RESEARCH

FACTORS AFFECTING DRUG INTERACTIONS AND THEIR CLINICAL IMPORTANCE IN GERIATRIC OUTPATIENTS

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Abstract

Introduction: Polypharmacy can lead to drug-drug interactions. The aim of this study was to determine the possible factors affecting the prevalence and clinical importance, and interrater reliability of clinical significance of drug interactions in geriatric outpatients.

Materials and Method: Potential drug-drug interactions in 228 patients treated in an outpatient geriatric clinic were evaluated in this cross-sectional, retrospective study. The potential significance of the interactions was reviewed separately by a geriatrician and a clinical pharmacist.

Results: A total of 1342 drugs were prescribed (median 6 [2-14], per patient). Mean age of the patients was 78±0.5 (65-96). Polypharmacy was present in 64.0% of the patients. A weak positive correlation was found between patient age and the number of drugs used (Rs =.205; p=.002). No drug interaction was detected in 18.0% of the patients. In the prescriptions of the remaining 187 patients 760 category C, 70 category D, and 18 category X interactions (Lexicomp®) were detected. A strong positive correlation was found between the number of drugs per patient and the number of drug interactions (Rs =.734; p<.001). There was a strong correlation between the number of interactions and the presence of polypharmacy (r_{pb}=.702, p<.001). The measure of agreement between the clinicians was more pronounced for category D and X interactions (Cohen's κ=.714 and 1, p<.001).

Conclusion: Advanced age, a higher frequency of concomitant use of drugs, and polypharmacy are factors that require clinicians to be aware of drug-drug interactions. Clinical pharmacists can work with geriatricians in outpatient clinics to prevent drug interactions.

Keywords: Drug Interactions; Polypharmacy; Health Services for the Aged; Pharmacist.

INTRODUCTION

Although drugs are one of the key elements of many treatment protocols, the use of multiple drugs introduces the risk of possible drug-drug interactions (pDDIs) that may result in harm. In fact, drug-drug interactions are leading cause of hospitalization (1,2). While many adverse drug reactions are unpredictable, the consequences of pDDIs are predictable and preventable (3,4). Hence, when geriatric patients attend outpatient clinics, this is an important opportunity for recognizing pDDIs and optimizing their treatment.

In a research conducted in a university hospital's geriatric inpatient unit, we previously determined that the main reason for possible drug-related problems was pDDIs (5). As a result of the development of electronic databases in the field of medicine, the use of systems that automatically perform drug interaction analyses has increased. While the use of such tools to assist clinical decision-making increases the quality of healthcare, it can also cause "alert fatigue" when physicians encounter numerous pDDI warnings (6). Therefore, to optimize drug prescription and better predict the interactions that may result in harm to the patient, it is important to determine which pDDIs may be clinically significant. Various studies have shown that the patient's age and gender, as well as the presence of polypharmacy, a high number of chronic diseases or certain diseases, may increase the clinical importance of drug interactions (3). In a study that evaluated the frequency of geriatric syndromes in patients presenting to a geriatric outpatient clinic in Turkey, polypharmacy was observed in 54.5% of the patients (7). Polypharmacy not only leads to negative clinical outcomes (8), but also the incidence of drug interactions and adverse reactions increases exponentially with the increase in polypharmacy (8,9).

Additionally, the geriatric population is subject to significant changes in body composition and, physiological and organ functions, which in turn affect all aspects of pharmacokinetics, including drug absorption, distribution, metabolism, and excretion. Alterations in receptor number and sensitivity in older adults also impact pharmacodynamics (10,11). Consequently, there are considerable differences in the effects of drugs on this population compared to younger people. To address this issue, several standardized tools are available for the planning of pharmacotherapy based on the individual needs and abilities of geriatric patients. It is also worth noting that when geriatric patients have certain diseases, the use of particular drugs may be inappropriate (12,13). A drug-drug interaction may become clinically more significant if one of the drugs causing the interaction is potentially inappropriate for use in the elderly (14). Thus, determining the relationship between inappropriate drug use and the clinical significance of pDDIs is important in terms of reducing the vulnerability of patients.

