analyze the characteristics of polypharmacy, predictors affecting its variability and its impact on possible cognitive impairment in adults over 60 years of age with a diagnosed chronic disease at risk for dementia.

A national prospective multicenter study started in 2022 in 46 outpatient clinics of family medicine specialists in primary care. Participants older than 60 years of age with a confirmed minimum of one chronic disease and at risk for dementia were included. A general and clinical information questionnaire and 3 standardized questionnaires were used – Mini-cog test, IADL test and Geriatric Depression Scale (GDS).

Eight hundred fifty-eight participants were analyzed, with female predominance (57.69%). Sex and age as independent predictors significantly affected the variability of polypharmacy consistently 0.7% *vs*. 0.5%.

Elevated cholesterol [OR=1.449 (1.09 – 1.92) 99% CI] and obesity [OR=1.695 (1.30 – 3.30) 99% CI] were associated with female sex. Four hundred ninety-seven participants (57.92%) received ≤2 groups of medications for treatment of chronic diseases. There was no significant association between the obtained Mini-cog test scores and the number of medication groups participants received (p=0.12).

The higher GDS score was significantly associated with polypharmacy (p=0.03). A non-significant negative correlation was found between the IADL score and the number of medication groups used for therapy of chronic diseases (p=0.38).

Keywords: polypharmacy, elderly, cognitive deficit

Introduction

According to the World Health Organization, the world population of people over 60 years of age will almost double from 12% to 22% between 2015 and 2050[1]. Regarding the age structure, the Macedonian population is getting older. In the period from 2011 to 2021, the proportion of the elderly population (65 and over) increased from 11.8% to 17.2%[2]. At the individual level, increasing age is associated with functional disability and dependence on activities of daily living[3], leading to poorer quality of life, increased health care costs, and

higher mortality[4]. The development of disability in the elderly population is often complex, multi-factorial, and is the result of interactions between physical, social, and attitudinal environments. Mainly, future activities will be aimed at undertaking activities in the direction of improving the quality of life, but primarily at the predisposing factors and their correlations[5,6] such as demographic characteristics (education, cohabitation, finances, age, sex)[7,8], personal (obesity, sarcopenia, habits and addictions) on one hand[9], and on the other hand, social activities[10], multimorbidity and use of medications for them[3].

A large number of different conditions and factors have been demonstrated to be associated with polypharmacy, but causality has not always been explicitly determined. Risk factors of polypharmacy can occur at several levels, among which of particular importance are those at the level of patients, of doctors and health care system[11].

Multimorbidity itself is associated with polypharmacy[12,13]. There are many definitions of polypharmacy[14,15], but it is usually defined as the use of more than two medications[14]. Polypharmacy is most often found in the elderly who have one or more chronic diseases and have a longer list of medications they take[11,16].

General functional abilities are related to cognitive abilities in adults. Elderly people who are isolated have a greater tendency to develop cognitive deficits and dementia[17]. It involves the development of greater inactivity and functional deficit, as well as the occurrence of many diseases[3,4]. Polypharmacy in adults results in interaction and opposite effects that can manifest as cognitive deficits and memory impairment, and this can result in disruption of daily life[18]. There is some evidence, mainly from observational studies, that polypharmacy in older age is associated with a number of adverse health outcomes, such as decreased functional and cognitive health status, increased risk of falls, adverse drug events, hospitalization, and mortality. However, not all studies have found these associations or connections[19]. Risks of adverse drug outcomes increase with an increasing number of medications used[20]. Wimmer *et al.* evaluated the association between medication regimen complexity in older people and clinical outcomes, and they concluded that regimen complexity was associated with medication non-adherence and increased hospitalization rates[21]. Frailty, multi-morbidity, obesity and reduced physical, as well as mental health status are risk factors for excessive polypharmacy. Sex, educational level, and smoking are apparently not related to excessive polypharmacy. It is noted that physicians should particularly pay attention to frail, obese patients with multi-morbidity and reduced health-related quality of life. It is recommended that all prescribed drugs are carefully checked for being evidence-based, safe, and adverse drug interactions[22].

