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Original Article

From Prescription to Plate: Evaluating Drug-Drug and Drug-Food Interactions in the Prescriptions Dispensed in Community Pharmacies of Northern Cyprus

Ozgur Karatasli[1], Syed Sikandar Shah[2,*], Aftab Alam[2], Syed Arman Rabbani[2], Mevhibe Tamirci[1]

[1]Department of Clinical Pharmacy, Faculty of Pharmacy, European University of Lefke, Mersin-10, TURKEY
[2]Department of Clinical Pharmacy and Pharmacology, RAK College of Pharmacy, RAK Medical and Health Sciences University, Ras Al Khaimah, UNITED ARAB EMIRATES.

ABSTRACT

Background: The effect of drug on a person may be different than anticipated when the drug interacts with another drug/drugs the person is taking, or the food, beverages and dietary supplements the person is consuming. **Materials and Methods:** A total of 750 prescriptions were obtained from four different pharmacies of the Turkish Republic of Northern Cyprus. These prescriptions were evaluated for the drug-drug interactions, drug-food interactions and the legibility of the prescription format and the availability of the information about the prescribed drugs. The prescriptions were examined regarding the availability of the information about the patient and physician name/surname, the age of the patient, the date of the prescription, the specialty of the physician and the name of the hospital/clinic. It was determined that 87.6% of the prescriptions did not include diagnostic information. **Results:** A total of 1461 drugs were written in 750 prescriptions, and the average number of drugs per prescription was 1.95±1.02. In total, 132 drug-drug interactions were observed in prescriptions. On classification of severity of these interactions, 10.6% were found to be major, 71.21% were moderate and 18.18% of them were minor. The most frequent Drug-Drug Interactions (DDIs) were detected between paracetamol-hyoscyamine (*n*=5) and ciprofloxacin-ketoprofen (*n*=4). The most common DDIs were between musculo-skeletal system drugs (42.9%), followed by DDIs between anti-infectives for systemic use (28.6%) and other drugs, and cardiovascular system drugs (21.4%). The most frequent drug-food interactions were between ciprofloxacin (*n*=22), chlorpheniramine (*n*=21) and metronidazole (*n*=18) with food. According to these, it was observed that the most common drug-food interactions was between anti-infective for systemic use, respiratory system drugs and antiparasitic products, insecticides and repellents. **Conclusion:** Drug-drug interactions and drug-food interactions are frequently overlooked and undervalued. Such interactions can have a significant role in the development of adverse drug reactions. Polypharmacy is one of the leading causes of DDIs, a comprehensive examination of the patient's health and medications should be performed prior to prescribing or adding additional prescriptions to their present treatment regimen.

Keywords: Drug-food interactions, Drug-drug interactions, Polypharmacy, Prescriptions.

Correspondence:
Dr. Syed Sikandar Shah
Ras Al Khaimah Medical and Health Sciences University, Al Juwais, Al Qussaidat, PO Box 11172, Ras Al Khaimah, UNITED ARAB EMIRATES.
Email: syed.sikandar@rakmhsu.ac.ae

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INTRODUCTION

Prescription writing is both a science and an art, and it is a fundamental talent that every prescriber should master. The therapeutic message is passed from the doctor to the patient via the pharmacist.[1] A prescription error could result in negative side effects and a potential Drug-Drug Interaction (pDDI). Toxicity or therapeutic failure can result from drug interactions.[2]

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A drug interaction is a change in the nature or impact of a drug caused by the administration of one or more drugs, foods, or beverages at the same time. Drug-drug interactions are a well-known factor influencing medication response and a common source of adverse drug responses.[3] Different sorts of interaction exist. Pharmacodynamic (PD) interaction is an interaction that can modify the nature or kind of response to a medicine. Changes in ADME (Absorption, Distribution, Metabolism, and Excretion) are a part of Pharmacokinetic (PK) interactions. The perpetrator either inhibits or induces the metabolic clearance of the substrate object drug, resulting in an increase or decrease in the therapeutic effect of the object drug due to a change in systemic plasma concentration.[4]

Prescription errors are said to occur in up to 11% of all prescriptions, with the majority of them being dose-related. The frequency of such errors has been the subject of various researches and is a topic of public discussion about patient safety.[5] Pharmacists have a significant role to play in the detection and prevention of drug-related issues and prescription errors. Drug-Drug Interactions (DDI) has been shown to have an impact on drug-related morbidity, including avoidable hospital admissions.[6] Furthermore, drug-drug interactions have become a key reason for drug withdrawals from the market and labeling modifications in recent years, partly due to a lack of proper risk management in daily clinical practice.[7]

Pharmacoepidemiologic investigations, largely conducted in Europe and the Americas, have discovered a range of probable DDI rates, ranging from 5% to 80%. Polypharmacotherapy, age, gender, major diagnosis and medicine, and the number of physicians a patient consults have all been linked to the occurrence of probable DDIs in prior studies.[8] Studies on the occurrence and causes of prescribing potentially dangerous drug combinations in general practice, as well as potential factors of drug-drug interactions linked dispensing in community pharmacies, were undertaken in a variety of mostly western countries.[9] Adverse medication responses caused by DDIs can be serious enough to require hospitalization. According to studies, DDIs account for up to 3% of all hospital admissions. However, due to the large number of medicines that can possibly interact, their prevention remains difficult in practical practice.[10]

Polypharmacy (the use of four or more medications in one prescription) is frequent, and it is known to increase the likelihood of Drug-Drug Interactions (DDIs).[11] Concurrent use of over-the-counter drugs and herbal therapies (e.g., St. John's wort), certain types of food, ethanol, and smoking exacerbates the condition. Pharmacists are crucial in protecting patients from the dangers of potential DDIs, especially when it comes to medications with a narrow therapeutic index.[12] Pharmacists can undertake a manual assessment of medications in a prescription, but the efficiency in detecting DDIs is only about 70% in a two-drug prescription, and the proportion drops dramatically as the number of prescriptions increases.[13] Drug-Drug Interactions (DDIs) are easily avoidable. However, a big number of pharmaceuticals are introduced to the market each year, and as a result, drug interactions are gradually increasing.[14] There are computerized medication interaction checker systems to help prevent this, but they are insufficient on their own because they can only help health professionals reduce potential interactions if they are integrated into their medical and practical expertise.[15]

The aim of this study was to analyze the type and severity of DDIs in prescriptions collected from four different districts (Lefkoşa-Girne-Lefke-Güzelyurt) in community pharmacies during a 5-month period (October 2021-February 2022). A total of 750 prescriptions were collected and entered into a program called SPSS. In this program, ATC Coding system was used for the classification of drugs. Depending on the severity; we classified interactions as major, moderate or minor. The major purpose is to look into the relationship between prescribing physician specialty and the frequency of DDIs, as well as to figure out which drug classes were involved in potential DDIs.

