Original Article

Determination and Comparison of Potential Drug–Drug Interactions Using Three Different Databases in Northern Cyprus Community Pharmacies

ZN Alkhalid, N Birand

Department of Clinical Pharmacy, Near East University, Faculty of Pharmacy, Nicosia, North Cyprus, Mersin, Turkey

Abstract

Background: Drug interactions are common drug-related problems that can lead to adverse drug reactions and hospitalization. **Aims:** The objectives of the study were to determine the potential drug–drug interactions (pDDIs) in Northern Cyprus community pharmacies and to compare three electronic databases regarding the frequency, mechanism, and severity of drug–drug interactions. **Material and Methods:** A retrospective observational study was conducted between July 1 and September 30, 2021, in Northern Cyprus community pharmacies using the Drugs.com, Lexicomp, and Medscape databases. The Mann–Whitney U-test was used to determine the difference between the values of the databases. Pearson's correlation was used to determine the association between DDIs and polypharmacy. **Results:** *A total of* 558 (52.1%) of 1072 prescriptions were included in the study. Drugs.com, Lexicomp, and Medscape databases detected 185, 176, and 213 potential drug–drug interactions in patients' prescriptions, respectively. There was a statistically significant difference in moderate drug interactions between the Medscape and Lexicomp databases (p = 0.02). Pearson's correlation showed a weak association (Medscape: r = 0.296, Lexicomp: r = 0.341, Drugs.com: r = 0.289, P = 0.0001) between pDDIs and polypharmacy. The assessment of agreement on severity of pDDIs characterized by Drugs.com and Lexicomp databases using the Kappa index was moderate agreement (0.509, P = 0.0001), while Drugs.com and Medscape databases using the Kappa index were moderate agreement (0.442, P = 0.0001), and Lexicomp and Medscape databases using the Kappa index were fair agreement (0.365, P = 0.0001). **Conclusions:** This study showed that Medscape detected more potential DDIs than Drugs.com and Lexicomp. Therefore, we propose that more than one database should be used to evaluate and identify pDDIs in pharmacy.

Keywords: *Community pharmacy, drug–drug interactions, Northern Cyprus, pharmacists*

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Introduction

Drug interactions are a common problem that occur when two or more medications are taken simultaneously during drug therapy and can lead to clinically significant, sometimes serious, events.[1,2] Physicians and pharmacists have the knowledge and ability to assess drug–drug interactions because of their training. Therefore, they can reduce the potential side effects and switch medications by monitoring drug–drug interactions for patients. Electronic databases are widely used in hospitals and community pharmacies for DDI assessment.[3] In a study by Sancar M *et al*., it was found that 39.2% of 1000 prescriptions in

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Address for correspondence: Dr. N Birand, Department of Clinical Pharmacy, Near East University, Faculty of Pharmacy, Nicosia, North Cyprus, Mersin 10, Turkey.
E-mail: nevzat.birand@neu.edu.tr

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public pharmacies in Istanbul, Turkey, had at least one potential DDI.[4] In previous studies conducted in Northern Cyprus, Laban *et al*. reviewed cancer while the Drugs.com database detected 394 DDIs and the Lexicomp database detected only 313 DDIs.[5] A study by Gökçekuş *et al*. showed that inappropriate combinations of drugs or foods were the second most common drug-related problem. However, the authors did not classify the drug interactions according to the mechanism or severity of interactions.[6] There is no previous study on the classification of drug–drug interactions in community pharmacies in Northern Cyprus. Therefore, this study was conducted to identify potential drug–drug interactions in Northern Cyprus community pharmacies, comparing three electronic databases in terms of frequency, mechanism, and severity of drug–drug interactions.

Material and Methods

Study design and setting

A retrospective observational study was conducted in Northern Cyprus community pharmacies between July 1, 2021 and September 30, 2021 using Drugs.com, Lexicomp, and Medscape databases.

