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Original Research Article

Potential drug-drug interactions among outpatients with chronic diseases at an Indonesian teaching hospital

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Abstract

Purpose: *To determine potential drug-drug interactions (PDDIs) among outpatients with Chronic Diseases and their correlation to patient's age, number of drug(s), and clinic visited.*
Methods: *A retrospective cross-sectional study was conducted. The data were collected from prescriptions of outpatients with chronic diseases at Prof Dr Chairuddin P Lubis Universitas Sumatera Utara, an Indonesian teaching hospital in 2023. Interactions were identified by the Lexicomp® Drug Interaction Checker. Data were analyzed statistically and presented as numbers and percentages. Correlation between variables was carried out using the chi-square test in SPSS V22.0.*
Results: *The results showed 1405 PDDIs from 313 patients. Most PDDIs based on interaction mechanism, severity, and reliability were pharmacodynamic, moderate, and fair. Cardiovascular, internal medicine and psychiatric outpatient clinics contributed the most PDDIs. Statistically, there was no correlation between patient's age and clinic visits to the number of PDDIs. Meanwhile, the amount of drugs correlated with PDDIs was significantly stated by a p-value of 0.000.*
Conclusion: *High percentages of PDDIs are found among outpatients with chronic diseases. The more drugs on the prescription, the more PDDIs result. Hence, the healthcare team participates in preventing drug-drug interaction.*

Keywords: *Chronic Diseases, Drug Interaction, Hospital, Outpatient, Polypharmacy*

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INTRODUCTION

Chronic diseases are defined as health conditions that last a year or more, necessitate ongoing medical attention and limit daily activities. They consist of cardiovascular diseases, diabetes, cancer, stroke, and other health conditions treated in various specialist clinics. Chronic disease patients tend to have multimorbidity, which leads to the common practice of polypharmacy [1]. The polypharmacy in outpatients needs attention considering its long-term use without professional health supervision. Adverse drug reactions caused by drug interaction could happen outside the hospital [2]. The healthcare team, especially the clinical pharmacist, had to be concerned about it.

The use of two or more drugs together possibly causes drug-drug interactions. Interaction occurs through pharmacokinetic or pharmacodynamic mechanisms. The effects of interaction on individuals range from mild to serious. The standard classification of drug-drug interactions based on severity level is major, moderate, and

minor. The reliability of drug-drug interaction indicates the quantity and nature of documentation for the interaction. It is classified as poor, fair, good, or excellent [3].

Potential Drug-Drug Interactions (PDDIs) are accessed through literature studies and software. The drug interactions checker software has been widely available and easier. It helps clinical pharmacists prevent drug-drug interactions [4]. The high number of prescriptions handled compared to the availability of staff makes preventing drug interactions more challenging.

Many studies have been conducted regarding drug interactions. The result though wide, however, focused more on inpatients who are monitored by healthcare professionals [5]. Meanwhile, studies on PDDIs in outpatients were limited. Through this study, an overview of PDDIs among outpatients with chronic diseases and their correlation to patient's age, number of drugs, and clinic visits will be presented. The study is geared towards arranging clinical interventions in preventing drug-drug interactions.

METHODS

A retrospective descriptive method was conducted at Prof Dr Chairuddin P Lubis Universitas Sumatera Utara Hospital, an Indonesian teaching hospital. All chronic disease prescriptions from outpatient clinics in 2023 were included in this study. The total population was 24,796 prescriptions, distributed in 16 outpatient clinics. The sample comprises 398 prescriptions and was randomly selected with a confidence level of 95 % (Raosoft). Non-polypharmacy prescriptions were excluded in this study. Patient's age, number of drugs, and clinic origin were collected.

This study was approved by the health research ethics committee of Universitas Sumatera Utara with registration no. 942/KEPK/USU/2023 on September 11th, 2023.

The PDDIs are identified by the Lexicomp® Drug Interaction Checker. This software was selected because it possesses one of the best performances of drug interaction checker [6]. The mechanism, severity level, and reliability data of PDDIs were accessed through this software in this study. The severity level was aligned to the reliability in addition to measuring the incidence rate. These three data (mechanism, severity level, and reliability data) are necessary in providing a comprehensive overview of PDDIs.

Statistical analysis

Data are presented as numbers and percentages. The correlation between patient's age, number of drugs, and clinic visits to PDDIs was carried out using the chi-square test in SPSS V22.0. The $p < 0.05$ stated the correlation of the variables.

RESULTS

The 398 prescriptions were represented as samples and were classified by patient's age and number of drugs as shown in Table 1.

The highest number of prescriptions were given to 40 to 65 years category, accounting for 52.01 %. This was followed by 66 years and above, with a percentage of 42.71 %. Furthermore, 90.48, 79.71, and 75.88 % of prescriptions in the age groups of under 40, 40 - 65, and > 65 years, respectively, had PDDIs. The number of PDDIs was not related to the difference in patient's age, as evidenced by *p*-value > 0.05.

The result also showed that 62.06 % of the prescriptions had 2 - 5 drugs, while 37.94 % had more than 5. There were PDDIs in between 66.4 % of the prescription category of 2 - 5 drug items. 98.68 % of prescriptions with a drug category above 5 items interacted.