MATERIALS AND METHODS

The present study was initiated after obtaining approval from research and ethics committee of European University of Lefke. The study was conducted over a period of five months starting from October 2022 till February 2022 in Lefke, Guzelyurt, Lefkosa and Girne districts of the Turkish Republic of Northern Cyprus.

A total of 750 prescriptions collected from four community pharmacies in different districts of Turkish Republic of Northern Cyprus (Lefke, Guzelyurt, Nicosia, and Kyrenia) represented the population by selecting pharmacies strategically from urban and semi-urban regions. These locations cover a diverse patient population in terms of socioeconomic status and healthcare accessibility.

All personal data from each prescription, including patients' name, address and insurance information were removed. These prescriptions were evaluated for the drug-drug interactions, drug-food interactions, legibility of the prescription format and the availability of the informations about the prescribed drugs.

The prescription format was analysed by evaluating the availability of informations such as, name/surname of the patient, diagnosis**,** age of the patient, date on the prescription**,** name/surname of the physician**,** speciality of the physician, name of the hospital/clinic and "Rp" symbol.

The prescribed drugs were analyzed based on the availability of information such as drug dosage, amount of active pharmaceutical ingredients, dosage form, drug package quantity and Drug usage directions/physcian warning information.

In addition, for each drug, the trade names, generic names and the Anatomical Therapeutic Chemical (ATC)* code were used for evaluation of drug-drug and drug-food interactions (Figure 1).

Analyses of the Drug-Drug and Drug-Food Interactions

The ATC classification system was utilized to categorize the medications. Drug interactions were investigated using drugs.com. Drug generic names were used to search for drug-drug interactions.[16]

The Drug Interactions Checker from the www.drugs.com database was used to identify potential DDIs. Furthermore, The Anatomical Therapeutic Chemical Classification System was used to classify all drugs. According to the severity of clinical importance, the found DDIs were classified as major, moderate, or minor.[17]

The Drug Interactions Checker from the www.drugs.com database was also used to identify potential drug-food interactions. The severity of the drug-food interactions were also classified as major, moderate or minor.[18]

Statistical Analyses

The obtained data were analysed by using SPSS 25.0 program. Frequency and descriptive analyses with±standard deviation were used to evaluate the format legibility of the prescriptions and drugs as well as the frequency of the drug-drug and drug-food interactions.

RESULTS

Within the scope of the study, 750 prescriptions collected from a total of 4 community pharmacies, each located in Lefke, Guzelyurt, Nicosia and Kyrenia districts, Northern Cyprus, during a 5 month period were examined. It was found that a total of 1461 drugs were written in these prescriptions, and the average number of drugs per prescription was 1.95±1.02.

Out of 750 prescriptions, 299 (39.9%) contained only one drug and the remaining 451 (60.1%) contained two or more drugs (Table 1).

Analysis of the Format Information of the Prescriptions

The prescriptions were examined regarding the availability of the informations about the patient and physician name/surname, the age of the patient, the date of the prescription, the specialty of the physician and the name of the hospital/clinic. It was determined that 87.6% of the prescriptions did not include diagnostic information. In addition, although the 12.4% of the prescriptions included the diagnosis information, the internationally accepted International Classification of Disease (ICD)-10 system had not been used in any of the prescriptions. It was also determined that age related information was missing in 94.9% of the prescriptions (Table 2).

In addition, it was determined that the 'Rp' symbol was not available in 32.8% (*n*=246) of the prescriptions or it was written illegibly in 12.8% (*n*=96) of them.

On analysis of the availability of physician's warnings and/or drug usage instructions, it was observed that this information was not included for 69.5% (*n*=1015) of the prescribed drugs.

On analysis of the presence of information about the prescribed drugs, it was found that most of the prescriptions included drug dosage (96.0%) and pharmaceutical form (87.5%), whereas 53.4% of the prescriptions did not include pharmaceutical active ingredient amount and 47.1% did not include drug package quantity (Table 3).

Analysis of Drug-Drug Interactions in Prescriptions

Prescriptions containing two or more drugs were reviewed electronically and manually for potential drug-drug interactions. At least one drug-drug interaction was found in 96 out of 451 prescriptions (21.3%) containing two or more drugs.

In 12 prescriptions, at least one major and in 68 prescriptions moderate drug-drug interactions were found. In total 132 drug-drug interactions were observed in prescriptions (Table 4).

On analysis of severity of DDIs, it was found that 10.6% of them were major, 71.21% of them were moderate and 18.18% of them were minor (Table 5).

It was determined that 85.7% (*n*=12) of the 14 major DDIs were involved in pharmacodynamic interactions, while only 2% (*n*=2) were involved in pharmacokinetic interactions.

The most frequent Drug-Drug İnteraction (DDI) were between paracetamol (N02BE01)-hyoscyamine (A03BA03) (*n*=5) and ciprofloxacin (J01MA02)-ketoprofen (M01AE03) (*n*=4). According to these, it was observed that the most common drug-drug interactions were between nervous system (ATC, N) and Alimenteracy Tract and metabolism (ATC, A) drugs, and between antiinfectives for systemic use (ATC, J) and musculo-skeletal system (ATC, M) drugs.