The aim of the paper was to analyze the characteristics of polypharmacy, the predictors acting on its variability, as well as its impact on possible cognitive disorders in adults diagnosed with a chronic disease at risk for dementia.

Material and methods

The research was a national prospective multicenter study that was conducted during 2022 in the territory of the Republic of North Macedonia. The study was implemented by 46 primary health care (PHC) practices in which family medicine specialists work. The selection of PHC practices was done randomly, with an even representation from all regions of the country. The implementation was preceded by an educational workshop on the methodology and application of the research materials.

Inclusion criteria were patients >60 years of age with a confirmed minimum of one chronic disease at risk for dementia (hypertension, diabetes, high cholesterol, atrial fibrillation, Parkinson's disease, stroke and obesity). The selection was preceded by oral informed consent for participation in the research, and a guarantee of anonymity and use of the data for scientific purposes exclusively. The general/clinical information questionnaire

included: 1) demographic characteristics (sex, age, place of residence, education, cohabitant, and family history of dementia); 2) clinical characteristics (diagnosed chronic diseases); 3) type of therapy (cardiological, antidiabetic, neuropsychiatric, antiparkinsonian, antilipemic, antiaggregative and supplementary therapy). Based on the questionnaire and the number of medication groups received, patients were divided into two groups: ≤2 medication groups and ≥3 medication groups, not including the complementary therapy. Three standardized questionnaires were also used: 1) Mini-cog test (for early dementia screening) where score 0=dementia, refer to a neurologist, 1-2=suspicion, refer to a neurologist, score 3=no dementia; 2) IADL test – the total scoring was according to the highest score, i.e. from 0 (low function, dependent) to 8 (high function, independent) for women and from 0 (low function, dependent) to 5 (high function, independent) for men; and 3) GDS test (geriatric depression scale) – total score is graded as 0-4 – normal finding; 5-9 mild depression; and 10-15 severe depression.

Statistical analysis

The data obtained during the study were statistically analyzed using the SPSS software package, version 22.0 for Windows (SPSS, Chicago, IL, USA). The analysis of the qualitative series was done by determining the coefficient of relations, proportions and rates, and they were shown as absolute and relative numbers. The quantitative series were analyzed using measures of central tendency (mean, median, minimum values, maximum values), as well as measures of dispersion (standard deviation). Pearson's Chi square test was used to determine the association between certain attributive dichotomous features. Mann-Whitney U test was used to determine the significance of difference between two independent numerical parameters with irregular distribution. Risk factors were quantified using odds ratio (OR) and confidence intervals (CI). Difference test was used to compare proportions. Spearman's rank correlation coefficient was used to determine the relation between numerical variables and irregular frequency distribution. Univariate linear regression analysis was used to determine and quantify independent significant predictors of polypharmacy. A level of $p<0.05$ was considered to be statistically significant.

Results

The study included 858 patients, 363 (42.31%) men and 495 (57.69%) women with a sex ratio of 0.73:1, with a significantly higher representation of female sex (Difference 15.38% [(8.62-21.94) CI 95%]; p=0.0001).

The average age in the entire sample was 75.3±6.2 years with a min/max of 63/94 years; 50% of the participants were aged <76 years for Median (IQR)=76 (70-80). Men had a mean age of 75.6±6.1 years, min/max 63/94 years and Median (IQR) = 76 (71-80). The average age in women was 75.2±6.2, with min/max 63/94 years, and Median (IQR) = 75 (70-80). There was no significant difference between sexes in terms of age (Z=1.139p=0.2548).

The proportion of participants with chronic diseases residing in towns was significantly higher compared to those coming from villages (Difference 32.64% [(28.07-37.01) CI 95%]; p=0.0001), without a significant association of the participants' sex with the place of residence (X^2=2.024, df=1, p=0.1548). The majority of men and women respectively had primary education, 171(47.1%) *vs*. 290(58.6%), followed by secondary education 131 (36.1%) *vs*. 159(32.1%) and higher education 61(16, 8%) *vs*. 46(9.3%). Male participants were significantly associated with a higher level of education (X^2=15.585, df=2, p=0.0004). Of all male and female patients, 248(68.3%) *vs*. 223(45.1%) respectively lived with a spouse, 77(21.2%) *vs.* 162(32.7%) lived with a family member/friend, and 37(10.19%) *vs.* 106(21.41%) were singles. Living with a spouse was significantly associated with male sex (X^2=47.167, df=2, p=0.00001).

