Vita Medica Scientica Journal

Vol.1, No.1, 10-19 (2025)
doi: 10.64514/vmsjournal.2025.2
ORIGINAL RESEARCH

Investigation of Drug-Drug Interactions in Patients Older than 65 Years with Polypharmacy

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Accepted 03 August 2025

Abstract

Objective: Our aim in this study is to evaluate the frequency of drug-drug interactions and related factors in patients aged 65 and older with multiple drug use.

Materials and Methods: Individuals aged 65 years and older with 4 or more drugs use who applied to family health centers Kayseri province Melikgazi, Kocasinan, Talas, Sarıoğlan, Pınarbaşı, Yahyalı, Tomarza and Hacılar districts in Turkey between October 2020 and February 2021 were included in the study. A questionnaire form was filled out on a voluntary basis by face-to-face interview method, in which sociodemographic information, current diseases and drugs they used were questioned. The drug-drug interactions were checked using the 'Medscape Drug Interaction Checker' system.

Results: Drug-drug interaction was observed in 82.8% of the patients participating in the study. The mean age of those with drug-drug interactions was older. Serious drug-drug interactions were observed in 21.7%, monitor closely in 79.1% and minor in 32.9% of the patients with drug-drug interaction. The prevalence of male gender, hypertension, coronary artery disease, chronic liver disease and chronic renal failure were significantly more common in those with serious drug-drug interaction in patients with drug-drug interaction. A positive and significant correlation was observed between the total number of drug-drug interactions and the number of comorbid disease or the number of drug used.

Conclusion: Our findings show that drug-drug interaction rates are observed at a very high rate in elderly individuals using multiple drugs and are also related to age, number of comorbid diseases and number of drugs used.

Keywords: Drug-Drug Interaction, Polypharmacy, Elderly

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To cite:
Mistik S, Durmus, A. Investigation of Drug-Drug Interactions in Patients Older than 65 Years with Polypharmacy. VMS Journal 2025;1(1):10-19
doi: 10.64514/vmsjournal.2025.2

Introduction

The elderly are the largest consumers of pharmaceutical and health care resources in developed countries. As more drugs become available and life expectancy continues to increase, drug consumption by elderly patients is hypothesized to increase further (1).

There are various definitions of polypharmacy, such as "using 2 or more drugs together for at least 240 days, using 2 or more drugs together, using 4 or more drugs together, using 5 or more drugs together" (2-5). In a study investigating polypharmacy with the participation of 1433 elderly people aged 65 and older in 12 cities in Turkey, it was determined that 38.2% of the patients used 4 or more drugs (6).

Drug-drug interaction (DDI) occurs when the activity of one drug is altered by another drug (7). It contributes to the majority of adverse drug reactions, which cause important medical and economic problems and are an important cause of hospital admissions, especially in elderly patients and patients with polypharmacy. It may also cause altered therapeutic effect and may require dose adjustment of drugs. (8,9,10). DDIs are a major concern, and the risk increases as more drugs are used to manage complex conditions (11).

It has been reported that DDIs cause increased hospitalization and length of stay, increased financial costs, and increased mortality and morbidity (12, 13). The number of potential DDIs increases with the age of the patient and the number of drugs (12,14).

DDIs can occur by pharmaceutical, pharmacokinetic or pharmacodynamic mechanisms. Pharmaceutical DDI is interaction that occur outside the body (15). Pharmacokinetic DDI occurs when one drug alters the absorption, distribution, metabolism or excretion of another (16). Pharmacodynamic DDI occurs when the pharmacological action of one drug is altered by another drug. It is classified as additive, synergistic and antagonistic. If the effect of the drug combination is the sum of the pharmacological effects of the individual drugs, it is additive, if it is more than the sum, it is synergistic, and if it is less than the sum, it is an antagonistic effect (7).

Our aim in this study is to evaluate the frequency of drug-drug interactions and related factors in patients aged 65 and older with multiple drug use.

Matherial and Methods

This study started with the approval of Erciyes University Ethics Committee dated 09.09.2020 and numbered 2020/418 and the approval of Kayseri Provincial Health Directorate's numbered 93079172-703.01.