It was observed that 10.6% (*n*=14) of the all DDIs were classified as major. The most common prescribed major DDI was between naproxen and diclofenac (Table 6). It was also observed that the most common DDIs were between musculo-skeletal system (ATC, M) drugs (42.9%) and followed by DDIs between antiinfectives for systemic use (28.6%, ATC, J) and other drugs and cardiovascular system drugs (21.4%, ATC, C).

It was observed that moderate DDIs were frequently prescribed by the cardiologists (18.9%) and it was followed by pediatricians (15.8%), internal medicine physicians (15.8%) and gynecologists (8.5%) (Figure 2).

It was detected that the prescriptions with major DDIs were prescribed by cardiologists (23.1%) and it was followed by chest disease specialists (15.4%), dermatologists (15.4%) and orthopedicians (15.4%) (Figure 3).

Analysis of Drug-Food Interactions in Prescriptions

While prescriptions containing two or more drugs were examined for potential drug-drug interactions, the drug food interactions were also evaluated. At least one drug-food interaction was found in 183 of 451 prescriptions containing two or more drugs. In total 239 drug-food interactions were found in prescriptions (Table 7).

The most frequent drug-food interactions were between ciprofloxacin (J01MA02) (*n*=22), chlorpheniramine (R06AB04) (*n*=21) and metronidazole (P01AB01) (*n*=18) with food. According to these, it was observed that the most common drug-food interactions was between antiinfectives for systemic use (ATC, J), respiratory system drugs (ATC, R) and antiparasitic products, insecticides and repellents (ATC, P).

DISCUSSION

Prescribing many medicines to patients at the same time (polypharmacy) is not highly suggested because it can lead to issues such as missed doses, overdosing, DDIs, and ADRs.[19] When administered simultaneously, many medications have the potential to interact with other drugs or substances. According to studies, the amount of medications used raises the risk of DDIs and ADRs considerably.[20] ADRs are a significant issue in both hospital and primary care settings. In an effort to lower the occurrence of ADEs, software that identifies potential harmful medication interactions has been routinely used.[21] Drugs.com was the program used for this particular study's assessment. In this study, the incidence of DDIs in all categories (Major, Moderate, and Minor) was investigated, and DDIs were discovered in 96 of 451 prescriptions (21.3%) containing two or more medicines, which is comparable to other studies. A number of short-term studies in Brazil reported on potential interactions among chosen categories of medications or patients, with DDI rates of 32% for pediatric patients and 22% for psychiatric patients.[22]

A study conducted in Canadian general medical wards found that the rate of probable drug interactions was around 60%, which is greater than our study. Similar studies indicated that the frequency of possible medication interactions ranged from 16% to 47%.[23]

A large percentage of patients in this study had possible drug-drug interactions, and many of them had several potential interactions. Polypharmacy and probable DDIs were found to be more common

Table 1: Analysis of the number of drug(s) written in prescriptions.

Number of the drug(s) written in prescriptions	Number of prescriptions	Percentage (%)
1	299	39.9
2	263	35.1
3	135	18.0
4	43	5.7
5	6	0.8
6	1	0.1
7	2	0.3
8	0	-
9	1	0.1
Total	750	100.0

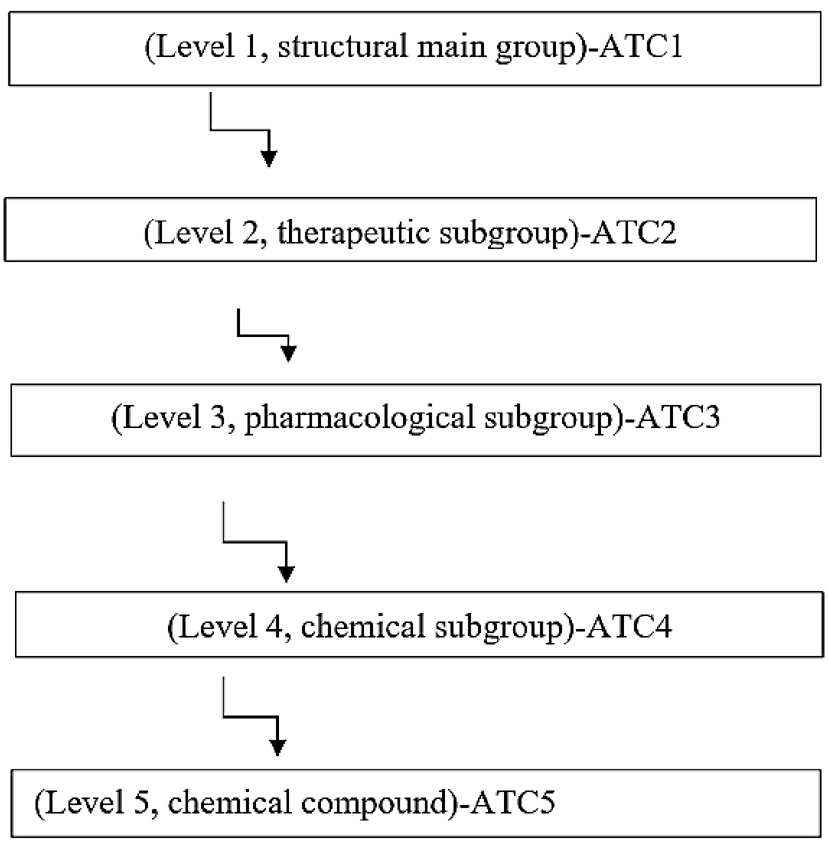

Figure 1: Subgroups of the ATC classification system at 5 different levels.

in older individuals (65 years and older), and polypharmacy was linked to the use of herbal and over-the-counter drugs.[24] In addition, probable DDI was linked to polypharmacy and a number of common chronic disorders (including hypertension, ischaemic heart disease and psychiatric conditions.[25]

Regardless of whether or not adverse effects occur, a potential drug interaction arises when two drugs that are known to interact are administered at the same time. In a real drug interaction, co-administration of another drug causes a clinically significant change in the impact of the object drug (precipitant drug.[26] Actual drug interactions must always occur before potential drug interactions. Knowing or forecasting those times when a potential interaction is likely to have substantial repercussions for the patient is the most important aspect of medication interactions in clinical practice.[27] Health practitioners should have practical understanding of the pharmacological mechanisms involved in drug interactions, pharmaceuticals linked with high risk, and the most vulnerable patient group in order to forecast the likely outcomes of administering two or more drugs. Polypharmacy is a significant contributor to pDDIs; the greater the number of drugs per prescription, the greater the risk of pDDIs.[28]