Table 1: Sample distribution based on age and number of drugs

Category	Total		Interaction		No Interaction		*P*-value
	n=398		n=313 (78.64%)		n=85 (21.36%)		
Ages (years)							
<40	21	(5.28%)	19	(90.48%)	2	(9.52%)	0.624
40-65	207	(52.01%)	165	(79.71%)	42	(20.29%)	
>65	170	(42.71%)	129	(75.88%)	41	(24.12%)	
Drug's Item							
2-5	247	(62.06%)	164	(66.40%)	83	(33.60%)	0.000
>5	151	(37.94%)	149	(98.68%)	2	(1.32%)	

The increasing number of drugs significantly increased the percentage of PDDIs, as evidenced statistically by *p* = 0.000. Drug interaction checks found that 313 prescriptions out of a total of 319 sampled had at least 1 drug interaction. A total of 1,405 PDDIs were found. The PDDIs ratio was 3.34 per prescription. This ratio was close to the value shown in a study in Jordan [7]. All PPDIs were classified based on their mechanism, severity level, and reliability, as shown in Table 2.

Table 2: PDDIs Based on Mechanism Severity Level and Reliability

Category PDDIs	Number of PDDIs	
Mechanism		
Pharmacokinetic	229	(16.30%)
Pharmacodynamic	1176	(83.70%)
Severity Level-Reliability		
1. Major	*105*	*(7.47%)*
a. Good	25	(23.81%)
b. Fair	78	(74.29%)
c. Excellent	2	(1.90%)
2. Moderate	*1145*	*(81.49%)*
a. Good	129	(11.27%)
b. Fair	1013	(88.47%)
c. Excellent	3	(0.26%)
3. Minor	*155*	*(11.03%)*
a. Good	54	(34.84%)
b. Fair	98	(63.23%)
c. Excellent	3	(1.94%)

Most PDDIs occurred based on pharmacodynamic mechanisms of up to 1,176 (83.70 %), while pharmacokinetic mechanisms were 229 (16.30 %). Based on the severity level, most interactions had moderate severity, up to 1,145 (81.49 %). Meanwhile, there were 155 minor and 105 major interactions, with percentages of 11.53 and 7.47 %, respectively. The severity and reliability levels were juxtaposed to predict the possibility of interaction occurrence. Fair reliability was the highest at each severity level. In this study, there were two major interactions with excellent reliability.

Major severity levels of PDDIs were found in 105 interactions from 16 combinations of drugs, as shown in Table 3. The most frequent interaction was a combination of spironolactone-candesartan. Meanwhile, 2 of the 105 major interactions, which were combinations of warfarin-aspirin and simvastatin-gemfibrozil, had excellent reliability. Occurrences of PDDIs were distributed in 16 outpatient clinics and most were found in the cardiovascular clinic, followed by the internal medicine and psychiatry. The three outpatient clinics mainly had pharmacodynamic and moderate PDDIs, as shown in Table 4. PDDI was not found in Ophthalmology-Clinic. There was no statistical correlation between outpatient clinics and the number of PDDIs (p = 0.628).

DISCUSSION

The prevalence of chronic diseases increases every year, accompanied by an increasing cost burden. The increasing cost burden is influenced by the tendency of polypharmacy. Polypharmacy in elderly patients had a 2.3 times tendency to be associated with adverse drug reactions [8]. This should be of great concern because in this study, most chronic diseases were suffered by elderly patients. This study found that the patient's ages did not correlate to PDDIs. On the contrary, most previous studies reported the correlation of age to the number of PPDIs [9]. This contradiction was caused by the selection of different age groups since most previous studies focused on the elderly population. Physiological changes in elderly patients can alter the pharmacokinetic and pharmacodynamic profile of a drug, but there were limitations in data regarding drug interaction risks in their population. Because they are excluded from most clinical trials [10]. The number of drugs affected the number of PDDIs and was statistically significant. Hence the number of PDDIs can be reduced by avoiding unnecessary polypharmacy [11].

Table 3: Major Drug Interaction

Drug A	Drug B	Reliability	Frequency
Spironolactone	Candesartan	Fair	68
Ramipril	Spironolactone	Good	15
Paclitaxel	Carboplatin	Fair	3
Diltiazem	Simvastatin	Good	3
Valsartan	Spironolactone	Fair	2
Doxorubicin	Paclitaxel	Good	2
Clopidogrel	Atorvastatin	Good	2
Captopril	Spironolactone	Good	2
Warfarin	Aspirin	Excellent	1
Ticagrelor	Aspirin	Fair	1
Spironolactone	Potassium chloride	Good	1
Simvastatin	Gemfibrozil	Excellent	1