There are six districts in Northern Cyprus. These districts are Nicosia, Famagusta, Girne, Güzelyurt, İskele, and Lefke. The current list of all community pharmacies in the six districts of Northern Cyprus was downloaded from the Northern Cyprus Pharmacy Association website. Then, one community pharmacy from each district was randomly selected and contacted by a pharmacist. Pharmacies that agreed to participate in the study were asked to present three-month old prescriptions. Data collection was conducted for one month. The most frequently used databases (Lexicomp, Medscape, and Drugs.com) in Northern Cyprus were used to check the patients' prescriptions for drug–drug interactions. All patients who were prescribed two or more medications were included in the study. Drug–herbal or food interactions were excluded from this study.

Data collection and analysis

Data were reviewed using the Lexi-interact tool from Lexicomp (Copyright 2018, Wolters Kluwer Clinical Drug Information, Inc), Medscape, and the Drugs.com databases.[7-9] Mechanisms of DDIs were categorized as pharmacodynamic, pharmacokinetic, and unknown. According to Lexicomp, interactions are classified into five categories: A, B, C, D, and X. According to Medscape, interactions are divided into four categories: Minor, Monitor, Serious-Use Alternative, and Contraindicated. According to Drugs.com, interactions are classified into four: Minor, Moderate, Major, and Unknown.

Ethical consideration

The study was approved by the Near East Institutional Review Board (IRB) of Near East University with approval number YDU/2021/96-1421.

Statically analysis

The study data were analyzed using Microsoft Excel 2016 and Statistical Package for the Social Sciences (SPSS), software version 21.0. According to the frequency of the databases, the data on mechanism and severity of drug–drug interactions were expressed in frequency and percentage. The Mann–Whitney U-test was used to determine the difference between the values of the databases. Pearson's correlation was used to determine the association between DDIs and polypharmacy. The kappa index was used to evaluate the agreement between the DDIs identified by the three drug interaction assessors. The kappa value ranges from 0 to 1. A value less than 0.00 is interpreted as no agreement, 0.01–0.20 as slight agreement, 0.21-0.40 as fair agreement, 0.41–0.60 as moderate agreement, 0.61–0.80 as substantial agreement, and 0.81–1.00 as almost perfect agreement. A *P* value of less than 0.05 ($p < 0.05$) was considered statistically significant.

Results

A total of 558 (52.1%) of 1072 prescriptions were included in the study, whereas 514 (47.9%) prescriptions containing a drug or cosmetic product were excluded. This study showed that drug–drug interactions were detected in patients' prescriptions [Figure 1 and Table 1]. Drugs.com has shown that 382 prescriptions (68.5%) had no interactions, while 176 prescriptions (31.5%) had drug interactions. Lexicomp has shown that 409 prescriptions (73.3%) had no interactions, while 149 prescriptions (26.7%) had drug interactions. Medscape has shown that 375 prescriptions (67.2%) had no interactions, while 183 prescriptions (32.8%) had drug interactions.

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According to Drugs.com, 58 (31.4%) pharmacokinetic interactions, 104 (56.2%) pharmacodynamic interactions, and 23 (12.4%) unknown mechanisms of drug–drug

interactions were identified. There were 25 (13.5%) major, 103 (55.7%) moderate, and 57 (30.8%) minor drug–drug interactions identified [Tables 2 and 3]. In the Lexicomp database, 63 (35.8%) pharmacokinetic interactions, 111 (63.1%) pharmacodynamic interactions, and 2 (1.1%) unknown mechanisms of drug–drug interactions were detected. Based on the severity of interactions, there were 41 (23.3%) category B, 89 (50.6%) category C, 23 (13%) category D, and 23 (13%) category X interactions [Tables 2 and 3]. According to the Medscape database, 80 (37.6%) pharmacokinetic interactions, 120 (56.3%) pharmacodynamic interactions, and 13 (6.1%) unknown mechanisms of drug–drug interactions were identified. There were 0 (0%) contraindicated drug interactions, 16 (7.5%) Serious-Use Alternative, 136 (63.8%) Monitor Closely, and 61 (28.6%) Minor severity of drug interactions [Tables 2 and 3].