In this analysis, PD interactions were found to be responsible for a higher percentage of major DDIs (85.71%) than PK interactions (14.29%). Despite the fact that PD drug interactions are important in some circumstances (such as synergism), they will cause clinically significant interactions. For example, combining Angiotensin-Converting Enzyme (ACE) inhibitors with potassium-sparing diuretics like spironolactone (Table) might cause life-threatening hyperkalemia.[29]

The frequency of pDDIs was likewise linked to the number of medications given out, according to this study. The ability of providers to detect and recognize clinically significant DDIs is

Table 2: Presence of format information in prescriptions.

Information to be included in the prescriptions	Number of prescriptions analysed (*n*=750)	
	Available % (*n*)	Not Available% (*n*)
Patient's name/surname	88.7 (665)	11.3 (85)
Patient's age	5.1 (38)	94.9 (712)
Diagnosis	12.4 (93)	87.6 (657)
Comorbidities	7.9 (59)	92.1 (691)
Date of prescription	73.5 (551)	26.5 (199)
Physician name/surname	651 (86.8)	99 (13.2)
Physician specialty	90.3 (677)	9.7 (73)
Name of the hospital/clinic	90.3 (677)	9.7 (73)

Table 3: Presence of informations about the prescribed drugs.

Information to be included in the prescriptions about the drugs	Number of prescriptions analysed (*n*=750)	
	Available % (*n*)	Not Available % (*n*)
Drug dosage	96.0 (1403)	4.0 (58)
Pharmaceutical active ingredient amount	46.6 (681)	53.4 (780)
Drug pharmaceutical form	87.5 (1278)	12.5 (183)
Drug package quantity	52.9 (773)	47.1 (688)

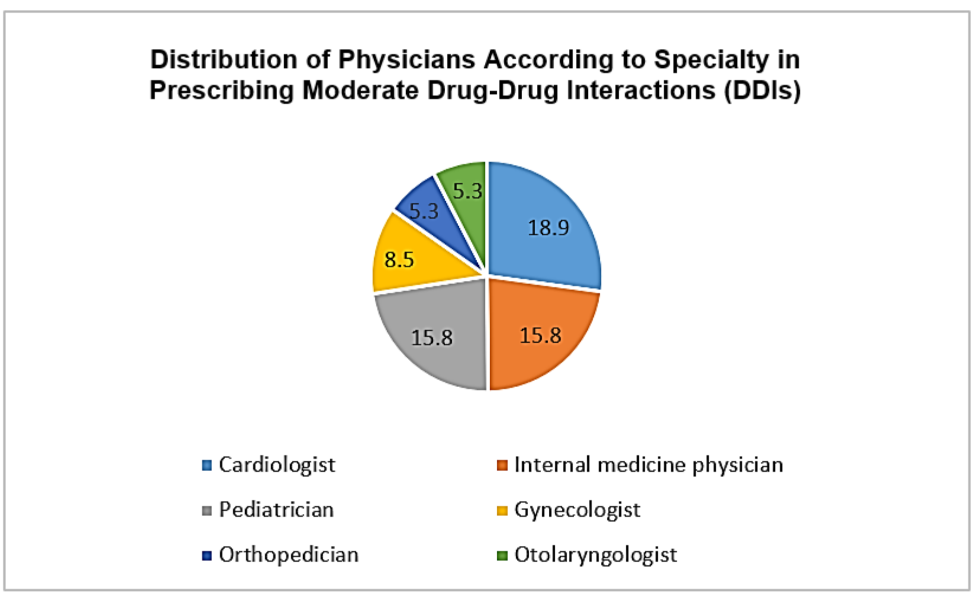

Figure 2: The distribution of moderate DDI prescriptions by physician specialty.

Table 4: Drug-drug interactions identified in the prescriptions.

