An investigation of inappropriate medication use and dangerous drug combinations in elderly patients with polypharmacy

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Abstract

Objective: Polypharmacy is common among the elderly patients. The aim of this study was to determine drugs used inappropriately in elderly with polypharmacy or causing a dangerous drug combination (DDC) and to investigate the relation between drug interaction and emergency department (ED) presentation symptoms.

Methods: This prospective study was performed with elderly patients aged over 65. Patients' demographic characteristics, presentation symptoms, comorbid diseases, and the names, numbers, dosages and side-effect of drugs used were recorded.

Results: DDC was present in 94.6% of patients, and 24.3% presented to the ED with drug interaction-related symptoms. The mean age of the patients with DDCs was 72.4±6.7 years, 68.3±5.5 years among those without DDC(p=0.016).The most common comorbid disease was hypertension(75.1%), the most commonly used drug group was anti arrhythmics (15.4%),and the most commonly used medication was aspirin(6.5%). The relation was observed between drug interaction-related presentation symptoms and coronary artery disease (CAD) (p=0.044). Correlation was determined between DDC and the anti-hypertensive drug group (p<0.001).Correlation was determined between drug interaction and subjects with presentation symptoms of dyspnea and bleeding (p<0.001 and p<0.001, respectively). Numbers of drugs used and frequency of presentation to hospital were higher in patients with DDCs (p<0.001; 0.040 respectively).Positive correlation was determined between frequency of presentation and number of drugs used(r: 0.514; p <0.001).

Conclusion: DDCs are more common as age increases in elderly. This situation especially remarkable in subjects with CAD and antihypertensive drugs users. Presentations to hospital caused by drug-drug interactions most commonly involve dyspnea and bleeding, and a higher number of drugs increase rates of DDC development and numbers of hospital presentations.

Key words: Emergency department; elderly; medicine; polypharmacy

Introduction

Old age is defined as a calendar age of 65 or over and is divided into three periods, early (65-75 years), middle (75-85 years) and advanced (>85 years) (1). The average life span in the 20th century, 46.5 years, rose to 66 by the 2000s, and is expected to increase to 76 by 2050. This also means that the proportion of elderly people in the world will grow still further in the years ahead (2, 3). Although old age is a physiological process, for reasons such as impairment in several organs that emerges with aging, a slowing in metabolic rate, and changes in drug pharmacodynamics (decreases in drug absorption, distribution and elimination or impairment of receptor sensitivity), drugs used for therapeutic purposes in elderly patients lead to more serious side-effects and even fatal outcomes at therapeutic doses (4).

Polypharmacy refers to multiple drug use or the combined use of two or more drugs for at least 240 days (5). The prevalence of polypharmacy increases with age, and stands at 35-40% in patients aged over 75 (6, 7).

Polypharmacy increases the incidence of side-effects, drug-drug interactions and dangerous drug combinations (DDCs), and is also a significant cause of mortality and hospitalization in elderly individuals (6-8). There are numerous criteria or classifications concerning the reliability of medication use in elderly patients, the most widely used being Beers criteria. These were first described in 1991, and were updated, assuming their present form, in 2015. Under the Beers criteria, medications used by elderly patients are divided into three categories, 'medications to avoid in older patients', 'medications to avoid in older patients with certain diseases and syndromes', and 'medications to be used with caution in older patients' (9). Nowadays, Beers criteria are frequently used to monitor the quality of life of elderly patients, and their importance is increasing all the time.

The aim of this study was to determine inappropriate drug use or medication combinations constituting a fatal risk in geriatric patients presenting to the emergency department

(ED), and to investigate the relation between presentation symptoms and medication use.

Materials and Methods

Following receipt of approval from the local ethical committee (No. 2017-05/04), this prospective study was performed with patients aged 65 and over presenting to the Kirikkale University Medical Faculty Hospital ED between 01 January and 30 July, 2017, and using multi-drugs for at least one year. Signed informed consent forms were obtained from patients and/or relatives to confirm that they were participating on a voluntary basis. The study was performed in accordance with the Declaration of Helsinki and the Good Clinical Practice Directive.