The presence of chronic diseases (hypertension, diabetes, atrial fibrillation, and Parkinson's disease) was not significantly associated with patients' sex. A significant association with the sex was established in: a) elevated cholesterol – the probability in women was 1.449 times higher [OR=1.449 (1.09 – 1.92) 99% CI]; b) stroke – the probability in men was 1.695 times higher [OR=1.69 (1.13 – 2.55) 99% CI]; and d) obesity – the odds in women were 2.071 times higher [OR=1.695 (1.30 – 3.30) 99% CI].

Majority of participants with chronic diseases received cardiology treatment, namely 797(92.37%), which was followed by 336(39.16%) who received antilipidemics and 237 (27.62%) participants who received antidiabetics (Table 1).

Table 1. General and Clinical Parametres

General parameters	N (%)	Clinical parameters	N (%)
Sex		**Chronic disease**	
Men	363 (42.31%)	**hypertension**	797 (92.89%)
Women	495 (57.69%)	**diabetes**	257 (29.95%)
Place of residence		**High cholesterol**	334 (38.93%)
Village	289 (33.68%)	**atrial fibrillation**	83 (9.67%)
Town	569 (66.32%)	**Parkinson's disease**	31 (3.61%)
Education		**stroke**	106 (12.35%)
Elementary	461 (53.73%)	**obesity**	98 (11.45%)
Secondary	290 (33.80%)	**Therapy – type**	
higher education	107 (12.47%)	**cardiological**	784 (91.37%)
Cohabitant		**antidiabetic**	237 (27.62%)
Single	143 (16.67%)	**neuropsychiatric**	135 (15.73%)
Spouse	471 (54.89%)	**Anti-Parkinskon's**	26 (3.03%)
Family member/friend	244 (28.44%)	**antilipidemic**	336 (39.16%)
[1]Family genesis		**anti-aggregational**	114 (13.29%)
No	774 (90.21%)	**supplements**	386 (44.99%)
Yes	74 (8.62%)		
Don't know	10 (1.16%)	**≤ 2 groups of medication**	497 (57.92%)
		≥3 groups of medication	361 (42.07%)

1Familygenesis for dementia (mother/father)
2Therapy – number (supplementary therapy not included)

The percentage representation of patients receiving daily ≤2 groups of medications for treatment of chronic diseases was significantly higher compared to those receiving ≥3 (Difference 15.85% [(11.14-20.46) CI 95%]; p= 0.0001). The number/percentage of patients receiving 4, 5, or 6 groups of medications per day was as follows: 98 (11.42%) vs. 29 (3.38%) vs. 2 (0.23%), respectively. Majority of patients 294 (34.27%) received 2 groups of medications per day for treatment of a chronic disease, and 232 (27.04%) received three groups of medications per day.

Sex and age as independent predictors significantly affected the variability of polypharmacy with 0.7% vs. 0.5% respectively. On average, female sex increased polypharmacy by 0.185, and each year of age decreased it by 0.012. Parameters such as education, place of residence and the cohabitant were not confirmed as independent predictors of polypharmacy variability (Table 2).

Table 2. Binary linear regression analysis for the influence of selected factors on the variability of polypharmacy

Model Enter	Unstandardized Coefficients		Standardized Coefficients	t	Sig.	95% Confidence Interval for B	
	B	Std. Error	Beta			Lower Bound	Upper Bound
R=0.082R²=0.007F=5.793df=1 p=0.016							
Sex	.185	.077	.082	2.407	.016*	.034	.336
R=0.067R²=0.005F=3.870df=1 p=0.049							
Age	(.012)	.006	(.067)	(1.967)	.049*	(.024)	.000
R=0.0146R²=0.001F=0.168df=1 p=0.662							
Education	(.022)	.054	(.014)	(.410)	.682	(.129)	.084
R=0.012R²=0.000 F=0.029df=1 p=0.866							
Place of residence	.056	.081	.024	.694	.488	(.102)	.214
R=0.017R²=0.001F=0.238df=1 p=0.626							
Cohabitant	(.028)	.058	(.017)	(.488)	.626	(.141)	.085