Sl. No.	Drug drug interactions	Severity	*n* (%)
1	Acetaminophen (N02BE01)-Echinacea (L03AH01)	Moderate	1
2	Acetaminophen (N02BE01)-Hyoscyamine (A03BA03)	Minor	2
3	Acetaminophen (N02BE01)-Phenobarbital (N05CA24)	Moderate	1
4	Acetylsalicylic acid (B01AC06)-Magnesium oxide (A02AA02)	Moderate	1
5	Albuterol (R03AC02)-Budesonide (R03BA02)	Minor	2
6	Albuterol (R03AC02)-Terbutaline (R03CC03)	Moderate	1
7	Amiodarone (C01BD01)-Apixaban (B01AF02)	Moderate	1
8	Amiodarone (C01BD01)-Clopidogrel (B01AC04)	Moderate	1
9	Amiodarone (C01BD01)-Furosemide (C03CA01)	Major	1
10	Amiodarone (C01BD01)-Metoprolol (C07AB02)	Moderate	1
11	amlodipine (C08CA01)-Atorvastatin (C10AA05)	Moderate	2
12	Amlodipine (C08CA01)-Lisinopril (C09AA03)	Minor	1
13	Amoxicillin (J01CA04)-Bifidobacterium infantis (A07FA01)	Moderate	2
14	Amoxicillin (J01CA04)-Clarithromycin (J01FA09)	Minor	1
15	Amoxicillin (J01CA04)-Lactobacillus acidophilus (A07FA51)	Moderate	2
16	Ascorbic acid (A11GA01)-Pseudoephedrine (R01BA52)	Minor	2
17	Atorvastatin (C10AA05)-Fenofibrate (C10AB05)	Major	1
18	Azelastine nasal (R01AC03)-Levocetirizine (R06AE09)	Moderate	1
19	Calcium (A12AA)-Magnesium (A12CC)	Moderate	1
20	Captopril (C09AA01)-Amlodipine (C08CA01)	Minor	1
21	Cefuroxime (J01DC02)-Furosemide (C03CA01)	Moderate	1
22	Cefuroxime (J01DC02)-Pantoprazole (A02BC02)	Moderate	1
23	Chlorpheniramine (R01BA53)-Cetirizine (R06AE07)	Moderate	1
24	Ciprofloxacin (J01MA02)-Diclofenac (M02AA15)	Moderate	1
25	Ciprofloxacin (J01MA02)-Ginkgo (N06DX02)	Moderate	1
26	Ciprofloxacin (J01MA02)-Ibuprofen (M01AE01)	Moderate	1
27	Ciprofloxacin (J01MA02)-Ketoprofen (M01AE03)	Moderate	4
28	Ciprofloxacin (J01MA02)-Metronidazole (P01AB01)	Moderate	3
29	Ciprofloxacin (J01MA02)-Ondansetron (A04AA01)	Moderate	1
30	Clarithromycin (J01FA09)-Fluticasone nasal (R03BA05)	Major	1
31	Clarithromycin (J01FA09)-Albuterol (R03AC02)	Moderate	1
32	Clarithromycin (J01FA09)-Budesonide nasal (R01AD05)	Moderate	2
33	Clarithromycin (J01FA09)-Mometasone nasal (R01AD09)	Moderate	1
34	Clarithromycin (J01FA09)-Terbutaline (R03CC03)	Moderate	3
35	Clarithromycin (J01FA09)-Ventolin (R03CC02)	Moderate	1
36	Clopidogrel (B01AC04)-Apixaban (B01AF02)	Major	1
37	Clopidogrel (B01AC04)-Pantoprazole (A02BC02)	Moderate	3
38	dexamethasone oftalmik (S01BA01)-nepafenac oftalmik (S01BC10)	Moderate	3
39	Diclofenac (M02AA15)-Diclofenac topical (M02AA15)	Moderate	3
40	Diclofenac (M02AA15)-Ketoprofen topical (M01AE03)	Moderate	1
41	Digoxin (C01AA05)-Magnesium oxide (A02AA02)	Minor	1

Sl. No.	Drug drug interactions	Severity	*n* (%)
42	Diphenhydramine (R06AA02)-Cetirizine (R06AE07)	Moderate	1
43	Doxycycline (J01AA02)-Amoxicillin (J01CA04)	Moderate	1
45	Doxycycline (J01AA02)-Isotretinoin (D10BA01)	Major	1
46	Doxycycline (J01AA02)-Magnesium (A12CC)	Moderate	1
47	Ergocalciferol (A11CC01)-Magnesium oxide (A02AA02)	Moderate	1
48	Eryhtromycin (J01FA01)-Itraconazole (J02AC02)	Major	1
49	Etodolac (M01AB08)-Diclofenac topical (M02AA15)	Moderate	1
50	Famotidine (A02BA03)-Aluminium hydroxide (A02AB01)	Minor	1
51	Famotidine (A02BA03)-Magnesium hydroxide (A02AA04)	Minor	1
52	Fluconazole (J02AC01)-Estriol (G03CA04)	Moderate	1
53	Flurbiprofen (M01AE09)-Moxifloxacin (J01MA14)	Moderate	1
54	Furosemide (C03CA01)-Metformin (A10BA02)	Moderate	1
55	Furosemide (C03CA01)-Metoprolol (C07AB02)	Moderate	2
56	Furosemide (C03CA01)-Pantoprazole (A02BC02)	Moderate	2
57	Furosemide (C03CA01)-Ramipril (C09AA05)	Moderate	1
58	Furosemide (C03CA01)-Sucralfate (A02BX02)	Moderate	1
59	Gliclazide (A10BB09)-Pseudoephedrine (R01BA52)	Moderate	1
60	Gliclazide (A10BB09)-Sertralin (N06AB06)	Moderate	1
61	Hydrochlorothiazide (C03AA03)-Amlodipine (C08CA01)	Minor	1
62	Hydrochlorothiazide (C03AA03)-Metformin (A10BA02)	Moderate	1
63	Ibuprofen (M01AE01)-Diclofenac (M02AA15)	Major	1
64	Ibuprofen (M01AE01)-Levofloxacin (J01MA12)	Moderate	1
65	Ibuprofen (M01AE01)-Piroxicam (M01AC01)	Major	1
66	Ibuprofen (M01AE01)-Potassium chloride (A12BA01)	Moderate	1
67	Iron polysaccharide (B03AE)-Lansoprazole (A02BC03)	Moderate	1
68	Isosorbide mononitrat (C01DA14)-Ramipril (C09AA05)	Moderate	1
69	Ketoprofen (M01AE03)-Acetylsalicylic acid (B01AC06)	Moderate	1
70	Ketoprofen (M01AE03)-flurbiprofen (M01AE01)	Major	1
71	Ketoprofen (M01AE03)-Indomethacin (M01AB01)	Major	1
72	Lisinopril (C09AA03)-Furosemide (C03CA01)	Moderate	1
73	Meloxicam (M01AC06)-Diclofenac topical (M02AA15)	Moderate	2
74	Methylprednisolone (H02AB04)-Moxifloxacin (J01MA14)	Major	1
75	Methylprednisolone (H02AB04)-Salbutamol (R03AC02)	Minor	1
76	Metoprolol (C07AB02)-Acetylsalicylic acid (B01AC06)	Minor	1
77	Metoprolol (C07AB02)-Ranolazine (C01EB18)	Moderate	1
78	Metoprolol (C07AB02)-Spironolactone (C03DA01)	Moderate	1
79	Metoprolol (C07AB02)-Sucralfate (A02BX02)	Minor	1
80	Metronidazole (P01AB01)-Secnidazole (P01AB07)	Moderate	3
81	Multivitamin (A11A)-Levofloxacin (J01MA12)	Moderate	1
82	Naproxen (M01AE02)-Diclofenac (M02AA15)	Major	2
83	Naproxen (M01AE02)-Esomeprazole (A02BC05)	Moderate	1
84	Naproxen (M01AE02)-Methylprednisolone (H02AB04)	Moderate	1
85	Naproxen (M01AE02)-Pantoprazole (A02BC02)	Moderate	1
86	Netilmicin (J01GB07)-Neomycin topical (D06AX04)	Moderate	1