The population of this cross-sectional analytical study consists of 99544 people aged 65 and older, living in Kayseri province, Melikgazi, Kocasinan, Hacılar, Pınarbaşı, Sarıoğlan, Talas, Tomarza and Yahyalı districts inTurkey. The sample of the study was calculated as 383 people (150 from Melikgazi, 132 from Kocasinan, 39 from Talas, 16 from Yahyalı, 16 from Pınarbaşı, 12 from Sarıoğlan, 12 from Tomarza, 6 people from Hacılar) by using Power analysis with a margin of error of 5% in the 95% confidence interval. The population aged 65 and older required for the analysis was taken from the Turkish Statistical Institute 2019 data.

Individuals aged 65 and older to participate in the study were randomly selected from the Family Health Centers in the specified districts among those who voluntarily agreed to participate in the study between October 2020 and February 2021. A total of 401 patients (150 from Melikgazi, 132 from Kocasinan, 40from Talas, 21 from Sarıoğlan, 20 from Pınarbaşı, 16 from Yahyalı, 12 from Tomarza, and 10 from Hacılar) were included in the study.

After individuals aged 65 and older have signed the informed consent form on a voluntary basis, a questionnaire form was filled by the researcher by face-to-face interview method. In the questionnaire form,

the patient's sociodemographic information (age, gender, occupation, educational status, marital status, income status), the patient's current diseases and medications were asked. The drugs used by the patients were confirmed via 'E-nabız' or 'Medeczane' systems.

Patients aged 65 and older and using 4 or more drugs were included in our study. In our study, the use of 4 or more drugs was accepted for polypharmacy. Patients who used less than 4 drugs or did not sign the informed consent form were not included in the study.

DDIs were checked using the Medscape Drug Interaction Checker on the https://reference.medscape.com/drug-interactioncheckerwebsite. In this system, drug-drug interactions are divided into 3 categories as serious, monitor closely and minor DDIs.

Statistical analysis of data was done in SPSS version 21.0 (IBM®, Chicago, USA) program. The distribution of the data was evaluated using Shapiro Wilk test. Descriptive statistics were expressed as mean and standard deviation in normally distributed numerical data and number and percentage in nominal data. Normally distributed numerical variables were analyzed between the two groups with the "The İndependent Samples t Test". Nominal data were evaluated between the two groups using the Pearson Chi-square test or Fisher's Exact test. "Spearman correlation test" was used for correlation analysis. In the statistical analyzes $p < 0.05$ level was considered statistically significant.

Results

Four hundred and one patients were included in our study. The mean age of 401 patients was 73.0 ± 6.0 years (range 65-94 years). While DDI was observed in 82.8% (n=332) of the patients, no DDI was observed in 17.2% (n=69) of the patients. The mean age of patients with DDI was 74.5 ± 6.4 years, and the mean age of patients without DDI was 72.7 ± 5.8 years. The mean age of those with DDI was higher (p=0.026). When those with and without DDI were compared, the frequency of male gender was significantly higher in those with DDI (p=0.024). (Table 1).

Serious DDIs frequently seen in patients are aspirin-ramipril (n=30) and aspirin-perindopril (n=10). Monitor closely DDIs frequently are aspirin-metoprolol (n=40), ramipril-aspirin (n=30) and metformin-insulin glargine (n=22). In the Medscape Drug Interaction Checker system, there are both serious and monitor closely DDIs between aspirin and ramipril or perindopril, and there are both monitor closely and minor DDIs between aspirin and hydrochlorothiazide. Common DDIs, distribution, level and effects of DDI are shown in Table 2.

The most common comorbidities observed in the all patients were hypertension 83.8% (n=336), diabetes mellitus 40.4% (n=162), coronary artery disease 26.4% (n=106), dyslipidemia 24.4% (n=98) and respiratory system diseases %20,4 (n=82).

In 332 patients with DDI, hypertension (p=0.009), coronary artery disease (p=0.012), chronic liver disease (p=0.004), and chronic kidney failure (p<0.001) were significantly more common in those with serious DDI (Table 3).