The prevalence of pDDIs in community-dwelling elderly people ranges from 4 to 46% and, depends on the setting (e.g., hospital, outpatient clinic, pharmacy) and the method of determining the interaction (4). An accurate assessment of the clinical significance of pDDIs is essential to reduce patient vulnerability, regardless of the healthcare practitioner involved in optimizing the patient's treatment. It should be determined whether physicians and pharmacists evaluate the severity of the interaction differently, particularly in cases where they have equal access to patient information.

Although geriatric outpatients are at high risk for drug-related adverse effects, the number of studies investigating the types and severity of potential drug-drug interactions in Turkey is limited. Therefore, the aims of this study were to determine i) the prevalence and predictors of pDDIs that may be clinically important in community-dwelling geriatric patients and ii) whether the clinical significance of pDDIs varies depending on the evaluator (physician vs. pharmacist).

MATERIALS AND METHOD

Study population and data collection

This study was conducted between November 2019 and November 2020 in the geriatric outpatient clinic of a tertiary university hospital in İzmir, Turkey. The incidence of clinically important drug-drug interactions has been reported as 16% in ambulatory geriatric patients (1,4). According to the Turkish Statistical Institute (TUIK), the number of elderly people living in İzmir was 493,673 in 2019 (15). The smallest sample size with a 5% margin of error and 95% confidence interval was calculated as 207 people, and it was decided to include 228 patients (+ 10%). A total of 676 patients applied to the outpatient clinic in the study period. The first 228 patients who met the inclusion criteria (aged ≥65 years, being treated with at least 2 drugs) and did not have missing information in their electronic medical files were included in this observational, cross-sectional, retrospective study.

The patients' age, gender, chronic diseases, and clinical data (vitals and biochemical markers), medications, drug administration routes, and complaints, were extracted from the patients' electronic medical files. The presence of polypharmacy was defined as the use of five or more drugs per patient. The active ingredients of the drugs were classified according to the Anatomical Therapeutic Chemical (ATC) code recommended by the WHO for drug utilization monitoring (WHO Collaborating Centre for Drug Statistics Methodology, Guidelines for ATC classification and DDD assignment 2023. Oslo, Norway, 2022. Available address: https://www.whocc.no/filearchive/publications/2023_guidelines_web.pdf), and the pharmaceutical forms were classified using the New Form Codes (NFC) (EMA New Form Code Classification Guidelines, Version 2023, Publication date: January 2023, Available address: https://www.ephmra.org/sites/default/files/2023-01/2023%20EPHMRA%20NFC%20Guidelines.pdf). Each patient's prescription was analyzed for pDDIs using the Lexi-Interact Online database (Lexicomp®) by one pharmacist (İZY). In this database, drug interactions are classified as A, B, C, D, and X. Category A represents no known interactions, Category B represents the specified agents can interact but there is no need for action. Category C interactions are between drugs that interact with each other, and the combination can usually be used with a monitoring plan. Category D interactions are more serious interactions that may need therapy modification. Lastly, in category X, concurrent use of the interacting members should generally be avoided because of significant risks. The interacting drugs, definition, and severity of the interaction were recorded.

During the drug interaction review, the drug interactions of each patient were examined separately by both of one geriatrician (ET) and one clinical pharmacist (EE). The possible interactions were classified as clinically significant/important or insignificant. The following factors were taken into consideration when determining the clinical importance of the pDDIs: interaction severity; potentially inappropriate medication (PIM) criteria (12,13); and patient factors, such as complaints, chronic diseases, vital values (arterial pressure, heart rate), and laboratory findings (serum creatinine, aspartate aminotransferase, alanine aminotransferase, alkaline phosphatase, albumin, fasting blood glucose, hemoglobin A1c, international normalized ratio, activated prothrombin time, serum sodium, potassium, and calcium levels).

