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Potential drug–drug interactions among prescriptions for elderly patients in primary health care

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Background/aim: Elderly patients are at high risk from drug–drug interactions (DDIs). This study evaluates the potential DDIs in Turkish elderly patients at a primary health care outpatient clinic.

Materials and methods: Online database systems were used to examine DDIs on the prescriptions of patients (n = 1206). The clinical severity of DDIs was classified by the Lexi-Interact Online database.

Results: Of the 5059 prescriptions, 33% were found to have DDIs. We detected 29 (0.9%) A, 380 (11.8%) B, 2494 (77.7%) C, 289 (9%) D, and 18 (0.6%) X risk rating category DDIs among the prescriptions. Prescriptions of female patients and patients aged between 65 and 72 years showed significantly higher number of DDIs. The frequency of DDIs increased both with the number of drugs and combined preparations per prescription. Acetylsalicylic acid and salbutamol were the most frequently prescribed drugs contributing to clinically important DDIs. Additionally, acetylsalicylic acid and escitalopram, which interact with each other, were found on the list of *Beers criteria*. The most predicted clinical outcomes of DDIs were increase in therapeutic efficacy and adverse/toxic reactions.

Conclusions: Prediction of DDIs in elderly patients will provide better prescribing and drug safety. Use of nonsteroidal anti-inflammatory agents, selective serotonin reuptake inhibitors, and beta-2 adrenergic receptor agonists should be closely monitored.

Key words: Polypharmacy, pharmacovigilance, drug safety, geriatrics

1. Introduction

Although combination therapies are generally used to achieve better therapeutic results, drug–drug interactions (DDIs) can lead to life-threatening adverse reactions (ADRs) or therapeutic failure by changing the therapeutic efficacy of drugs. DDIs have been reported to cause 4% of drug-related emergency visits (1). Changes in the pharmacokinetic properties of drugs may produce adverse drug reactions or therapeutic failure. The pharmacodynamics of DDIs can produce additive, synergistic, or antagonistic pharmacological effects (2).

ADRs can be considered an important public health problem, particularly in the elderly patients (3). Polypharmacy and DDIs play critical roles in the production of ADRs and are related to an increased risk of mortality (4,5). Among identified adverse drug events, preventable adverse drug events have been reported to be 27% in primary care and 42% in long-term care, where prescribing and monitoring stages of pharmaceutical care were emphasized for prevention of adverse drug events (6,7). Potentially inappropriate medications have been identified in *Beers Criteria* (8), which aimed to prevent poor outcomes in elderly patients such as ADRs, hospitalization, morbidity, or mortality (8). In the elderly population DDIs can be diagnosed as severe adverse outcomes (9). Increased sensitivity to DDIs in elderly patients and the most frequent ADRs experienced by this age group have been shown in many studies (10–12). Elderly patients exposed to polypharmacy are at high risk of DDIs that depend on age-related changes in pharmacokinetics or pharmacodynamics of drugs, and multiple co-morbidities.

Another important factor for the increased vulnerability of elderly patients to DDIs can be poor compliance, underuse, overuse, or misuse of the medications (13). Moreover, elderly patients who will undergo surgical treatment or treatment in an intensive care unit have been reported to have a high risk for the occurrence of DDIs (14). Although there are publications investigating the use of inappropriate drugs in Turkish elderly patients (15,16), there are no data evaluating potential DDIs in Turkish elderly patients.

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This study aimed to assess: 1) the prevalence of potential DDIs in the elderly patients of an outpatient clinic in a family practitioner center in İstanbul, Turkey; 2) the effects of sex, age, number of drugs, and combined preparations on the frequency of DDIs; 3) the most common drugs/drug groups contributing to DDIs with different risk rating categories and potentially inappropriate medications according to *Beers Criteria*; 4) the clinically important predicted outcomes associated with DDIs.