Table 1: Information of prescriptions according to six community pharmacies

Number of Medication	*n* (%)
Medications	
Less than five medications	529 (94.5%)
Equal to Five and more than five medications	29 (5.5%)
Number of Prescriptions	***n* (%)**
Districts of North Cyprus	
Lefkoşa	140 (25.1%)
Mağusa	91 (16.3%)
Girne	155 (27.8%)
İskele	68 (12.2%)
Güzelyurt	72 (12.9%)
Lefke	32 (5.7%)
Total	558 (100%)

Table 2: Mechanism of drug-drug interactions according to all databases

Databases	Drugs.com *n*	Lexicomp *n*	Medscape *n*
Pharmacokinetic	58 (31.4%)	63 (35.8%)	80 (37.6%)
Pharmacodynamic	104 (56.2%)	111 (63.1%)	120 (56.3%)
Unknown	23 (12.4%)	2 (1.1%)	13 (6.1%)

There were no statistically significant differences in pharmacokinetic interactions and pharmacodynamic interactions among all databases. For unknown interactions, there were statistically significant differences between the Drugs.com and Lexicomp databases and between Medscape and Lexicomp ($p = 0.0001$ and $P = 0.01$, respectively). For unknown interactions, there was no statistically significant difference between Medscape and Drugs.com ($p = 0.107$) [Table 4].

There was no statistically significant difference among all databases in the major drug interaction category. There were no statistically significant differences between the Drugs.com and Medscape databases and between Drugs.com and Lexicomp in moderate drug interactions. There was a statistically significant difference in moderate drug interactions between the Medscape and Lexicomp databases ($p = 0.02$). There was no statistically significant difference in minor drug interactions between all databases. There was no statistically

Table 3: Severity of drug–drug interactions according to all databases

Drugs.com *n*		Lexicomp *n*		Medscape *n*	
Major	25 (13.5%)	B	41 (23.3%)	Contraindicated	0 (0%)
Moderate	103 (55.7%)	C	89 (50.6%)	Serious-Use Alternative	16 (7.5%)
Minor	57 (30.8%)	D	23 (13%)	Monitor Closely	136 (63.8%)
-	-	X	23 (13%)	Minor	61 (28.6%)
Total Interaction	185 (100%)	Total Interaction	176 (100%)	Total Interaction	213 (100%)

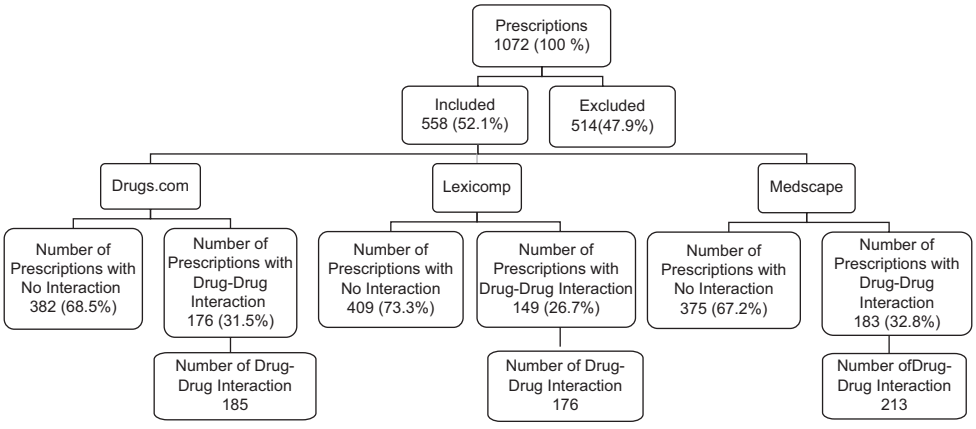

Figure 1: Study sample size

Table 4: Comparison of severity and mechanism of drug-drug interactions according to all databases