Table 4: Distribution of PDDIs in Outpatient Clinics

Clinic	Mechanism				Severity Level					
	Pharmacokinetic n=229 (16.30%)		***Pharmacodynamic n=1176 (83.70%)***		***Major; n=105 (7.47%)***		***Moderate n=1145 (81.49%)***		***Minor; n=155 (11.03%)***	
Cardiovascular	179	(78.17%)	970	(82.48%)	91	(86.67%)	951	(83.06%)	107	(69.03%)
Digestive Surgery	2	(0.87%)	0	(0.00%)	0	(0.00%)	2	(0.17%)	0	(0.00%)
Endocrine	2	(0.87%)	2	(0.17%)	0	(0.00%)	2	(0.17%)	2	(1.29%)
Pediatric										
Geriatric	2	(0.87%)	4	(0.34%)	0	(0.00%)	5	(0.44%)	1	(0.65%)
Internal medicine	23	(10.04%)	105	(8.93%)	6	(5.71%)	104	(9.08%)	18	(11.61%)
Metabolic endocrinology	5	(2.18%)	9	(0.77%)	0	(0.00%)	10	(0.87%)	4	(2.58%)
Nephrology	1	(0.44%)	4	(0.34%)	1	(0.95%)	3	(0.26%)	1	(0.65%)
Neurology	3	(1.31%)	9	(0.77%)	0	(0.00%)	12	(1.05%)	0	(0.00%)
Oncology and Gynecology	4	(1.75%)	0	(0.00%)	2	(1.90%)	0	(0.00%)	2	(1.29%)
Oncology Surgery	2	(0.87%)	1	(0.09%)	2	(1,90%)	1	(0.09%)	0	(0.00%)
Ophthalmology	0	(0.00%)	0	(0.00%)	0	(0.00%)	0	(0.00%)	0	(0.00%)
Pediatric	0	(0.00%)	1	(0.09%)	0	(0.00%)	1	(0.09%)	0	(0.00%)
Psychiatry	2	(0.87%)	38	(3.23%)	1	(0.95%)	28	(2.45%)	11	(7.10%)
Pulmonology	2	(0.87%)	33	(2.81%)	1	(0.95%)	25	(2.18%)	9	(5.81%)
Rheumatology	1	(0.44%)	0	(0.00%)	0	(0.00%)	1	(0.09%)	0	(0.00%)
Urology	1	(0.44%)	0	(0.00%)	1	(0.95%)	0	(0.00%)	0	(0.00%)

Most PDDIs were pharmacodynamic mechanisms with moderate severity levels. Pharmacodynamic drug-drug interactions occur when the pharmacological effect of one drug is altered by that of another drug in a combination. It may be expected to achieve synergistic or addictive effects in therapy management. Even though there is a need to ensure that it is appropriate polypharmacy through medication review, especially in elderly patients [12]. A medication review should be conducted to assess unnecessary and ineffective prescribing, as well as drug safety and costs [13]. These issues are the expected roles of the clinical pharmacist in the healthcare team.

Not all PDDIs have clinical consequences. The majority of PDDIs reliability in this study was fair. Fair reliability means more or less than two case reports and other supporting data, or theoretical interactions based on known pharmacology. A severity level with excellent reliability should be monitored due to the high risk and probability. The effects of drug-drug interactions on outpatients can occur at home when consumed without the supervision of a healthcare professional. The effect may lead to patient hospitalization [2].

The two major-excellent PDDIs were observed in aspirin-warfarin and simvastatin-gemfibrozil. The combination of aspirin and warfarin increased the risk of bleeding, which was the most common clinical consequence found in the cardiovascular population [14]. The use of simvastatin combined with gemfibrozil causes rhabdomyolysis. Patients with rhabdomyolysis experience muscle weakness, myalgia, and fatigue. Therefore, patients need to be well-educated about the risks of PDDIs. The cardiovascular clinic had the most prescriptions with polypharmacy as well as PDDIs. Similarly, the internal medicine clinic and the psychiatry clinic also contributed to the high number of PDDIs, consistent with previous studies [15].

A previous study found that cardiovascular clinics had at least 1 PDDI, but the level of risk occurrence was relatively low [16]. Several drugs in psychiatry clinics have shown high potential for interactions. Some of them interacted via pharmacokinetic mechanisms specifically via the metabolism pathway [17]. Therefore, drug-drug interaction checking should be implemented, at least up to the third outpatient clinic visit. A high prevalence of potential drug-drug interactions needs proper monitoring to prevent adverse events [18]. Tele-pharmacy is an option for monitoring adverse drug reactions during drug use at home. This study's results were limited to the area of the hospital studied. Different results may be found depending on the type of hospital services.

CONCLUSION

The increased number of drugs prescribed is consistent with the high number of PDDIs. Most PDDIs occur via pharmacodynamic mechanisms, with moderate severity, and fair reliability. Cardiovascular clinics contribute the most to PDDIs. The healthcare team needs to collaborate in monitoring and educating patients.

DECLARATIONS

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Ethical approval

This study was approved by the health research ethics committee of Universitas Sumatera Utara with the registration no. 942/KEPK/USU/2023 on September 11, 2023.

Availability of data and materials

The datasets used and/or analyzed during the current study are available from the corresponding author upon reasonable request.

Conflict of Interest

No conflict of interest is associated with this work.

Contribution of authors

The authors declare that this work was done by the authors named in this article and all liabilities pertaining to claims relating to the content of this article will be borne by them.

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