Patients' age, sex, alcohol use or smoking status, herbal medication use, medications used, comorbid diseases ED presentation symptoms and frequency of presentations were recorded. Relations between DDCs, drug-drug interactions and side-effects and presentation symptoms were checked using Beers criteria and the 'drug interactions checker' from the Medscape web site (9, 10).

Subjects who refused to participate, patients aged under 65, using less than two medications, taking drugs for purposes of suicide, patients with whom clear communication could not be established (with clouded consciousness, impaired cognitive functions, or with speech or hearing disabilities) and trauma patients were excluded.

Statistical Analysis

All data were analyzed on SPSS 23.0 (Statistical Package for the Social Sciences Inc., Chicago, IL, USA) software. Normality of distribution was assessed using the Shapiro-Wilks test. Quantitative data were expressed as median and interquartile range (IQR), and qualitative data as number (n) and frequency (%). Non-parametric data were analyzed using the Mann-Whitney U test and the Kruskal-Wallis test, while categorical data were analyzed using the Chi-square and Fisher Exact tests. Spearman's rho correlation test was used to compare quantitative data. p values <0.05 were regarded as statistically significant.

Results

During the study period, 3313 patients aged 65 or over presented to the ED. Of these, 1029 were excluded because of presenting due to trauma, 1302 due to absence of polypharmacy, 563 because clear communication could not be established, and 119 due to declining to take part in the study, which was eventually completed with 300 patients.

The mean age of the patients was 72.2 ± 6.7 years (range: 65-91), and 54% (n=162) were women. DDCs was determined in 94.6% (n=284) of patients, and 24.3% (n=73) of presentation symptoms were associated with drug interactions. Women constituted 55.3% of the subjects with DDCs and 50.7% of those with presentation symptoms associated with drug interactions. No statistically significant relation was observed between gender and DDCs or presentation symptoms being associated with drug interactions (p=0.061; 0.514, respectively).

The mean age of the patients with DDCs was 72.4 ± 6.7 years, compared to 68.3 ± 5.5 in subjects without DDCs (p=0.016). The mean age of subjects with presentation symptoms associated with drug interactions was 71.2 ± 5.7, compared to 72.5 ± 7.0 in those whose symptoms were not associated with drug interactions (p=0.156) (Table 1).

Mean numbers of medications used per day were 6.8 ± 2.5 in patients with DDCs and 5.5 ± 1.4 in without DDCs (p=0.04). Mean numbers of medications used per day by patients with presentation symptoms associated with drug interactions were 6.7 ± 2.5, compared to 7.0 ± 2.2 in the other patients (p=0.086). Mean numbers of presentations to the ED were 8.3 ± 6.3 /year in patients with DDCs and 1.9 ± 0.4 /year in without DDCs (p<0.001). Mean numbers of presentations to the ED were 9.4 ± 7.1 /year in patients with presentation symptoms associated with drug interactions and 7.1 ± 6.1 /year in the other patients (p=0.045) (Table 1). Positive correlation was determined between frequency of presentations to the EDs among elderly and numbers of medications used (r: 0.514; p<0.001).

Eighteen different drug groups, 192 different pharmacological contents, and 2011 different medications were used. The three most common drug groups were antiarrhythmics (15.4%), antithrombotics and anticoagulants (13.1%) and antihypertensives (10.2%), and the three most commonly used medications were aspirin (6.5%), metoprolol (4.7%) and furosemide (4.7%) (Table 2). The only relation was determined between subjects with DDCs and anti-hypertensive group drugs (p<0.001); no relation was determined between presentation symptoms associated with drug interactions and any drug group (Table 3).

We observed 438 different DDCs in our patients. The most common of these were 'aspirin + anticoagulant' (10.7%), 'aspirin + metoprolol' (9.8%) and 'aspirin + ACE inhibitors' (8.7%) combinations. The most common side-effect resulting from drug interactions in these combinations was 'bleeding' (including gastrointestinal bleeding, intracranial hemorrhage, epistaxis, hematuria, alveolar haemorrhage), which was most prevalent in the "aspirin + anticoagulant" combinations. The next most common side-effect was dyspnea, most prevalent in the 'metoprolol + bronchodilators' combination (Table 4).