Of 332 patients with DDI, 21.7% (n=87) had serious DDI, 79.1% (n=317) had monitor closely DDI, and 32.9% (n=132) minor DDI.

In patients with DDI, the frequency of male gender was significantly higher in patients with serious DDI (p=0.006). The frequency of serious DDI differed significantly according to the occupation (p=0.015) and education level (p=0.024) of the patients. When the education level was grouped as low education (no formal education + primary school) and higher education (middle school + high school + university), it was observed that the education level of those with serious DDI was higher (p=0.001) (Table 4).

The correlation between number of DDI and age, number of comorbid disease and

number of drug were analyzed. A positive and significant correlation was observed between the number of comorbid disease and the total number of DDI (p<0.001), the number of monitor closely DDI (p<0.001) and the number of minor DDI (p=0.015).

Table 1. The sociodemographic variables of the patients and the distribution of the patients with and without DDI

		All patients (n=401)	Patients With DDI (n=332)	Patients Without DDI (n=69)	p
Age	Mean ±	73,0 ± 6,0	74,5 ± 6,4	72,7 ± 5,8	0,026†
Gender	n(%)				0,024††
Woman		218 (54,4)	172 (51,8)	46 (66,7)	
Man		183 (45,6)	160 (48,2)	23 (33,3)	
Occupation	n(%)				0,123††
Retired		177 (44,1)	155 (46,7)	22 (31,9)	
Housewife		209 (52,1)	163 (49,1)	46 (66,7)	
Employee		7 (1,7)	7 (2,1)	0	
Small business		3 (0,7)	3 (0,9)	0	
Farmer		4 (1)	3 (0,9)	1 (1,4)	
Other		1 (0,2)	1 (0,3)	0	
Education status	n(%)				0,648††
No formal		86 (21,4)	69 (20,8)	17 (24,6)	
Primary school		235 (58,6)	193 (58,1)	42 (60,9)	
Middle school		28 (7)	24 (7,2)	4 (5,8)	
High school		27 (6,7)	25 (7,5)	2 (2,9)	
University		25 (6,2)	21 (6,3)	4 (5,8)	
Marital status	n(%)				0,082††
Married		316 (78,8)	267 (80,4)	49 (71)	
Single		85 (21,2)	65 (19,6)	20 (29)	
Income status	n(%)				0,081††
Low		55 (13,7)	50 (15,1)	5 (7,2)	
Middle		294 (73,3)	236 (71,1)	58 (84,1)	
High		52 (13)	46 (13,9)	6 (8,7)	
†İndependent samples T test ,††Chi-squared test					

Similarly, there was a positive correlation between the number of drug used by the patients and the total number of DDI (p<0.001), the number of serious DDI (p=0.009), the number of monitor closely DDI (p<0.001) and the number of minor DDI (p<0.001) (Table 5).

Discussion

In our study, DDI was observed in 82.8% of the patients. The rate of patients with serious DDI was 21.7%. Our results were that DDIs are high in the geriatric population. Results supporting the rates in our study have been reported in the literature. However, due to the evaluation of DDIs with different databases and/or systems, the evaluation of different patient groups such as the general population, outpatients, and hospitalized patients, and the different definition of polypharmacy (≥3 drugs, ≥4 drugs, ≥5 drugs), the DDI rates show a wide distribution between studies. Significant methodological differences between studies limit direct comparison of studies. In a systematic review of 34 studies and 9577 patients by De Oliveira et al. (17), it was reported that DDI rates in elderly patients ranged from 8.3% to 100%. The wide distribution of rates was attributed to investigation of DDI by different methods. In

this study, unlike our study, only hospitalized patients were evaluated.

Among DDIs, serious DDIs are more important than others. In our study, serious DDIs were evaluated according to comorbidities in elderly patients and serious DDIs were observed to be higher in patients with hypertension, coronary artery disease, chronic liver and chronic kidney disease.