Ethics

The authors complied with Good Clinical Practice standards throughout the study. This study was approved by the Ethics Committee for Medical Research of the Faculty of Medicine at Ege University (20-12T/3; 08.12.2020) and was conducted according to the World Medical Association Declaration of Helsinki. Informed consent was obtained from all individual participants included in the study.

Statistical analysis

The database was constructed using Microsoft Excel. Continuous variables are expressed as means ± standard error of mean (SEM). Categorical data are presented in terms of frequencies. Normality testing was performed using the Shapiro-Wilk test. The correlation statistics of data that did not show normal distribution were calculated using the Spearman's test. The Mann-Whitney-U test was used for comparisons between the subgroups of continuous variables with non-parametric distribution. Categorical data were evaluated using Chi-Square test. Point-biserial analysis was performed for correlation statistics between categorical and continuous variables. Inter-rater reliability was measured using Cohen's kappa (κ). All statistical tests were performed using SPSS version 25.0 (IBM SPSS Statistics for Windows, Version 25.0; IBM Corp., Armonk, NY, USA). A p value ≤ .05 was considered statistically significant.

RESULTS

Demographic characteristics of patients

The average age of the 228 patients included in this study was 78 ± 0.5 years. The minimum and maximum ages of the patients were 65 and 96, respectively. Among the patients, 139 (61%) were female, and 89 (39%) were male (Table 1). There was no difference between the average age of the male and female patients (female = 78 ± 0.7 years and male = 78 ± 0.7 years).

The median number of chronic diseases per patient was 3 (min-max: 0 - 7). The estimated glomerular filtration rate (eGFR) was considered normal in 61.35% of the patients, while 80 patients had varying degrees of renal disease (Table 1). Serum creatinine or eGFR values were not found in the electronic files of 21 patients. Most of the patients (n = 165, 72.37%) presented to the outpatient clinic due to active complaints, while the remainder presented for routine check-up or prescription refill.

Prescription and drug use patterns

There were 1342 prescribed drugs (Table 1). There was a weak positive correlation between patient age and the number of drugs used (Rs = .205; p = .002). Female patients used fewer drugs compared to male patients (p = .030; female = 5.69 ± 0.23 drugs/patient and male = 6.18 ± 0.24 drugs/patient).

According to the ATC classification, the most commonly detected drugs were; the cardiovascular system (31.4%), nervous system (21.6%), gastrointestinal system (19.6%), blood and blood forming organs (11%), and genitourinary system and sex hormones (4.0%) (Figure 1). The most prescribed

Table 1. Demographic characteristics of patients.

Patients (n=228)		**Number of patients (%)**
Female/Male		139 (60.96%) / 89 (39.04%)
Age distribution	65-74	85 (37.28%)
	75-84	90 (39.47%)
	>85	53 (23.25%)
Number of patients with polypharmacy	1-4 drugs	82 (35.96%)
	≥5 drugs	146 (64.04%)
Number of drug-drug interactions per patient [Median (min-max)]: 3 (1 – 24)		
Number of chronic diseases per patient [Median (min-max)]: 3 (0 – 7)		
The 10 most common chronic diseases: Hypertension Diabetes mellitus Depression Coronary artery disease Dementia Hypothyroidism Congestive heart failure Urinary incontinence Benign prostatic hyperplasia Arrhythmia		 133 72 48 44 43 37 35 35 28 28
Renal function: eGFR (mL/min/1,73 m^2)	>60	127 (61.35%)
	30-59	68 (33.83%)
	15-29	10 (4.98%)
	<15	2 (0.99%)
Mean serum creatinine (mg/dL): 1.79 ± 0.52		