2. Materials and methods

This retrospective study was performed in the outpatient clinics of the Adem Yavuz Family Practitioner Center in İstanbul, where 8 family practitioners serve a population of approximately 32,000 patients. All units of the center use Server AHBS family practitioners information software for prescriptions, diagnoses, and demographical data of the patients. Elderly patients (aged 65 or older, n = 1206) who had consulted our medical center between the dates of 01.11.2010 and 01.11.2011 were included. This time period was chosen because it was the time when the family practitioner system was officially started in Turkey. The prescriptions (n = 5059) of the elderly patients were examined for possible DDIs. There is no data management system to check the DDIs in our center. DDIs were determined by the following databases: Micromedex Health Care Series Volume 148, Rx Media 2013, Lexi Comp's Drug Information Handbook 19th Edition, Lexi-Interact Online interactions checker, and PubMed. The clinical severity of DDIs was classified as an A, B, C, D, or X risk rating category according to the Lexi-Interact Online database system (Table 1) (2). The potentially inappropriate medications on the list of the most frequently prescribed drugs contributing to DDIs were detected according to *Beers Criteria* (8). The data were processed for statistical analysis using the Mann–Whitney U, Spearman, or Kruskal–Wallis test with SPSS version 17.0. Approval for the study was obtained from the Marmara University Ethical Committee (09.2012.0025).

3. Results

Of the 1206 elderly patients 61% were female. The mean age of the patients was 72.9 ± 6.2 years. The total number of drugs prescribed for female patients (n = 730) was 9123, whereas male patients (n = 246) had 5308 drugs on their prescriptions. There were 374 different diagnoses classified according to the ICD-10-CM coding system on the prescriptions of the patients. The most frequent diagnoses were classified as follows: cardiovascular system diseases (ICD-10-CM/I) (20%), musculoskeletal and connective tissue diseases (ICD-10-CM/M) (15%), and digestive system diseases (ICD-10-CM/K) (14.4%). Among 83.7% of the prescriptions there were at least two drugs that could be analyzed for potential DDIs. There were 972 drugs with different generic names and 542 drugs with different active ingredients in the 4872 prescriptions with at least one drug. The minimum, median, and maximum number of drugs in a single prescription was 1, 3, and 10, respectively. The most frequently prescribed drugs are shown in Table 2.

Of the 1206 patients, 54.7% had potential DDIs. Among 5059 prescriptions written for the 1206 elderly patients, 1670 (33%) were found to cause potential DDIs, with 19.6% having one DDI and 13.4% having more than one DDI. The total number of DDIs among the 5059 prescriptions was 3210. When these were analyzed we detected 29 (0.9%) in the A risk rating category, 380 (11.8%) in the B risk rating category, 2494 (77.7%) in the C risk rating category, 289 (9%) in the D risk rating category, and 18 (0.6%) in the X risk rating category of DDIs. Table 3 presents the 5 most frequently prescribed drugs contributing to DDIs. Acetylsalicylic acid was the most frequently prescribed drug contributing to the A, C, and D risk rating category DDIs, whereas amlodipine besilate was the most frequently prescribed drug for the B risk rating category DDIs and it was salbutamol for the X risk rating category DDIs. The number of prescriptions and number of potential DDIs were analyzed in female and male patients in order to investigate the effect of sex on the frequency of DDIs (using $P < 0.01$, Mann–Whitney U test). Although both female and male patients were on polytherapy with drugs that may result in clinically relevant DDIs, the number of DDIs was significantly higher in the female patients than in the male patients (Table 4). A statistically significant difference was found in the number of interactions between different age groups (Table 4). Elderly patients aged between 65 and 72 years had significantly higher number of DDIs than did the older age (81–88 years) group ($P < 0.01$, Kruskal–Wallis statistics). The relationship between the number of drugs per prescriptions and DDIs was analyzed. A greater number of drugs on the prescriptions caused significantly more potential DDIs ($P < 0.01$, Spearman's rho = 0.524). The percentage of DDI occurrences was 70% and higher in the patients with at least 7 drugs on their prescriptions. The number of potential DDIs was also compared between prescriptions with or without combined drug preparations. Of the 2649 prescriptions with combined preparations, 2256 (70.3%) were found to have potential DDIs, whereas the percentage of prescriptions with DDIs was 29.7 for the prescriptions without combined preparations (n = 2410) ($P < 0.001$, Mann–Whitney U test). Mostly antihypertensive agents in combined preparations such as valsartan/hydrochlorothiazide or ramipril/hydrochlorothiazide had a C risk rating DDI with NSAIDs or antidiabetics, which can cause a decrease in antihypertensive effect and hypoglycemic effect or