Dependent variable: number of therapeutic drugs * significant for p<0.05

There was no significant association of Mini-cog dementia test scores with receiving ≤2 or ≥3 groups of medications for a chronic disease (p=0.1221) (Table 3).

The GDS test score was significantly associated with taking ≤2 or ≥3 groups of medications for a chronic disease (p=0.0311). Patients receiving ≤2 medication groups were 1.70 times more likely to have major depression compared to those receiving ≥3 medication groups [OR=1.70 (1.09 – 2.65) 99%CI], i.e., patients receiving ≥3 groups of medications were 1.47 times more likely to have mild depression compared to those receiving ≤2 medications [OR=1.47 (1.09 – 1.97) 99% CI] (Table 3).

Table 3. Mini-cog test and GDS test according to polypharmacy

Tests	[1]Therapy – N (%)		
	≤ 2 groups of medications	≥3 groups of medications	
Mini-cog test – dementia (N=856)			
positive = 0	75 (15.15%)	46 (12.74%)	
doubtful = 1-2	167 (33.74%)	146 (40.44%)	X^2=4.206, df=2, p=0.1221
negative = 3	253 (51.11%)	169 (46.815)	
GDS test – depression (N=856)			
Normal results = 0-4	304 (61.41%)	202 (55.96%)	
Mild depression= 5-9	130 (26.26%)	124 (34.35%)	X^2=6.938, df=2, p=0.0311*
Severe depression = 10-15	61 (12.32%)	35 (9.70%)	

[2]Therapy–number (supplementary therapy not included)

X^2 = Pearson Chi-square test; * significant for p<0.05

A non-significant negative correlation was determined between the IADL score and the number of medications used for the therapy of chronic diseases ($R_{(856)}$=-0.030; p=0.377) with the increase in the number of medications taken; the functionality of patients of both sexes decreased non-significantly **(**Figure 1).

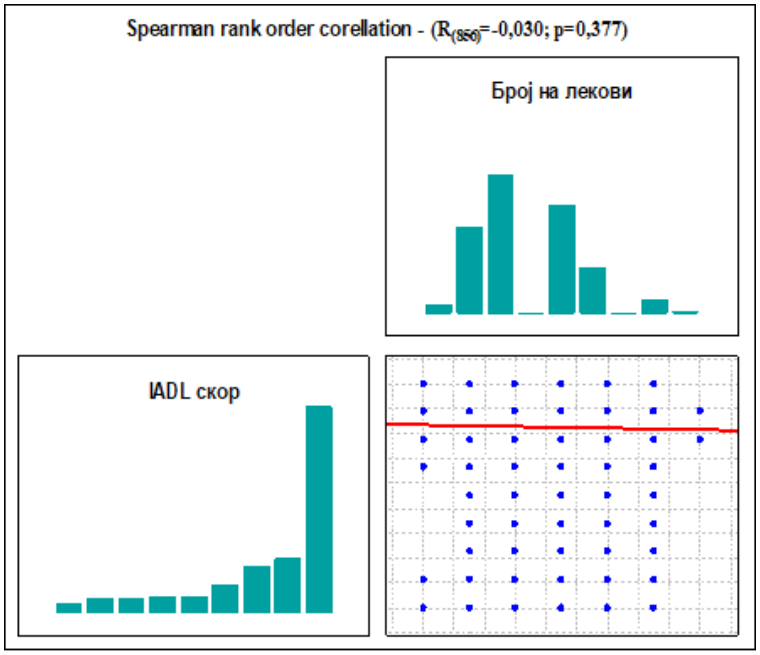

Fig. 1. Correlation of IADL score and the number of medications used for therapy of chronic diseases

Discussion

Age and sex

Women over 60 years of age were associated with polypharmacy and multimorbidity in our study. Compared to other studies, there was no significant difference between sexes in terms of age. Compared to studies from Turkey, America and Mexico where there was a multicultural and multinational population coverage, the male predilection in older age was observed[10].