Table 2. Common DDIs, distribution, level and effects of DDI

DDI	n (%)	DDI level	Effect
Aspirin-Ramipril	30 (7,5)	Serious (Use Alternative)	Coadministration may result in a significant decrease in renal function. NSAIDs may diminish the antihypertensive effect of ACE inhibitors.
Ramipril-Aspirin		Monitor Closely	Either increases toxicity of the other. May result in renal function deterioration in elderly or volume depleted individuals.
Aspirin-Perindopril	10 (2,5)	Serious (Use Alternative)	Coadministration may result in a significant decrease in renal function. NSAIDs may diminish the antihypertensive effect of ACE inhibitors.
Perindopril-Aspirin		Monitor Closely	Either increases toxicity of the other. May result in renal function deterioration in elderly or volume depleted individuals.
Aspirin-Metoprolol	40 (10)	Monitor Closely	Aspirin decreases effects of metoprolol. Metoprolol and aspirin both increase serum potassium.
Metformin-Insulin Glargine	22 (5,5)	Monitor Closely	Either increases effects of the other. Antidiabetic agents are often used in combination; dosage adjustments may be required.
Aspirin-Insulin Glargine	19 (4,7)	Monitor Closely	Aspirin increases effects of insulin glargine. Insulin dose adjustment may be required.
Aspirin-Clopidogrel	18 (4,5)	Monitor Closely	Either increases toxicity of the other. The need for simultaneous use are common for patients with cardiovascular disease; monitor closely.
Amlodipine-Metformin	16 (4)	Monitor Closely	Amlodipine decreases effects of metformin. Patient should be closely observed for loss of blood glucose control.
Aspirin-Hct	15 (3,7)	Monitor Closely	Aspirin increases and hydrochlorothiazide decreases serum potassium. Effect of interaction is not clear, use caution.
Hct-Aspirin		Minor	Significance Unknown
Ramipril-Metformin	14 (3,5)	Monitor Closely	Ramipril increases toxicity of metformin. Increases risk for hypoglycemia and lactic acidosis.
Levothyroxine-Metformin	13 (3,2)	Monitor Closely	Levothyroxine decreases effects of metformin. Patient should be closely observed for loss of blood glucose control.
Hct-Metformin	16 (4)	Minor	Significance Unknown.

Hct: Hydrochlorothiazide

The high rate of serious DDIs in these diseases may be an important reason why the diseases are associated with many organs and systems. Especially in the treatment of cardiovascular system diseases, the use of multiple drugs is required (18).

Similar results have been reported previously for some of these diseases. Marquito et al. (19) identified drug interactions in patients with chronic kidney disease by the database MICROMEDEX® and found that 74.9% of prescriptions had potential drug interactions and 16.8% of these interactions were great severity. As a result, it was stated in the study that chronic kidney disease was related to high prevalence of serious drug interactions. Bacic-Vrca et al. (20) examined DDIs in elderly patients with arterial hypertension and, in support of our findings, reported that DDIs are common in elderly individuals with

Table 3. Distribution and analysis of comorbid diseases of those with and without serious DDI in patients with DDI

	Patients With Serious DDI (n=87)	Patients Without Serious DDI (n=245)	P
Hypertension	83 (95,4)	207 (84,5)	0,009†
Diabetes Mellitus	33 (37,9)	116 (47,3)	0,129†
Dyslipidemia	28 (32,2)	62 (25,3)	0,215†
Coronary Artery Disease	34 (39,1)	61 (24,9)	0,012†
Cerebrovascular Diseases	5 (5,7)	17 (6,9)	0,701†
Respiratory System Diseases	23 (26,4)	49 (20)	0,211†
Malignancy	2 (2,3)	8 (3,3)	1,000††
Heart Failure	8 (9,2)	10 (4,1)	0,070†
Thyroid diseases	6 (6,9)	32 (13,1)	0,169†
Chronic Liver Disease	7 (8)	3 (1,2)	0,004††
Chronic Renal Failure	10 (11,5)	3 (1,2)	<0,001††
Osteoporosis	8 (9,2)	38 (15,5)	0,143†
Benign Prostatic Hyperplasia	16 (18,4)	35 (14,3)	0,362†
Rheumatic Diseases	12 (13,8)	33 (13,5)	0,940†
Psychiatric Diseases	13 (14,9)	22 (9)	0,120†
Gastrointestinal Diseases	5 (5,7)	17 (6,9)	0,701†
Urinary System Diseases	4 (4,6)	10 (4,1)	0,765††
Neuropathy	4 (4,6)	4 (1,6)	0,214††
Vertigo	1 (1,1)	9 (3,7)	0,464††
Cardiac Dysrhythmia	2 (2,3)	3 (1,2)	0,609††
Musculoskeletal Diseases	4 (4,6)	13 (5,3)	1,000††
Parkinson Disease	2 (2,3)	4 (1,6)	0,654††
Eye Disease	1 (1,1)	6 (2,4)	0,681††
Other	7 (8)	19 (7,8)	0,931†
†Chi-squared test ††Fisher's exact test Data are shown as n (%).			