Table 1. Lexi-Interact Online DDI risk rating category.

Risk Rating	ACTION	DESCRIPTION
A	No Known Interaction	Data have not demonstrated either pharmacodynamic or pharmacokinetic interactions between the specified agents
B	No Action Needed	Data demonstrate that the specified agents may interact with each other, but there is little to no evidence of clinical concern resulting from their concomitant use.
C	Monitor Therapy	Data demonstrate that the specified agents may interact with each other in a clinically significant manner. The benefits of concomitant use of these two medications usually outweigh the risks. An appropriate monitoring plan should be implemented to identify potential negative effects. Dosage adjustments of one or both agents may be needed in a minority of patients.
D	Consider Therapy Modification	Data demonstrate that the two medications may interact with each other in a clinically significant manner. A patient-specific assessment must be conducted to determine whether the benefits of concomitant therapy outweigh the risks. Specific actions must be taken in order to realize the benefits and/or minimize the toxicity resulting from concomitant use of the agents. These actions may include aggressive monitoring, empiric dosage changes, choosing alternative agents.
X	Avoid Combination	Data demonstrate that the specified agents may interact with each other in a clinically significant manner. The risks associated with concomitant use of these agents usually outweigh the benefits. These agents are generally considered contraindicated.

an increase in the adverse/toxic reactions of NSAIDs. Additionally some of the most frequently prescribed drugs such as the NSAIDs acetylsalicylic acid, diclofenac, and etodolac and one of the most frequently prescribed drugs contributing to DDIs, escitalopram, were found to be on the list of potentially inappropriate medications of *Beers Criteria.* An interaction that can lead to an increase in bleeding and clotting disorders was detected between acetylsalicylic acid and escitalopram.

Table 2. The most frequently prescribed 10 drugs, number of times, and percentages they have been detected in all analyzed prescriptions (n = 5059).

Drugs	(n)	(%)
Paracetamol	736	3.8
Diclofenac sodium	680	3.5
Hydrochlorothiazide	529	2.7
Acetyl salicylic acid	326	1.7
Ibuprofen	325	1.7
Pseudoephedrine hydrochloride	313	1.6
Lansoprazole	311	1.6
Flurbiprofen	305	1.6
Vitamin B6	293	1.5
Etodolac	291	1.5

The predicted clinical outcomes among the most frequently prescribed drugs that contribute to DDIs are indicated in Table 5 with examples for each risk rating category DDI. The predicted clinical outcomes of the potential DDIs were evaluated according to the risk rating categories of the DDIs. Increase in therapeutic drug effect, which was mostly identified under C risk rating category DDIs, was the most frequently predicted clinical outcome among the whole group of expected therapeutic results related to various types of DDIs (Table 6). Increases in adverse or toxic reactions were the most frequently predicted clinical outcomes for the D and X risk rating category DDIs (Table 6).

4. Discussion

The results of this study not only show the prevalence of potential DDIs in elderly patients but also give valuable information about the most frequently prescribed drugs having a potential to generate DDIs in this population. Further, this study indicates the impacts of the demographical characteristics of patients, number of drugs, or combined preparations per prescription on the occurrence of DDIs in elderly patients. More than half of the patients (54.7%) had potential to be exposed to DDIs. Of the 5059 prescriptions, 33% were found to

Table 3. The frequency of the most prescribed 5 drugs which contribute to DDIs are shown for each of drug interaction risk rating category.