In our study, sex and age as independent predictors significantly affected the variability of polypharmacy with 0.7% *vs*. 0.5% respectively. On average, female sex increases polypharmacy by 0.185, and each year of age decreases it by 0.012. Parameters such as education, place of residence, and cohabitant were not confirmed as independent predictors of polypharmacy variability.

In England, in a study of adults over 75 years of age, 36% took four or more medications[23]. Similarly, in a study of a non-institutionalized population in the United States[18], the largest medication users were people over 65 years of age: 57%-59% took at least five medications. It is also estimated that 50% of Medicare beneficiaries receive five or more medications[24].

Several studies show that the average number of drugs increases with increasing age, since age is one of the most common risk factors for the prevalence of diseases, i.e., multimorbidity and excessive polypharmacy. In a Swedish study, in an entire national population, the prevalence of polypharmacy varied from 18.4% in the 40-49 years age group to 30.2%, in the 50-59 age group, to 42.3% in patients aged 60 to 69, to 62.4% in the 70-79 age group to 75.1% in the 80-89 age group, and to 77.7% in the age group 90 years and above[11]. Several studies have defined the female sex as a risk factor for excessive polypharmacy, but no sex factor could be identified in the elderly[11]. Patient education level may also be a risk factor for excessive polypharmacy, but there are some conflicting results. Some studies have argued that less educated individuals have an increased risk of excessive polypharmacy, while other studies have found no association between excessive polypharmacy and the level of education[11].

Number of medications

The percentage of patients receiving daily ≤2 groups of medications for treatment of chronic diseases was significantly higher compared to those receiving ≥3 (Difference 15.85% [(11.14-20.46) CI 95%]; p= 0.0001). There were 98 (11.42%) *vs*. 29 (3.38%) *vs*. 2 (0.23%), patients who took 4, 5 or 6 medications per day, respectively. Compared to the literature, the average number of medications used was 4.5[10]. The polypharmacy analysis showed use of 4 chronic medications or 5 chronic medications, respectively[10]. Polypharmacy was observed again with a lower percentage of 54.5% and 37.9% in the oldest age group, of over 80 years of age. In another study in the USA, in comparison to our results patients, aged 65 and older representing approximately 13% of the population took about 30% of all prescribed medications in 2002[10]. Similar to this study, around 20% of the population in England is over 60 years of age, and 52% of all prescriptions in 2000 were prescribed for this age group[23].

Cardiovascular medications are often on the top of the list for drug interactions. In Bjerrum's study, the prevalence of excessive polypharmacy increased with age, and by age 70 two-thirds of all medication users received excessive polypharmacy. Medication use was 50% more prevalent in women than in men, but in those aged over 70 the results in relation to sex did not differ in terms of prevalence of enormous excessive polypharmacy. Cardiovascular medications and analgesics were often involved in excessive polypharmacy in the elderly, while asthma medications, psychotropic medication and anti-ulcer medication predominated in young individuals exposed to excessive polypharmacy. This study recommends that doctors should strengthen their supervision over the prescription and use of analgesics or medications for cardiovascular diseases, anemia, asthma and diabetes[25]. In a study by Hovstadius of the entire national population (a population of 2.2 million people), the prevalence of five most commonly prescribed groups of prescription drugs was determined. It included the following groups of medications: antibacterial drugs (48.2%), analgesics (40.3%), psycholeptics (35.9%), anti-thrombotic agents (33.4%) and beta-blocking agents (31.7%).