hypertension and that important DDIs can be prevented by computer-based screening method. Subramanian et al. (21) emphasized that patients with hypertension are sensitive to DDI and that comorbidity, polypharmacy, and advanced age are important factors in DDI.

In our study, a positive and significant correlation was observed between the total number of DDI sand the number of comorbid diseases or the number of drugs used. The increase in the number of comorbidities increases the number of pharmacological treatments. The high number of comorbidities in the elderly population and the high number of pharmacological treatments accordingly make this population susceptible to drug interactions (22). Similar to our findings, many studies have shown that the number of drugs used is an important determinant of DDIs (8, 23, 24). Therefore, DDIs in elderly individuals with polypharmacy should be questioned during routine examination.

Although only individuals aged 65 and older were evaluated in our study, it was observed that those with DDI were older. There is an increase in the incidence of chronic diseases with age, and therefore the number of drugs used also increases. There are many data on the elderly population being more prone to drug interactions (25, 26). The change in drug metabolism with age is an important reason for DDIs in the elderly. Decreased renal capacity and impaired liver metabolism with age are among the most important causes of pharmacokinetic changes. The decrease in the functional capacity of the kidneys reduces the excretion of hydrophilic substances from the kidneys,

so dose adjustments may be required in drugs (27). Liver tissue shrinks with age, and a decrease in cytochrome p450 oxidase activity is observed (28). The change in plasma protein concentrations that enable the transport of exogenous and endogenous substances such as drugs with age is another reason that predisposes the elderly to DDIs (29).

Table 4. Distribution and analysis of sociodemographic variables of those with and without serious DDI in patients with DDI

		Patients With Serious DDI (n=87)	Without Serious DDI (n=245)	P
Age	Mean ± SD	72,8 ± 6,5	72,7 ± 5,6	0,809†
Gender	n(%)			0,006††
Woman		34 (39,1)	138 (56,3)	
Man		53 (60,9)	107 (43,7)	
Occupation	n(%)			0,015††
Retired		51 (58,6)	104 (42,4)	
Housewife		32 (36,8)	131 (53,5)	
Employee		1 (1,1)	6 (2,4)	
Small Business		2 (2,3)	1 (0,4)	
Farmer		0	3 (1,2)	
Other		1 (1,1)	0	
Education Status	n(%)			0,024††
No formal education		15 (17,2)	54 (22)	
Primary school		43 (49,4)	150 (61,2)	
Middle school		9 (10,3)	15 (6,1)	
High school		10 (11,5)	15 (6,1)	
University		10 (11,5)	11 (4,5)	
Education Level	n(%)			0,001††
Lower education		58 (66,7)	204 (83,3)	
Higher education		29 (33,3)	41 (16,7)	
Marital status	n(%)			0,755††
Married		69 (79,3)	198 (80,8)	
Single		18 (20,7)	47 (19,2)	
Income Status	n(%)			0,373††
Low		10 (11,5)	40 (16,3)	
Middle		62 (71,3)	174 (71)	
High		15 (17,2)	31 (12,7)	
†Independent samples T test ,††Chi-squared test				

In our study, it was observed that serious DDIs were more frequent especially in male patients. In some studies, DDIs were more common in women (30), and in some studies in men (21). It has been stated that women consult a physician more frequently, pay attention to their symptoms and to seek care for them than men (30,31,32). The fact that women visit family physicians more often may have caused the detection and prevention of serious DDIs. This may be the reason why serious DDIs were less common in women in our study.