The three most common comorbid diseases in elderly patients were hypertension (HT) in 76.1%, diabetes mellitus (DM) in 54.3%, and coronary artery disease at 37.3%. No relation was determined between DDC and comorbid diseases, although a correlation was observed between presentation symptoms and CAD (Table 5).

The three most common symptoms on presentation to the ED were dyspnea (27.7%), chest pain (20.3%), and headache and/or dizziness (13.3%). While no relation was determined between DDCs and presentation symptoms, correlations were observed between dyspnea and bleeding, and drug interaction (p<0.001; <0.001, respectively) (Table 6).

Examination of the medications used by elderly patients based on Beers criteria revealed that;

- Medications always to be avoided were used at a level of 38.9%,

- Medications to be avoided in elderly patients with certain diseases and syndromes were used at a level of 13.4%,

- Medications to be used with caution in elderly patients were used at a level of 29.4%.

Table 1. Relations between presentation symptoms associated with DDCs and drug interactions and demographic data

	DDCs			Relation between presentation symptoms and drug interaction		
	Yes mean±SD	**No mean±SD**	***P***	**Yes mean±SD**	**No mean±SD**	***P***
Age (year)	72.4±6.7	68.3±5.5	**0.016**[*]	71.2±5.7	72.5±7.0	0.156
Number of drugs (per day)	6.8±2.5	5.5±1.4	**0.040**[*]	6.7±2.5	7.0±2.2	0.086
Number of presentations (year)	8.3±6.3	1.9±0.4	**<0.001**[*]	9.4±7.1	7.1±6.1	**0.045**[*]

DDCs, Dangerous drugs combinations; [*] Pearson Chi-square test

Table 2. Drug groups and the 10 most commonly used medications in elderly patients

Drug group	n (%)
• Antiarrhythmics (Alpha, beta, calcium channel blockers, and others)	310 (15.4)
• Antithrombotics and anticoagulants (Aspirin, UFH, LWMH, warfarin, and others)	263 (13.1)
• Antihypertensives (ACE inhibitors, ARB, Nitrates and others)	206 (10.2)
• NSAIDs (Acetaminophen, and others)	184 (9.1)
• Antidiabetics (Insulin preparations, and oral antidiabetics)	173 (8.7)
• Bronchodilators	162 (8.1)
• Gastrointestinal system drugs (PPI, motility regulators, and others)	159 (7.9)
• Neurology drugs (Antiepileptics, antiparkinsons, and others)	77 (3.8)
• Psychiatric drugs (Antidepressants, antipsychotics and others)	72 (3.6)
• Antilipidemic drugs	64 (3.9)
• Diuretics (Loop, thiazid diuretics, potassium sequestrants, and others)	52 (2.6)
• Hormone preparations (including steroids, thyroid drugs and others)	51 (2.5)
• Antibiotics (Beta lactams, Quinolones and others)	35 (1.7)
• Vitamins and minerals	35 (1.7)
• Genitourinary system drugs	32 (1.6)
• Other drug groups	136 (6.7)
Drug name	
• Aspirin (Acetylsalicylic acid)	131 (6.5)
• Metoprolol	94 (4.7)
• Furosemide	94 (4.7)
• Metformin	62 (3.1)
• Hydrochlorothiazide	61 (3.0)
• Insulin	59 (2.9)
• Clopidogrel	59 (2.9)
• Salbutamol	47 (2.3)
• Amlodipine	46 (2.2)
• Carvedilol	41 (2.0)

UFH, unfractionated heparin; LMWH, low molecular weight heparin; ACE, angiotensin converting enzyme inhibitors; ARB, Angiotensin receptor blockers; NSAID, Non-steroidal anti-inflammatory drugs; PPI, Proton pump inhibitors