Chronic diseases

Regarding the number of chronic diseases, our study showed that the presence of chronic diseases (hypertension, diabetes, atrial fibrillation, and Parkinson's disease) was not significantly associated with the patients' sex. A significant association with sex was established in: a) elevated cholesterol – the probability in women was 1.449 times higher [OR=1.449 (1.09 – 1.92) 99% CI]; b) stroke – the probability in men was 1.695 times higher [OR=1.69 (1.13 – 2.55) 99% CI]; and d) obesity – the probability in women was 2.071 times higher [OR=1.695 (1.30 – 3.30) 99% CI]. Compared to an epidemiological study[10], the average number of chronic diseases was 2.6. More than a half had 3 chronic diseases. There were only 5.6% of men, elderly people without known chronic diseases, while 18.7% had only one chronic disease[10]. In Bluth's study[26], diabetes, cerebrovascular disease, anxiety/depression, and chronic pain significantly affected IADL, pain being predominant and it increased disability. In the CHAMP Study[26] of community-dwelling old men from Australia, 17.9% were older than 70, while 27.5% had one chronic disease on admission to hospital[26].

Association of multimorbidity, personal characteristics with polypharmacy

Chronic conditions and various specific diseases have been shown to be linked with polypharmacy, for example, cardiovascular diseases, anemia, and respiratory disease. Factors associated with both polypharmacy and excessive polypharmacy include poor self-reported health[27]. The study by Jyrkkä *et al*. showed that the factors associated with polypharmacy

and excessive polypharmacy were not uniform. Age ≥85, female sex and moderate self-reported health were factors associated only with EPP, while poor self-reported health and several specific disease states were associated with both polypharmacy and excessive polypharmacy. Using many medications daily in this study[27] required a thorough assessment of the need and effects associated with the use of these medications.

In Hajjar's systematic review of nine studies, chronic diseases such as depression, hypertension, anemia, asthma, angina, diverticulosis, osteoarthritis, gout, and diabetes mellitus were associated with polypharmacy[28]. The literature review showed that polypharmacy increases and is a known risk factor for morbidity and mortality. There are several rigorously designed intervention studies (five studies) that have been shown to implement rational prescribing in older adults[28]. Healthcare professionals should be aware of the risks and fully evaluate all medications at each patient visit to prevent adverse medication effects from drug interactions[28].

Depression

Our data showed that the GDS score for assessing depression in adults was significantly associated with receiving ≤2 or ≥3 groups of medications for a chronic disease (p=0.0311). Patients receiving ≤2 groups of medications were 1.70 times more likely to have major depression compared to those receiving ≥3 groups of medications [OR=1.70 (1.09 – 2.65) 99% CI], i.e. patients receiving ≥3 groups of medicines were 1.47 times more likely to have mild depression compared to those receiving ≤2 groups of medicines [OR=1.47 (1.09 – 1.97) 99% CI], *versus* literature data where depression and dementia were not clinical diagnoses associated with polypharmacy, but suggested for investigation by results obtained from GDS and MMSE with 41.1% and 32.8%, respectively[10].

IADL

Our national research showed the existence of a non-significant negative correlation between the IADL score and the number of groups of medicines used for treating chronic diseases, i.e., with the increase in the number of medicines taken, the functionality of patients of both sexes decreased non-significantly. In our research, a significant negative correlation was established between the IADL score and the number of medicines taken as therapy for chronic diseases ($R_{(856)}$=-0.030; p=0.377) – with the increase in the number of medicines taken, the patients' functionality of both sexes decreased insignificantly. Compared to the literature, those over 80 years of age were four times more likely to have difficulty with ADLs. Those who were separated or divorced were five times more likely to have difficulty with IADL. Those who lived with others or had poor memory were twice more likely to have difficulty with IADL[4].

Dementia

In our study, there was no significant association of Mini-cog dementia test scores with the number of medication groups being taken (p=0.1221), in contrast to literature reporting lower dementia screening scores[4].

Conclusion

There are numerous risk factors for patients with excessive polypharmacy. Our study has shown that age and sex were associated with polypharmacy. Risk factors related to health comorbidities and other sociodemographic factors have not been observed to result in the development of excessive polypharmacy. Patients with less prescribed group of medications had an increased risk of major depression. Interventions to improve medication prescribing knowledge may have the greatest potential to better manage excessive polypharmacy and

improve quality of life in older adults.

Conflict of interest statement. None declared.

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