87	Nitrofurantoin (J01XE01)-Hyoscyamine (A03BA03)	Minor	1
88	Paracetamol (N02BE01)-Hyoscyamine (A03BA03)	Minor	5
89	Paroxetine (N06AB05)-Risperidone (N05AX08)	Moderate	1
90	Pentoxifylline (C04AD03)-Clopidogrel (B01AC04)	Moderate	1
91	Piroxicam (M01AC01)-Ketoprofen topical (M02AA10)	Moderate	1
92	Rasagiline (N04BD02)-Metoclopramide (A03FA01)	Moderate	1
93	Salbutamol (R03AC02)-Moxifloxacin (J01MA14)	Moderate	1
94	Sildenafil (G04BE03)-Ambrisentan (C02KX02)	Moderate	1
95	Spironolactone (C03DA01)-Metformin (A10BA02)	Moderate	1
96	Spironolactone (C03DA01)-Ramipril (C09AA05)	Major	1
97	Sucralfate (A02BX02)-Aluminium hydroxide (A02AB01)	Moderate	1
98	Terbutaline (R03CC03)-Budesonide (R03BA02)	Minor	1
99	Tinidazole (P01AB02)-Secnidazole (P01AB07)	Moderate	1
100	Valsartan (C09CA03)-Nebivolol (C07AB12)	Moderate	1
101	Vitamin b12 (B03BA)-Rabeprazole (A02BC04)	Minor	1
102	Zinc sulfate (A12CB01)-Moxifloxacin (J01MA14)	Moderate	1
Total			132

critical for avoiding negative outcomes caused by DDIs. Providers can control DDIs through proper prescribing and monitoring. Computerized medical systems have proven to be effective in detecting and preventing drug mistakes.[30]

The most common drug classes involved in drug interactions, according to this study, are pharmaceuticals that affect the cardiovascular system and the gastrointestinal tract. Similar findings were observed by the study conducted where cardiovascular drugs were the most frequent drug class associated with potentially severe DDIs.[31] Various medicines and multiple diseases were identified to be possible predictors of DIs using logistic regression. As the number of prescriptions prescribed rises, the risk of drug interactions rises as well. The number of DIs raised in this study as the number of drugs provided increased. This is consistent with findings from previous research groups, which found that patients who were subjected to polypharmacy were at risk of adverse medication interactions.[31]

Polypharmacy may be caused by a prescriber's lack of therapeutic understanding, a prescriber's disregard for possible adverse effects of medicine, a lack of clinical practice guidelines, or a lack of therapeutically appropriate drug. Low drug prescribing can help patients avoid drug interactions, unpleasant side effects, patient non-compliance, bacterial resistance, and financial hardship.[25] An increase in medicine also increased the chance of medication mistakes. Overall, 37.9% of encounters were prescribed antibiotics, which was greater than the WHO norm and lower than the prior study's 43%. Western Nepal's tertiary care hospital had a lower value of 28.30%, Chinese county hospital had a lower value of 29.9%, and Nigeria's tertiary care hospital had a lower value of 34.4%. Under a previous study, drug prescribing in the generic name was found to be very inadequate at 2.9%, compared to the WHO norm of 100 and 44%. In a similar study, generic prescribing was found to be 13% in western Nepal, 96.12% in Chinese county hospitals, and 100% in an Ethiopian public hospital.[32]

Several studies have found that medications cause 5-12% of all hospitalizations, and that only a few drug classes, namely anticoagulants, antiplatelets, NSAIDs, and antihypertensives, cause the majority of hospitalizations due to their side effects. In particular, when it comes to antithrombotics, combining antiplatelets and/or anticoagulants increases the risk of serious bleeding. Clopidogrel and apixaban were revealed to have a significant pharmacological interaction in our study. Combining them raises the risk of bleeding and can result in fatal hemorrhage.[33]

The majority of probable DDIs were identified in cardiologist's prescriptions. These doctors are known for prescribing more drugs per prescription than others. The most common major DDI in this study was between Naproxen (NSAID) and Diclofenac (NSAID). Combining these drugs increases the risk of gastrointestinal side effects such inflammation, bleeding, ulceration, and, in rare cases, perforation. It has previously been discovered that cardiac patients are more likely than other patient groups to experience medication interactions.[34]

The findings provide a picture of the problem of DDIs in prescriptions dispensed in community pharmacies in Cyprus, and they highlight the necessity for a more reliable DDI screening method.

Electronic prescriptions, bar codes to aid in the identification of patients and their medications, the deployment of a precise system giving innovative scientific data, and cautious medication selection are only a few of the options highly suggested to physicians nowadays.[35]

Anti-infective, Central Nervous System (CNS), and cardiovascular medicines were found to be the most common drug classes involved in pDDIs, according to the findings of the current investigation. Antimicrobials were the most commonly used drugs in the study, and they were also the source of a large number of pDDIs. Anti-infective drugs are routinely used in ICUs, and they have clinically important interactions. For the current investigation, there are a few limitations to consider. Although age is a significant determinant in the prevalence of DDIs, it is not included in most prescriptions. The second restriction is the use of a single DDI database (drugs.com), which may limit the number of pDDIs. Using multiple pieces of software at the same time, on the other hand, may yield more accurate results (Baniasadi *et al*., 2015).

There were 67 drug-food interactions, with the majority of these being modest (Table 7). The most prevalent drug-food interactions were ciprofloxacin with food, which is a moderate interaction, chlorpheniramine with food, which is also a moderate interaction, and metronidazole with food, which is a major interaction. When combined with alcoholic beverages or products containing propylene glycol or alcohol, metronidazole can cause a reaction in certain patients that is comparable to the disulfiram reaction. Taking ciprofloxacin with dairy products may reduce its effectiveness. Patients should avoid consuming alcohol or other beverages containing propylene glycol while taking metronidazole and for three days after finishing treatment, according to reports. Metronidazole is likewise prohibited if disulfiram has been taken within the last two weeks. Chlorpheniramine which is an antihistaminic drug, it is recommended to take these medications on an empty stomach because they interact with food and are more effective. Due to the presence of casein and calcium, ciprofloxacin absorption is reduced when taken with milk. The effect of combining certain fruit juices on the absorption and dissolution profiles of ciprofloxacin pills was investigated, and it

Table 5: The severity of drug-drug interactions identified in prescriptions.