Table 3. Relations between DDCs and drug interactions and drug groups

Drug groups	DDCs			Drug interaction		
	Yes (n=284)	No (n=16)	*P*	Yes (n=73)	No (n=227)	*P*
Antihypertensives	257	10	**<0.001**[*]	64	203	0.677
Oral antidiabetics	146	7	0.551	41	112	0.310
Antiarrhythmics	111	3	0.103	28	86	0.943
PPI	80	4	>0.999	23	67	0.242
Bronchodilators	69	1	0.130	13	57	0.199
NSAIDs	56	3	>0.999	17	42	0.371
Antibiotics	38	-	0.237	12	26	0.265
Insulin preparations	31	4	0.088	9	26	0.839
Antithrombotics	14	-	>0.999	4	10	0.751
Anticoagulants	19	1	>0.999	6	14	0.590
Antidepressants	26	3	0.193	8	21	0.668

DDCs, Dangerous drugs combinations; NSAID, Non-steroidal anti-inflammatory drugs; PPI, Proton pump inhibitors; [*] Pearson Chi-square test

Table 4. Effects deriving from DDCs and drug interactions with 10 most commonly used medications in elderly patients

Drug name or group	Drug name or group	Interaction results	n (%)
Aspirin	Anticoagulants (including warfarin)	increase bleeding	47 (10.7)
Aspirin	Metoprolol	increase bleeding	43 (9.8)
Aspirin	ACE inhibitors	increase bleeding	39 (8.7)
Metoprolol	Bronchodilators	dyspnea	36 (8.2)
Metoprolol	Other antiarrhythmics	bradycardia, syncope	23 (5.2)
Furosemide	Metformin	volume retention, hypoglycemia	19 (4.2)
Insulin	ACE inhibitors	hypoglycemia	19 (4.2)
Aspirin	NSAIDs	increase bleeding	15 (3.4)
NSAIDs	ACE inhibitors	renal failure, hypertension	12 (2.6)
Warfarin	NSAIDs	increase bleeding	11 (2.5)

DDCs, Dangerous drugs combinations; ACE, angiotensin converting enzyme; NSAID, Non-steroidal anti-inflammatory drugs

Table 5. Relations between DDCs and drug interactions and chronic or/and comorbid diseases

Comorbid disease	DDCs			Relation between presentation symptoms and drug interaction		
	Yes (n=284)	No (n=16)	*P*	Yes (n=73)	No (n=227)	*P*
HT	216	9	0.133	54	171	0.816
DM	153	7	0.430	153	7	0.408
CAD	109	3	0.114	20	92	**0.044***
COPD	99	5	0.768	19	85	0.075
CHF	58	1	0.211	16	43	0.548
PTE	24	1	>0.999	5	20	0.598
Psychiatric disease	22	1	>0.999	4	19	0.419
Acute infection	18	–	0.610	2	16	0.259
Arrhythmia	15	–	>0.999	5	10	0.372
CRF	12	1	0.517	1	12	0.201
Other	107	9	0.147	129	39	0.109

DDCs, Dangerous drugs combinations; HT, Hypertension; DM, Diabetes mellitus; CAD, Coronary artery disease; COPD, Chronic obstructive pulmonary disease; CHF, Congestive heart failure; PE, Pulmonary thromboemboli; CRF, Chronic renal failure; * Pearson Chi-square test

Table 6. Relations between DDCs and drug interactions and presentation symptoms

Complaint	DDCs			Relation between presentation symptoms and drug interaction		
	Yes (n=284)	No (n=16)	*P*	Yes (n=73)	No (n=227)	*P*
Dyspnea	77	6	0.393	63	7	**<0.001**[*]
Chest pain	60	1	0.208	61	9	0.061
Headache/dizziness	57	3	0.598	60	10	0.916
Nausea and vomiting	36	2	>0.999	38	19	0.072
Abdominal pain	31	2	0.692	33	4	0.083
Urticaria	28	2	0.719	30	6	0.439
Diarrhea	20	5	0.448	25	5	0.601
Bleeding[†]	15	2	0.227	17	15	**<0.001**[*]
Weakness	13	2	0.364	15	3	0.372
Palpitation	4	–	>0.999	4	1	>0.999
Other[‡]	5	1	>0.999	9	1	>0.999