DDI risk rating category	1	%	2	%	3	%	4	%	5	%
A	Acetyl salicylic acid	7.7	Hydrochlorothiazide	6.0	Heparins	4.7	Spironolactone	4.7	Amlodipine besilate	3.7
B	Amlodipine besilate	5.7	Hydrochlorothiazide	4.1	Diclofenac sodium	3.3	Gliclazide	3.3	Etodolac	2.5
C	Acetyl salicylic acid	4.4	Diclofenac sodium	4.4	Etodolac	2.7	Escitalopram oxalate	2.4	Flurbiprofen	2.4
D	Acetyl salicylic acid	5.2	Diclofenac sodium	4.5	Etodolac	3.2	Escitalopram oxalate	2.9	Flurbiprofen	2.9
X	Salbutamol sulfate	12.7	Tiotropium	7.8	Ipratropium bromide	6.9	Budesonide	4.9	Formoterol	4.9

Table 4. The effects of sex and age on the number of prescriptions and number of potential DDIs.

Characteristics of patients	Patients (n)	Number of prescriptions	Number of DDIs	Number of DDIs/number of prescriptions (%)
Sex				
Male	476	1924	1151	59.8
Female	730	3135	2059	65.7
Total	1206	5059	3210	
Age (years)				
65–72	592	2743	1564*	57.0
73–80	400	1627	1151	70.7
81–88	195	644	463	71.9
89–96	19	45	32	71.1
Total	1206	5059	3210	

*, $P < 0.01$(different from older age group, 81–88 years).

have potential DDIs. Both sex and age were related to the number of DDIs. The frequency of DDIs both increased with the number of drugs per prescription and with the existence of combined preparations in the prescriptions. Acetylsalicylic acid was the most frequently prescribed drug contributing to the clinically important C and D risk rating category DDIs, whereas salbutamol was the most frequently prescribed drug relevant to the X risk rating category DDIs. Increase in therapeutic drug effect and increase in adverse/toxic reactions were the most critical predicted outcomes associated with potential DDIs.

It has been shown that as the number of elderly patients with polypharmacy increases (17) the probability of poor outcomes related to clinically relevant DDIs leading to ADRs or therapeutic failures becomes a vital issue for public health. Elderly patients can be considered a much more susceptible population than adult patients to develop ADRs due to age dependent physiological changes in the pharmacodynamic and pharmacokinetics of drugs, to polypharmacy being prescribed, and to co-morbid diseases. Although there are studies investigating inappropriate drug use for Turkish elderly patients (15,16), this is the first study evaluating the potential of DDIs in Turkish elderly patients in an outpatient setting in family practice systems. Various findings of other studies evaluating DDIs in different elderly populations need to

Table 5. DDI risk categories and predicted clinical outcomes among the most frequently prescribed drugs that contribute to DDIs.