eGFR, Estimated glomerular filtration rate

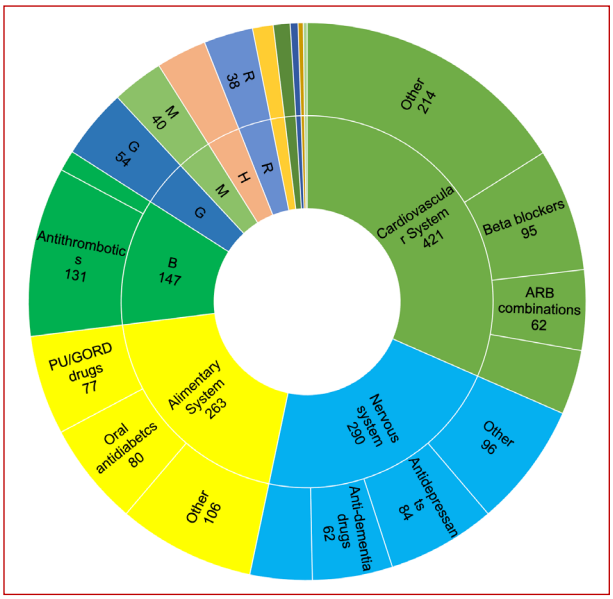

Figure 1. The most commonly prescribed drug types based on the ATC classification system.

ARB, angiotensin receptor blocker; B, blood and blood forming organs; G, genitourinary system and sex hormones; H, sstemic hormonal preparations, excluding sex hormones and insulins; M, musculo-skeletal system; PU/GORD, Peptic ulcer/ Gasroesophageal reflux disease; R, respiratory system

drug groups were antithrombotics (9.8%), beta-blockers (7.1%), antidepressants (6.3%), oral antidiabetics (6.0%), and drugs for peptic ulcer and gastro-esophageal reflux disease (5.7%) (Figure 1). The most prescribed drugs were acetylsalicylic acid, metoprolol, levothyroxine, sertraline, pantoprazole, metformin, clopidogrel, furosemide, atorvastatin, and amlodipine.

The majority (91.4%) of the drugs were administered orally. According to NFC classification oral ordinary or coated tablets, normal or retard capsules, and parenteral pre-filled pens were the most prescribed pharmaceutical forms (Table 2).

Polypharmacy and drug interactions

Polypharmacy was present in 146 (64%) patients. The frequency of polypharmacy was higher in male patients compared to females (p = .047; female = 59.0% and male = 71.9%).

Table 2. The most commonly prescribed drug formulations based on the New Form Codes (NFC) classification system

NFC category	Pharmaceutical form	N (%)
ABC	Oral solid ordinary film-coated tablets	449 (33.46%)
AAA	Oral solid ordinary tablets	364 (27.12%)
ABD	Oral solid ordinary enteric-coated tablets	129 (9.61%)
BBC	Oral solid retard film-coated tablets	64 (4.77%)
BAA	Oral solid retard tablets	56 (4.17%)
ACA	Oral solid normal capsules	51 (3.80%)
FRF	Parenteral ordinary pre-filled pens	29 (2.16%)
BCA	Oral solid retard capsules	20 (1.49%)
ABA	Oral solid ordinary coated tablets	20 (1.49%)
ACY	Oral solid ordinary other capsules	19 (1.42%)

Table 3. Distribution of drug interactions and examples of the most frequently encountered interactions