DDCs, Dangerous drugs combination; [*] Pearson Chi-square test; [†] Bleeding (including gastrointestinal bleeding, intracranial hemorrhage, epistaxis, hematuria, alveolar haemorrhage); [‡] Other (including constipation, and urinary retention)

Discussion

The prevalence of drug-drug interactions and side-effects is growing because of an increase due to aging in the prevalence of chronic diseases (and thus in the numbers of medication used), the use of herbal therapies, the use of prescribed or over-the-counter medicines, and changes induced by dose repetitions resulting from forgetfulness and in drug metabolism (11, 12). This is related to gender, as well as aging. Studies have shown that since women have longer life expectancies than men, they are also exposed to more chronic disease, and thus to more drug interactions or DDCs development (13, 14). Topbaş et al. reported mean ages of 69.9 years for women and 70.5 for men in elderly patients regularly using medications (15), while Arslan et al. reported mean ages of 77.1 for women and 74.3 for men (16). The mean age of the patients in our study was 72.2, and the majorities were women. Mean age was higher in patients with DDCs than in those without DDCs, and the difference was statistically significant. However, although the number of women was higher among the subjects with DDCs, we determined no correlation between DDC and gender. Although these findings are similar to those of previous studies, DDC development was associated only with increased age, and was independent of gender.

Chronic and/or comorbid diseases are common among elderly individuals (6, 17). Ünsal et al. reported the presence of at least one chronic disease in 82% of elderly patients, the most common being HT, DM and COPD (18). Chiovanda et al. reported a different sequence, in the form of pulmonary system diseases, DM and cardiovascular system diseases (19). Although the sequences vary from study to study, the risk of polypharmacy and associated drug-drug interaction or DDCs due to the presence of chronic diseases or new diseases persists.

Studies on this subject have reported that simultaneous use of anticholinergic drugs, the use of antidiabetic drugs with alcohol, steroids, antihypertensive or antipsychotics, the use of antibacterial medications with mono-amino oxidase inhibitors, and the use of diuretics with antihypertensive all lead to severe drug interactions and DDCs development (20, 21). The most common diseases in our study were HT, diabetes mellitus, and CAD. Moreover, in addition to newly developing infections, musculoskeletal system disorders were also present in some patients. This all indicated that numerous drugs to be used for both new and old diseases will result in new interactions, side-effects and DDCs. However, we determined no correlation between comorbid diseases and DDCs development. Presentation symptoms associated with drug interactions were only correlated with CAD. This may be due to medications from several groups (antiarrhythmic, antihypertensive, diuretic, antithrombotic, anticoagulant, etc.) being used together in CAD. We attributed the lack of any relation between comorbid diseases and DDCs to the absence of combinations that might result in a statistically significant finding due to medications that might cause DDCs being distributed to different patients.

Since multidrug use in elderly patients can give rise to new side-effects, this can suppress the symptoms and findings of existing diseases. Emerging side-effects may also constitute a primary cause of presentation symptoms (22, 23). Cahir et al. reported the most common side effects resulting in presentations to hospital due to drug interactions in elderly patients as bleeding, dyspepsia, dizziness and impairment of the decision-making mechanism. They attributed the emergence of these to warfarin, aspirin, NSAID and psychotropic drugs, respectively (24). Banerjee at al. reported dyspnea and falls as the most commonly seen side-effects (20), Arslan et al. reported abdominal pain and nausea-vomiting (16), while Uz et al. reported constipation as the most common side-effect (25).

The most frequent presentation symptom in our study was dyspnea, and a correlation was determined with drug interaction. Dyspnea is associated with several acute (seasonal conditions and respiratory tract infections) or chronic (COPD, bronchitis, pulmonary embolism, heart failure, kidney failure, etc.) diseases. At the same time, it may also emerge in association with the use of bronchodilator medications and β-blockers, with cardiac dysfunction, or with other drug combinations that reduce the effectiveness of diuretics.