DDI Severity	Number of DDIs (n)	Percent of DDIs (%)
Major	14	10.60
Moderate	94	71.21
Minor	24	18.18
Total	132	100.0

Table 6: Major DDIs recognized in prescriptions.

Drug combination	Frequency (%)
Amiodarone (C01BD01)-Furosemide (C03CA01)	1
Atorvastatin (C10AA05)-Fenofibrate (C10AB05)	1
Clarithromycin (J01FA09)-Fluticasone nasal (R03BA05)	1
Clopidogrel (B01AC04)-Apixaban (B01AF02)	1
Doxycycline (J01AA02)-Isotretinoin (D10BA01)	1
Eryhtromycin (J01FA01)-Itraconazole (J02AC02)	1
Ibuprofen (M01AE01)-Diclofenac (M02AA15)	1
Ibuprofen (M01AE01)-Piroxicam (M01AC01)	1
Ketoprofen (M01AE03)-Flurbiprofen (M01AE01)	1
Ketoprofen (M01AE03)-Indomethacin (M01AB01)	1
Methylprednisolone (H02AB04)-Moxifloxacin (J01MA14)	1
Naproxen (M01AE02)-Diclofenac (M02AA15)	2
Spironolactone (C03DA01)-Ramipril (C09AA05)	1
Total	14

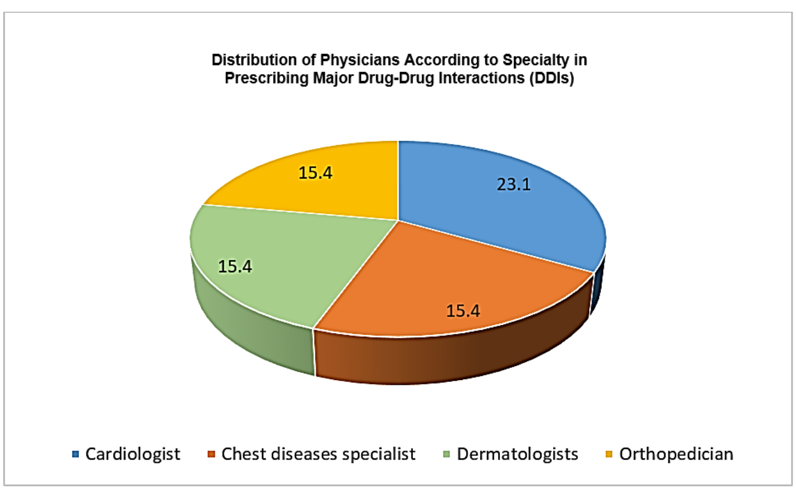

Figure 3: The distribution of the physician specialist who prescribed the major DDIs.

Table 7: Drug-food interactions identified in prescriptions.

Sl. No.	Drug-food interactions	Severity	*n* (%)
1	Alendronate (M05BA04)-Food	Moderate	1
2	Aluminium hydroxide (A02AB01)-Food	Major	5
3	Amiodarone (C01BD01)-Food	Major	1
4	Amlodipine (C08CA01)-Food	Minor	7
5	Ampicillin (J01CA01)-Food	Moderate	1
6	Atorvastatin (C10AA05)-Food	Moderate	7
7	Azelastine nasal (R01AC03)-Food	Moderate	5
8	Budesonide (R03BA02)-Food	Moderate	3
9	Caffeine (N06BC01)-Food	Minor	4
10	Calcium carbonate (A02AC01)-Food	Moderate	1
11	Calcium (A12AA)-Food	Moderate	1
12	Candesartan (C09CA06)-Food	Moderate	1
13	Captopril (C09AA01)-Food	Moderate	1
14	Cetirizine (R06AE07)-Food	Moderate	12
15	Chlorpheniramine (R06AB04)-Food	Moderate	21
16	Chlorzoxazone (M03BB03)-Food	Moderate	4
17	Ciprofloxacin (J01MA02)-Food	Moderate	22
18	Citalopram (N06AB04)-Food	Moderate	1
19	Clarithromycin (J01FA09)-Food	Minor	14
20	Dienogest (G03DB08)-Food	Moderate	1
21	Digoxin (C01AA05)-Food	Minor	1
22	Diltiazem (C08DB01)-Food	Moderate	1
23	Enalapril (C09AA02)-Food	Moderate	1
24	Erythromycin (J01FA01)-Food	Moderate	1
25	Escitalopram (N06AB10)-Food	Moderate	1
26	Esomeprazole (A02BC05)-Food	Moderate	4
27	Estradiol (G03CA03)-Food	Minor	2
28	Estriol (G03CA04)-Food	Minor	1
29	Ferrous gluconate (B03AA03)-Food	Moderate	2
30	Ferrous sulfate (B03AA07)-Food	Moderate	5
31	Fexofenadine (R06AX26)-Food	Moderate	4
32	Folic acid (B03BB01)-Food	Moderate	8
33	Gabapentin (N03AX12)-Food	Moderate	2
34	Gliclazide (A10BB09)-Food	Moderate	1
35	Hydroxyzine (N05BB01)-Food	Moderate	2
36	Iron polysaccharide (B03AB)-Food	Moderate	2
37	Itraconazole (J02AC02)-Food	Moderate	1
38	Levocetirizine (R06AE09)-Food	Moderate	4
39	Levofloxacine (J01MA12)-Food	Moderate	5
40	Lisinopril (C09AA03)-Food	Moderate	4
41	Loratadine (R06AX13)-Food	Minor	4
42	Losartan (C09CA01)-Food	Moderate	2
43	Metformin (A10BA02)-Food	Major	5
44	Methylprednisolone (H02AB04)-Food	Moderate	3
45	Metoclopramide (A03FA01)-Food	Moderate	1
46	Metoprolol (C07AB02)-Food	Moderate	5
47	Metronidazole topical (D06BX01)-Food	Moderate	5
48	Metronidazole (P01AB01)-Food	Major	18
49	Omega 3 (C10AX06)-Food	Moderate	3
50	Oxytetracycline topical (D06AA03)-Food	Moderate	1
51	Paroxetine (N06AB05)-Food	Moderate	1
52	Pregabalin (N03AX16)-Food	Moderate	1
53	Propranolol (C07AA05)-Food	Moderate	1
54	Ramipril (C09AA05)-Food	Moderate	2
55	Ranolazine (C01EB18)-Food	Major	1
56	Rasagiline (N04BD02)-Food	Moderate	1
57	Risperidone (N05AX08)-Food	Moderate	1
58	Sertraline (N06AB06)-Food	Moderate	1
59	Sildenafil (G04BE03)-Food	Moderate	1
60	Simvastatin (C10AA01)-Food	Major	2
61	Sucralfate (A02BX02)-Food	Moderate	4
62	Tadalafil (G04BE08)-Food	Moderate	1
63	Tamsulosin (G04CA02)-Food	Moderate	2
64	Tinidazole (P01AB02)-Food	Moderate	3
65	Trimethobenzamide (R06AA10)-Food	Moderate	1
66	Triprolidine (R06AX07)-Food	Moderate	1
67	Valsartan (C09CA03)-Food	Moderate	3