Interaction category	Drug Interaction n=889 (%)	Patient n=228 (%)
X Carvedilol – Rivastigmine Metoprolol - Rivastigmine Bisoprolol - Rivastigmine Rasagiline - Sertraline Lorazepam - Olanzapine Ketoconazole - Lercanidipine Diclofenac - (Codeine + Naproxen) Olanzapine - Tiotropium Doxazosin - Silodosin Quetiapine - (Umeclidinium + Vilanterol) Doxazosin - Tamsulosin Ketoprofen - Tenoxicam Escitalopram - Rasagiline Escitalopram - Citalopram Propiverine - Tiotropium (Ipratropium + Salbutamol) - Carvedilol Amiodarone - Quetiapine	18 (%2.02)	18 (%7.89)
D Esomeprazole - Clopidogrel Acetylsalicylic Acid - Ginkgo biloba Gliclazide - (Metformin + Vildagliptin) (Levodopa + Benserazide) - Olanzapine Acetylsalicylic Acid - Enoxaparin Gliclazide – Linagliptin Quetiapine – (Levodopa + Benserazide) Diclofenac – Sertraline Enoxaparin – Sertraline Escitalopram – Ginkgo biloba Morphine – Pregabaline (Paracetamol + Codeine) – Tramadol Iron – Levothyroxine Digoxin – Ranolazine Warfarin - Amiodarone	70 (%7.87)	49 (%21.49)
C Acetylsalicylic Acid – Sertraline Acetylsalicylic Acid – Clopidogrel Quetiapine – Sertraline Clopidogrel – Pantoprazole Amlodipine – Clopidogrel Insulin glargine – Metoprolol Gliclazide – Metformine	760 (%85.49)	120 (% 52.63)
A or **B**	41 (%4.61)	41 (%17.98)

There were no interactions between the drugs used by 41 patients (17.98%). In the remaining 187 patients, 848 pDDIs were identified. The median number of pDDIs per patient was 2 (min-max: 0-24). The majority of the pDDIs were category C interactions (n = 760, 85.5%) and occurred in 120 patients (52.6%). A further 70 possible category D interactions were found in 49 patients (21.5%), and 18 possible category X interactions were found in 18 patients (7.9%). A selection of the most frequently encountered pDDIs is shown in Table 3.

There was a strong positive correlation between the number of drugs used per patient and the number of pDDIs (Rs = .734; p < .001). According to the point-biserial correlation analysis, there was a strong correlation between the number of pDDIs and the presence of polypharmacy (r_{pb} = .702, p < .001). The number of pDDIs was significantly higher in patients with polypharmacy (p< .001; 5.49±0.37 and 1.61±0.16 for patients with and without polypharmacy, respectively).

Similar numbers of pDDIs were recorded in the female and male patients (4.47 ± 0.45 and 4.63 ± 0.40, respectively). However, there was a weak positive correlation between the number of pDDIs and the female gender (r_{pb} = .216, p <.001).

Clinician judgment of drug interaction significance

The geriatrician and the clinical pharmacist determined that 580 of the 848 pDDIs (68%) were clinically non-significant. Of the remaining pDDIs, 58 (7%) were considered important by the clinical pharmacist but not by the geriatrician, 49 (6%) were considered important by the geriatrician but not by the clinical pharmacist, 161 (19%) were considered clinically important by both of them (Figure 2). When individual assessments performed by the geriatrician and pharmacist were compared, the measure of agreement between the clinicians was more pronounced for the pDDIs in the more severe category. The clinicians had a perfect agreement on the significance of category X interactions (Cohen's κ = 1, p<.001) and substantial agreement on the significance of category D interactions (Cohen's κ = 0.714, p<.001). Their level of agreement was