Drugs/risk categories	Drugs contributing to DDIs	Predicted clinical outcome
Acetylsalicylic acid		
C	acarbose, gliclazide, insulin	increase in hypoglycemic effect of acarbose
C	ramipril, furosemide	decrease in antihypertensive effect
C	sertraline	increase in antiplatelet activity, bleeding and clotting disorders
C	doxycycline	decrease in therapeutic efficacy of doxycycline
C	methylprednisolone, betamethasone	increase in adverse/toxic reactions of steroids
D	etodolac, ibuprofen, naproxen, diclofenac	increase in antiplatelet activity, bleeding and clotting disorders
D	warfarin	increase in anticoagulant activity, bleeding and clotting disorders
Diclofenac		
C	dexketoprofen	increase in antiplatelet activity, bleeding and clotting disorders
C	hydrochlorothiazide	decrease in antihypertensive effect
C	digoxin	increase in adverse/toxic reactions of digoxin
D	acetylsalicylic acid, escitalopram	increase in antiplatelet activity, bleeding and clotting disorders
D	escitalopram	decrease in therapeutic efficacy of escitalopram
Etodolac		
C	flurbiprofen	increase in antiplatelet effect, bleeding and clotting disorders
D	acetylsalicylic acid, escitalopram	increase in antiplatelet effect, bleeding and clotting disorders
Escitalopram		
C	acetylsalicylic acid, enoxaparin	increase in antiplatelet effect, bleeding and clotting disorders
D	flurbiprofen, meloxicam, naproxen	increase in antiplatelet effect, bleeding and clotting disorders
	tizanidine, famotidine, formoterol	QT prolongation, unwanted/life-threatening ventricular arrhythmias
Flurbiprofen		
C	carvedilol, metoprolol	decrease in antihypertensive effect
D	acetylsalicylic acid	increase in antiplatelet effect, bleeding and clotting disorders
Salbutamol		
X	propranolol, carvedilol	decrease in bronchodilatory effect of salbutamol
Tiotropium		
X	ipratropium	increase in anticholinergic effect
Ipratropium		
X	tiotropium	increase in anticholinergic effect
Formoterol		
X	beta blockers (propranolol)	decrease in bronchodilatory effect of salbutamol

be considered. A study organized in an outpatient setting in the US showed that 2.58% of visits with at least one prescription had one or more DDI. In the same study, the relationship between the number of drugs and occurrence of DDIs was demonstrated and the most frequently prescribed drug (6.60%) contributing to clinically relevant DDIs was warfarin (18). Leone et al. (19), using an Italian spontaneous reporting database, reported that 21.7% of the reports included ADRs associated with DDIs. In the same study, the percentage of reports with potential DDIs showed an increase with the number of concomitantly administered drugs and with an increase in the percentage of male patients. The reports of elderly patients with 8 or more medications had a high percentage (88.3%) of potential DDIs (19). Two/thirds (65%, n = 229) of the ambulatory elderly patients in Nigeria were reported to have potential DDIs. The risk of occurrence of DDIs was found to be significantly higher in female patients and patients with at least 6 medications on their prescriptions. Angiotensin-converting enzyme inhibitors were the most

Table 6. The number of the most frequently predicted clinical outcomes related to different risk rating category DDIs.

Predicted clinical outcomes	A	B	C	D	X	Total
Bleeding and clotting disorders	-	7	473	171	-	651
Decrease in therapeutic effect	-	226	590	35	2	853
Increase in therapeutic effect	-	109	707	20		836
Increase in adverse/toxic reactions	-	29	663	57	16	765
Increase/decrease in absorption of drug	-	16	11	3	-	30
Induction/inhibition of microsomal hepatic enzymes	-	-	40	5	-	45
Increase/decrease in elimination	-	-	5	-	-	5
P-glycoprotein mediated interactions	-	-	12	-	-	12
No interaction	29	-	-	-	-	29
Total number of various predicted clinical outcomes	29	387	2501	291	18	3226

frequently interacting drug group (20). In a main hospital in Italy, the contribution of DDIs to ADRs was explored in elderly patients. Of the 1054 Italian patients, 343 were found to be affected by ADRs, particularly warfarin, acenocumarol, and allopurinol. The total number of DDIs was 912, of which 31.5% of them potentially contributed to ADRs (21). These various findings may depend on distinct therapeutic regimens in different countries and ethnic differences in drug response of the patients. Therefore national literature sources, indicating the most common inappropriate drugs or drug combinations, play an important role in the development of quality of life of elderly patients.