In our study, it was observed that serious DDIs were more common in patients with higher education levels. Haider et al. (33) stated that those with low education level are prone to polypharmacy and potential DDIs. There is also evidence that individuals with lower education levels have better

Table 5. The correlation between number of DDI and age, number of comorbid disease and number of drug

	Total Number of DDI	Number of Serious DDI	Number of Monitor Closely DDI	Number of Minor DDI
Age				
Correlation Coefficient	0,081	0,029	0,075	0,037
P	0,142	0,791	0,184	0,672
Number of comorbid disease				
Correlation Coefficient	0,271	0,136	0,273	0,212
P	<0,001	0,209	<0,001	0,015
Number of drug				
Correlation Coefficient	0,505	0,280	0,527	0,308
P	<0,001	0,009	<0,001	<0,001
* Spearman correlation test				

adherence to treatment (34). In addition, it was emphasized that individuals with low education level may trust their physicians more, so education level may not be a predictive factor in treatment compliance (35). This relationship, which was described between treatment adherence and education level, may have led to more follow-up of serious DDIs at higher education level in our study. According to our findings, it can be said that the higher level of education of the patients does not protect them from DDIs, and that necessary training should be given to individuals with higher education about DDIs.

In our study, frequently observed DDIs included aspirin-ramipril and aspirin-metoprolol. Different medical treatments and DDIs have been reported according to the patient population evaluated in the literature. Subramanian et al. (21) found that among the antihypertensive drugs and other cardiovascular drugs, the interaction of aspirin with enalapril was common among the hypertensive patients. With the knowledge of frequently used drugs, awareness of DDIs can increase.

Limitations

In our study, DDIs were evaluated with one system. This system categorizes DDIs in three levels: serious, monitor closely, and minor. The clinical significance of particularly minor DDIs is unknown. Although there are many methods for the evaluation of DDIs, the lack of a standardized approach limits direct comparison between studies. In addition, our study was planned in a cross-sectional design. The causes and results of DDIs can be shown with prospective studies, and the results that can be obtained by using methods to prevent DDIs can be evaluated.

Since some drug active ingredients cannot be found in Medscape Drug Interaction Checker, they could not be included in our study even if there are interactions of those drugs. These active ingredients are: Betahistine, Diosmin, Zofenopril, Gliclazide, Fenyramidol, Cilazapril, Otilonium Bromide, Trimetazidine, Dobesylate Calcium, Thioctic Acid, Bilastine, Benidipine, Benserazide, Rupatadine Fumarate, Propiverine, Hyoscine Butylbromide, Medazepam, Opipramol, Guanifenesin, Alginic Acid, Nimesulide, Thiocolchicoside, Dexketoprofen, Propyphenazone, Zinc.

Conclusion

In our study, in which we evaluated elderly patients with polypharmacy, DDIs were observed in 82.8% of the patients. Serious DDIs were observed in 21.7%, monitor closely in 79.1% and minor in 32.9% of the patients with DDIs. Serious DDIs were found to be associated with male gender, education level, hypertension, coronary artery disease, chronic liver disease, and chronic kidney

disease. It was observed that the total number of DDI and the total number of serious DDI increased as the number of drug used increased. The total number of DDI also increased as the number of comorbid disease increased.

Our findings showed that DDI rates are quite high in elderly individuals with polypharmacy. For this reason, DDIs should be evaluated in addition to their routine examinations in elderly individuals. DDIs can be detected and reduced by the use of drug interaction checker programs at the time of patient admission to healthcare services or prescribing new prescriptions. Knowing that the elderly and patients with polypharmacy are prone to DDIs may enable new drugs to be questioned in terms of interaction.

Acknowledgement

The authors declare that they did not receive any funding or support for the present study and that there are no potential conflicts of interest related with it. This study has been presented as an oral presentation at the 9. International Medicine and Health Sciences Congress. Paris, France. 27-29 December 2023.

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