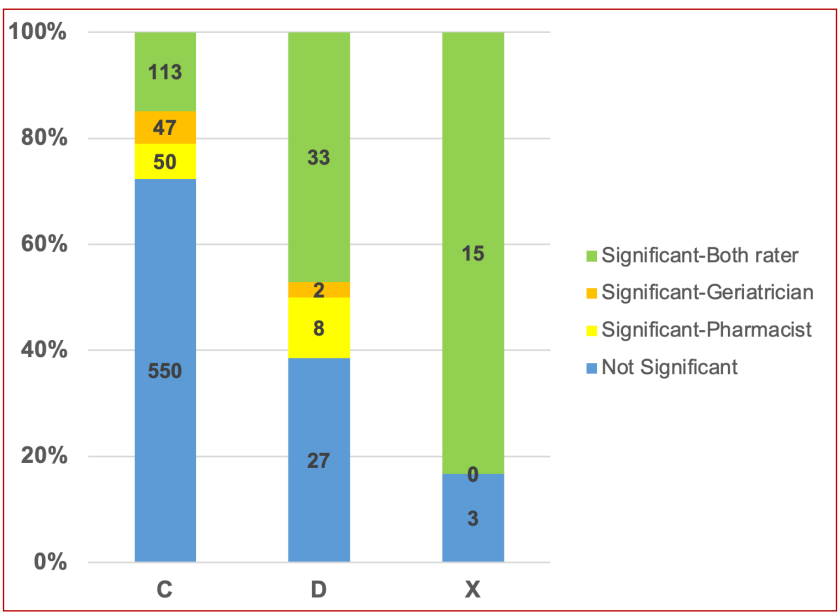

Figure 2. The clinical importance of the drug interactions according to the clinicians.

lower but still significant for category C interactions (Cohen's $\kappa = 0.619$, $p < .001$).

Possible interactions between quetiapine and sertraline, a proton pump inhibitor and clopidogrel, and acetylsalicylic acid and piracetam or Ginkgo biloba were most frequently rated as potentially significant by both clinicians.

DISCUSSION

Polypharmacy, which is commonly defined as the regular use of five or more drugs, is associated with increased PIM use, adverse events, and drug interactions (5,16–18). Polypharmacy is increasing worldwide at an alarming rate, and medicines optimization is complicated by the risks associated with drug interactions (9,19). As a result, patients are presenting to emergency departments with preventable drug-related adverse reactions or events (9).

In a study that involved ambulatory patients aged 50 years and older, it was found that an average of 5.9 drugs/patient had been prescribed, and polypharmacy was present in 69.9% of the patients (20). Similarly, in our study of 228 ambulatory elderly people presenting to the geriatric outpatient clinic of a tertiary hospital, it was found that a median of 6 drugs/patient had been prescribed, the polypharmacy rate was high (64%), and pDDIs were present in 82% of patients. The number of pDDIs was significantly higher in polypharmacy patients in our study. Consistent with findings reported in the literature, there was a weak positive correlation between patient age and the number of drugs used. In a prospective cohort study of 433 patients, adjusted odds ratios for drug interactions were found to increase from 0.91 to 4.40 in patients aged 65-69 years and 80 years or older (21). A repeated cross-sectional analysis of community-dispensed prescribing data performed in Scotland revealed that people aged ≥ 65 years were more likely to have at least one potentially serious DDI, and the proportion of elderly with any DDI increased with age (33.8%, 42.5%, and 46.0% in patients aged 60-69, 70-79, and 80+ years, respectively) (9). Therefore, it is crucial to review geriatric patients' prescriptions to prevent potential harm from pDDIs. Clinical pharmacists play a significant role in reviewing and determining the clinical relevance of pDDIs (5,22,23). Although clinical pharmacists are mainly involved in inpatient healthcare services in Turkey (5), the high pDDI rates detected in our study suggest that it might be useful to place pharmacists in geriatric outpatient clinics.

The results of previous studies are conflicting about the effect of gender on the prevalence of pDDIs. In a study, there were no significant differences between female and male patients (21). However, in another study by Neto et al., female gender was identified as a predictor for clinically important pDDIs (24). This discrepancy may be attributed to the fact that the former study was performed in public primary healthcare units where patients were attended by general practitioners. Although female patients used fewer drugs, the number of pDDIs was not significantly lower in female patients compared to male patients. As the female gender is a known factor for drug-related adverse events, geriatricians in our clinic might have paid more attention to this issue. The relationship between gender, polypharmacy, and drug interactions should be evaluated with further prospective studies.