was discovered that simultaneous drinking of grape fruit juice can reduce ciprofloxacin absorption. The most relevant drug-food interactions are those that are linked to a high risk of treatment failure due to a significantly reduced bioavailability in the fed state. Chelation with dietary components is a common source of these interactions. In addition, the physiological reaction to meal intake, notably gastric acid secretion, might affect the bioavailability of a variety of drugs. In our study moderate Drug-Drug İnteractions (DDIs) accounted for 71.21% of the detected cases, highlighting their clinical significance despite being less severe than major interactions. These interactions can still pose risks, particularly for patients with compromised health or those on multiple medications. Some may necessitate dose adjustments or close monitoring-such as the combination of beta-blockers and calcium channel blockers, which can lead to excessive blood pressure reduction or bradycardia. If left unaddressed, moderate DDIs can increase the likelihood of adverse drug reactions, potentially resulting in hospitalization or treatment failure. Given these concerns, prescribers must carefully assess patient conditions and provide clear monitoring guidelines. To enhance patient safety, healthcare professionals should rely on the most reliable electronic drug interaction checkers to identify and mitigate potential risks effectively. It is necessary to take the medicine 2 hours after or 1 hour before meals to avoid such interactions.[36]

Our study also revealed that 85.7% of major Drug-Drug İnteractions (DDIs) were pharmacodynamic in nature, primarily resulting from additive, synergistic, or antagonistic effects between medications. For instance, additive toxicity was observed with NSAIDs like naproxen and diclofenac, increasing the risk of gastrointestinal bleeding and renal impairment. Synergistic effects, such as the combination of ACE inhibitors with potassium-sparing diuretics, can lead to severe hyperkalemia, while antagonistic effects, like the combination of beta-agonists and beta-blockers, may reduce drug efficacy and exacerbate conditions such as uncontrolled hypertension or asthma. Certain patient groups are particularly at risk, including the elderly, who are more susceptible due to polypharmacy and diminished metabolic capacity, as well as patients with chronic conditions like cardiovascular diseases, diabetes, or renal impairment, who often take multiple medications. Additionally, patients on multiple prescriptions face an increased likelihood of significant interactions. To mitigate these risks, monitoring strategies such as routine medication reviews, especially for elderly and high-risk patients, the use of Clinical Decision Support Systems (CDSS) in pharmacy and healthcare settings, and patient education on the signs of interactions and the importance of adherence to prescribed regimens are crucial.

Pharmacists in all practice settings must be on the lookout for potential drug-food interactions and advise patients on which foods or beverages to avoid while taking specific drugs. Pharmacists must stay current on potential drug-food interactions of medicines, particularly today's new treatments, in order to correctly counsel patients. Pharmacists frequently address potential side effects and how to take the prescription with patients while presenting pharmacological information. It's critical to tell patients about when to take their medicines in connection to their food intake. Drug-food interactions can result in the drug's absorption being delayed, reduced, or increased. Certain drug's absorption, metabolism, and excretion may be affected by food. Because they often consume more drugs for their chronic medical conditions, elderly adults may be at a higher risk for drug-food interactions.

LIMITATIONS

This study acknowledges certain limitations that may influence the interpretation of findings. The absence of detailed patient demographics, such as gender and comorbidities, limits insights into potential risk factors for drug interactions. Additionally, the five-month study period may not fully capture seasonal variations in prescribing trends. While pharmacy selection was based on prescription volume, accessibility, and geographic diversity, the findings may not be entirely representative of all community pharmacies. Moreover, the lack of age-related data in most prescriptions prevented a direct analysis of key confounding factors, despite existing evidence linking polypharmacy and drug interactions to elderly patients and those with chronic illnesses. Future research integrating electronic health records could provide a more comprehensive understanding of these variables.

CONCLUSION AND SUGGESTIONS

Our study concluded that 21.3% of prescriptions containing two or more systemic medications had potential DDIs and ADRs, with the cardiovascular system being the most commonly affected area. Drug interactions (DIs) are often overlooked but can have both positive and negative impacts, playing a significant role in the development of Adverse Drug Reactions (ADRs) and Adverse Drug Events (ADEs). Polypharmacy is a major contributor to Drug-Drug İnteractions (DDIs), making it essential for healthcare providers to conduct a thorough review of the patient's health and medication regimen before prescribing additional treatments. When a DI is unavoidable, patients should be closely monitored to ensure the safety and efficacy of the prescribed medications. To minimize the risk of drug-food interactions, medications should be taken either two hours after or one hour before meals.

CONFLICT OF INTEREST

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