We found that acetylsalicylic acid and salbutamol were the most commonly prescribed drugs contributing to clinically important C, D, and X risk rating category DDIs. A well-known D risk rating category DDI is between acetylsalicylic acid and nonsteroid anti-inflammatory drugs (NSAIDs) or vitamin K antagonists such as warfarin. Toxicity in the upper gastrointestinal tract is a serious effect of NSAIDs (22) and concomitant use of salicylates and NSAIDs or anticoagulants can increase the risk of gastrointestinal bleeding (23,24). Moreover, combination therapies of NSAIDs and steroids or antidepressants can lead to unwanted bleeding reactions (22,25). Prophylactic therapy with gastroprotective agents is recommended for patients who have to be treated with these combination therapies (22). Salicylates can diminish the antihypertensive effect of angiotensin converting enzyme (ACE) inhibitors (26). This C risk rating category DDI requires the blood pressures of the patients to be closely monitored in order to adjust for the effect of ACE inhibitors. Another important C risk rating category DDI of acetylsalicylic acid has been reported for hypoglycemic agents. Salicylates were shown to enhance the effect of drugs lowering blood glucose levels (27). Therefore the blood glucose of patients should be followed closely for dose adjustments of these agents. The bronchodilatory effects of salbutamol, an adrenergic beta-2 receptor agonist, can be antagonized by adding beta-receptor blockers to the therapy. This DDI in the X rating category is contra-indicated according to the Lexi-Interact Online database. Patients on therapy with beta-receptor agonists are recommended to avoid taking beta-receptor blockers (28).

One of the interesting findings of this study concerned the most frequently prescribed drugs, NSAIDs such as diclofenac sodium, acetyl salicylic acid, flurbiprofen, and etodolac. These were detected not only to be among the most frequently prescribed drugs but also the most frequently prescribed drugs contribute to the clinically important DDIs in the C and D risk rating category. Moreover, some of the most frequently prescribed drugs were found to be on the list of potentially inappropriate medications of *Beers Criteria* (8). In this guideline avoidance of chronic use of NSAIDs was recommended in order to prevent the risk of gastrointestinal bleeding and peptic ulcer diseases, particularly in patients aged >75 years (8). NSAIDs were also shown to be the most common inappropriately used drug group in Turkish elderly patients (16). Therefore prescription of NSAIDs should be checked in order to improve prescribing and drug safety in elderly patients. Table 3, listing the most frequently prescribed drugs contributing to DDIs, shows that escitalopram, a selective serotonin re-uptake inhibitor (SSRI), is on the list of *Beers Criteria*. SSRIs are potentially inappropriate medications that should be used with caution due to the risk of inappropriate antidiuretic hormone secretion or hyponatremia (8). According to our results, escitalopram was involved in the DDI of D risk rating category, which needs to be closely monitored in patients. Concurrent use

of SSRIs and carbamazepine can lead to carbamazepine toxicity (29). Moreover, combinations of SSRIs and lithium can cause a serotonin syndrome (30).

The lack of information about clinical outcomes in elderly patients associated with DDIs in our study may be its most important limitation. Although the frequency of the use of inappropriate drug combinations with NSAIDs, salbutamol, tiotropium, budesonide, or ipratropium was found to be high, the patients could not be checked for the therapeutic results of the DDIs. Nor could we determine even the most frequently predicted clinical outcomes. The clinical relevance of these interactions should be checked in order to provide evidence-based therapies. Another limitation may be the generalization of our data to the whole country. The patients of only one outpatient clinic in İstanbul participated in this study. However, our data can be considered to reflect the general population due to the cosmopolitan structure of İstanbul with diverse people from all over the country. This study is the first one on DDIs in outpatient clinics among Turkish elderly patients and further studies including more than one outpatient clinic in different cities in Turkey should be planned for improving the quality of life of patients in the older age group.

This study shows that clinically relevant DDIs that may need therapeutic modification are fairly common in elderly patients in outpatient clinics in Turkey. The prescription of NSAIDs, escitalopram, and the drugs in the contraindicated combination therapies (salbutamol, tiotropium, and ipratropium) should be closely monitored in elderly patients in order to prevent DDIs and optimize the management of the medication in this older population.

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