The prevalence of severe DDIs and the related risk of adverse drug reactions are both very high in patients with PIM use (14); thus, special care must be taken when reviewing pDDIs in geriatric patients. In our study, the most commonly prescribed drugs were those that affect the cardiovascular system (31.4%) and nervous system (21.6%). The elderly group are more prone to experiencing drug-related adverse events associated with these two particular systems. In addition, high-risk and/or potentially inappropriate drugs such as antithrombotics,

antidepressants (especially selective serotonin reuptake inhibitors; SSRIs), and oral antidiabetics, were among the most prescribed drugs or drug groups (9.8%, 6.3%, and 6.0% of patients, respectively), which are referred to as potential PIMs in explicit criteria (12,13). However, the explicit criteria cannot replace the clinical opinion of a health professional. For example, four interactions between beta-blockers and rivastigmine were identified in our study. This is a category X interaction due to the potential for severe bradycardia, and this combination is also listed as a PIM according to the STOPP (Screening Tool of Older Persons' Prescriptions) criteria (Version 2). Yet, three of these four interactions were rated as clinically insignificant by both clinicians because the patients' heart rates were well above 60 beats per minute. In contrast, there were a number of duplication errors identified (e.g., two non-steroidal anti-inflammatory drugs, two SSRIs), all of which were rated as clinically significant by both clinicians.

When individual assessments performed by the geriatrician and clinical pharmacist were compared, the measure of agreement between the clinicians was found to be more pronounced for the pDDIs in the more severe categories. It has been reported that alerts generated by clinical decision support systems related to pDDIs are frequently overridden (56%-96%), with the most commonly stated reason being: "will monitor as recommended" (25). This is in line with our findings, as both the geriatrician and the clinical pharmacist rated 72% of the possible interactions in category C (monitor therapy) as not significant. Disregarding the recommendations of clinical decision support systems has been shown to increase the risk of adverse events (25). However, no decision support system has been developed that is 100% sensitive and specific in a real-world setting (25). Consequently, one of the ways to prevent the negative outcomes of pDDIs may be to implement internal reviews in geriatric assessment teams. With physicians and pharmacists in the geriatric assessment teams approaching patients and drug-related problems from different perspectives, the clinical consensus they reach on the importance of possible drug interactions may reduce the likelihood of harm due to drug interactions. Our previous finding of an 85% acceptance rate of pharmacist interventions in patients treated in a geriatric ward (5) may serve as a good indicator of the possible harmony that could be achieved between the two professions in geriatric assessment teams. In the present study, there was a perfect or substantial agreement between geriatricians and clinical pharmacists on the clinical significance of the high risk attributed to the interactions by the clinical decision support system.

Limitations

Because of the retrospective and cross-sectional design of this study, some patients' laboratory test values were not available at the data acquisition time point. When clinical data were missing, the geriatrician and clinical pharmacist relied on their expertise and professional judgment to define the clinical importance of the drug interactions.

CONCLUSION

When prescribing drugs for their elderly patients, clinicians should be aware of potential drug-drug interactions. The interaction risk could be particularly prominent in people with advancing age, greater number of concomitant drug use, or polypharmacy. Elderly people with polypharmacy often have complex treatment regimens that can lead to adverse events and drug interactions. In our study, the most important pDDIs were a result of the concomitant use of a beta-blocker and an acethylcholine esterase inhibitor, two serotonergic agents (selective serotonin re-uptake inhibitor and monoamine oxidase B inhibitor), two central nervous system depressants (a benzodiazepine and an antipsychotic), two drugs with prominent anticholinergic properties, two QTc prolonging

agents, two drugs that can increase bleeding risk (i.e. antiplatelet agents, P2Y12 antagonists, factor Xa inhibitors vitamin K inhibitor), and pharmacological duplications (non-steroidal anti-inflammatory drugs or alpha 1 receptor blockers). We found a substantial level of agreement between geriatricians and clinical pharmacists on the clinical significance of pDDIs. This presents an opportunity for clinical pharmacists and geriatricians to work together in outpatient clinics to prevent adverse events related to drug interactions. Although clinical pharmacists in Turkey generally work in inpatient settings, given the high risk of pDDIs in geriatric ambulatory patients, collaborative practices should be implemented to address this issue.

Conflict of Interest

There are no financial disclosures or sponsors to declare. The authors report no conflict of interest in this work.

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