The medications that most commonly cause drug interactions in elderly patients are anticoagulants, NSAIDs, antihypertensives, antiarrhythmics, antidiabetics, diuretics and antibiotics (6, 21, 26). Warfarin is the best known oral anticoagulant and interacts with several medications (27). In addition to reducing the effect of diuretics and β-blockers, NSAIDs also adversely affect gastrointestinal system (GIS) and renal blood supply, but are commonly used in all age groups, not only by the elderly (28). Sari et al. investigated the relation between GIS bleeding and medication use in elderly patients and determined an association with NSAID, aspirin and warfarin use (29). In our study, both aspirin and NSAIDs were frequently used by elderly patients. The most commonly employed combinations were 'aspirin + metoprolol', 'aspirin + furosemide' and 'aspirin + anticoagulant'. In addition, we determined that antithrombotics, anticoagulants, antiarrhythmics, antihypertensives, diuretics, and angiotensin receptor blockers were frequently used together during the treatment of inter-related diseases such as CAD and HT. Although this is essential for the routine treatment of various diseases, it also leads to bleeding associated with drug-drug interactions. Another finding was that the incidence of DDCs was significantly higher in patients using anti-hypertensive medications. We attribute this to monotherapy being insufficient in the treatment of HT, to patients using numerous and various anti-hypertensive medications on the market together under different names (although their contents are the same), or to the addition of further drugs to treat secondary organ damage occurring due to HT.

The number of daily medications used is another cause of interaction-related effects. Studies have reported 2-9 medications a day being used in elderly patients (6, 30, 31). Several studies have shown that an increase in the numbers of drugs used also raises the probability of drug interactions, DDCs and side-effects (11, 12, 32). Field et al. reported that the risk of adverse reactions in multidrug use increased to 13% in patients using two medications, to 58% in those using five, and to 82% in those using seven or more (32). Bjorkman et al. reported a positive correlation between the probability of drug-drug interaction and numbers of medications used (33). In contrast, Pozzi et al. reported that an increase in hospital presentations associated with drug interactions was correlated, not with the numbers of medications used, but with the combined used of potentially inappropriate medications (34). In our study, the prevalence of DDCs increased in subjects using larger daily numbers of medications. Numbers of

presentations to hospital were also significantly high in these patients. A higher number of medications facilitates potential side-effects, drug-drug interactions, the emergence of DDCs and an increased number of ED presentations. We think that although more DDCs emerged in patients using higher numbers of medications, numbers of presentations to the ED were not solely associated with the mean number of medications used, and that various combinations may result in hazardous interactions irrespective of medication numbers.

Studies have reported that elderly people constitute 9-23% of patients presenting to the ED, and that polypharmacy causing drug interactions in these patients increases both outpatient treatment and hospitalization (35, 36). Numbers of medications used in elderly individuals are related to drug interactions and numbers of presentations to hospital (37, 38). Sehgal et al. showed a positive correlation between multidrug use and DDCs and numbers of presentations to hospital (39). The level of patients presenting to the ED due to drug interactions in the present study was 24.3%. This was statistically significantly higher than the level in patients presenting with both DDCs and drug interaction. In addition, we also determined positive correlation between numbers of presentations and numbers of medications used. These findings are in agreement with previous studies reporting that increased numbers of medications used in elderly patients also increase DDC- and drug interaction-related hospital presentations.

Conclusion

Numbers of medications used and DDCs increase with age in elderly. This particularly applies to subjects with CAD, and using antihypertensive drugs. An increase in the number of medications used results in an increase in drug interactions and hospital presentations, the main presentation symptoms being dyspnea and bleeding. Under these conditions, dyspnea is generally caused by combined use of bronchodilators and β-blockers, while bleeding is generally caused by combined aspirin and warfarin. Further, wide-ranging studies regarding rational medication use and patient safety in the elderly are now needed.**Limitations:** The most important limitations of our study were the absence of control group and low number of patients. The other limitations are as follows: Long-term follow-ups of the patients were not performed and evaluation about the other subjects, except pain scale was not made.

the Authors responsibilities. The study was conducted under defined rules by the Local Ethics Commission guidelines and audits.

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