	Drugs.com *n*	Lexicomp *n*	Medscape *n*	*P* (Drugs.com Vs Lexicomp)	*P* (Drugs.com Vs Medscape)	*P* (Medscape Vs Lexicomp)
Mechanism of Drug–Drug Interaction						
Pharmacokinetic	58	63	80	0.709	0.149	0.257
Pharmacodynamic	104	111	120	0.629	0.389	0.647
Unknown	23	2	13	0.0001*	0.107	0.01*
Severity of Drug–Drug Interaction						
Major	25	23	16	0.784	0.180	0.339
Moderate	103	89	136	0.395	0.106	0.02*
Minor	57	41	61	0.143	0.721	0.07
Contraindicated	N/A	23	0	-	-	-
Total Interaction	185	176	213	0.700	0.325	0.176

Serious-Use Alternative=Major, Monitor Closely=Moderate; Medscape. A=No Interaction, B=Minor, C=Moderate, D=Major X=Contraindicated; Lexicomp. N/A=Not Available * $P<0.05$ was considered the statistically significant difference between databases by using the Mann–Whitney U-test

significant difference in the number of DDI between all databases [Table 4]. Pearson's correlation showed a weak association (Medscape: r = 0.296, Lexicomp: r = 0.341, Drugs.com: r = 0.289, $P = 0.0001$) between potential DDIs and polypharmacy. The assessment of agreement on severity of pDDIs characterized by Drugs.com and Lexicomp databases using the Kappa index was moderate agreement (0.509, $P = 0.0001$), Drugs.com and Medscape databases using the Kappa index were moderate agreement (0.442, $P = 0.0001$), and Lexicomp and Medscape databases using the Kappa index were fair agreement (0.365, $P = 0.0001$).

Discussion

This study examined the frequency, mechanism, and severity of DDIs in patients' prescriptions and compared the databases with three different drug interaction checkers. Community pharmacists can detect and prevent drug interactions by checking the prescriptions of every patient who comes to the community pharmacy. With the electronic databases available to health care professionals in the pharmacy, this task can be accomplished in a very short time.

A study conducted in the oncology department of a university Hospital showed that there were more pharmacodynamic drug interaction mechanisms compared to pharmacokinetic drug interactions as detected by Drugs.com, Medscape, and Lexicomp databases.[5] In our study, pharmacodynamic interaction was higher than pharmacokinetic interaction in all databases, so our results are consistent with previous studies based on drug interaction mechanism. Therefore, health professionals should consider the risk of this pharmacodynamic interaction when prescribing medications to patients.

A study conducted at a South Indian teaching hospital showed that 91% of 204 prescriptions contained 856 drug interactions and most of the drug interactions were moderate.[10] A study by Chatsisvili *et al*. showed that over 85% of DDI were moderate interactions.[11] In this study, the most common severity of drug interactions was moderate in all databases. Our results on the severity of drug interactions were similar to previous studies. Therefore, patients should be monitored regularly by pharmacists until the end of therapy, and they should inform the physician if they observe any drug-related problems.

Shetty *et al*. reported that about 3% of drug interactions belong to category X.[12] Lexicomp is the only database that acknowledged this category of severity of drug interactions. In the present study, 13% of category X interactions was identified. The frequency of category X interaction identified in this study was higher compared to previous studies. Due to the high frequency of category X, pharmacists in Northern Cyprus should regularly monitor drug interactions for each patient's medications.

As shown in the results of the present study, pharmacists should be able to prevent potential drug interactions before patients take their medications due to the high frequency of drug interactions. According to our results, the most important drug interactions were clopidogrel and omeprazole or more than one NSAID such as naproxen and diclofenac. Moderate interactions included pantoprazole and levothyroxine or ramipril and furosemide. Minor interactions included, for example, clarithromycin and omeprazole or paracetamol (acetaminophen) and metoclopramide.

Limitations of the study

Only six community pharmacies in the six districts in Northern Cyprus were included in this study. The number of prescriptions evaluated was not very high;

hence, the findings cannot be generalized. We therefore recommend that more pharmacies be included in future studies.

This study showed that Medscape detected more potential DDIs than Drugs.com and Lexicomp. The Lexicomp database provided more detailed information on drug interactions although it detected fewer potential DDIs than the other databases in this study. We recommend that pharmacists use more than one database to screen for drug interactions when evaluating their patients' medications.

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Conflicts of interest

There are no conflicts of interest.

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