



DETECTING DRUG-DRUG INTERACTIONS INDUCED BY ANTI-HYPERLIPIDEMICS: AN OBSERVATIONAL STUDY

*ANTİHİPERLİPİDEMİKLER KAYNAKLI İLAÇ ETKİLEŞİMLERİNİN TESPİTİ:
GÖZLEMSEL BİR ÇALIŞMA*

Zehra Betül CENGİZ¹ , Miray ARSLAN^{2*}

¹Van Yüzüncü Yıl University, Faculty of Pharmacy, 65080, Van, Türkiye

²Van Yüzüncü Yıl University, Faculty of Pharmacy, Department of Pharmacy Management, 65080, Van, Türkiye

ABSTRACT

Objective: *This study aimed to reveal drug-drug interactions (DDIs) due to antihyperlipidemic drugs through programs used to detect DDIs.*

Material and Method: *250 prescriptions containing at least one anti-hyperlipidemic drug and a drug from a different pharmacological group were evaluated in terms of DDIs between November 2022 and April 2023. Evaluations were performed using three different DDI checking programs (RxMediaPharma®, Medscape, and Drugs.com) on prescriptions filled by a community pharmacy in Van.*

Result and Discussion: *Anti-hyperlipidemic drug-induced DDIs were detected in 115 of the prescriptions. DDIs occurred between 38 active ingredient pairs. It was determined that 85% of the interactions were caused by atorvastatin. The most common DDI was found between atorvastatin and pantoprazole. For only 7 of the 38 different ingredient pairs, all three programs yielded a result indicating an interaction. DDIs induced by anti-hyperlipidemic drugs were generally found to be at moderate levels. However, it is seen that the three DDI checking programs used in the study provide different results in detecting DDIs.*

Keywords: *Antihyperlipidemics, community pharmacy, drug-drug interactions, observational study*

ÖZ

Amaç: *Bu çalışma antihiperlipidemikler kaynaklı ilaç-ilaç etkileşimlerini (DDI), DDIs tespit etmede kullanılan programlar aracılığıyla ortaya koymayı amaçlamaktadır.*

Gereç ve Yöntem: *Kasım 2022 ile Nisan 2023 tarihleri arasında en az bir anti-hiperlipidemik ilaç ve farklı bir farmakolojik gruptan ilaç içeren 250 reçete, DDI açısından değerlendirildi. Değerlendirmeler, Van'daki bir serbest eczaneden alınan reçeteler üzerinden üç farklı DDI kontrol programı (RxMediaPharma®, Medscape ve Drugs.com) kullanılarak gerçekleştirildi.*

Sonuç ve Tartışma: *Reçetelerin 115'inde anti-hiperlipidemik ilaçlara bağlı DDI'lar tespit edilmiştir. DDI'lar 38 aktif madde çifti arasında meydana gelmiştir. Etkileşimlerin %85'inin atorvastatinden kaynaklandığı belirlendi. En sık DDI, atorvastatin ve pantoprazol arasında bulunmuştur. 38 farklı madde çiftinden yalnızca 7'si için, üç program da etkileşim sonucunu vermiştir. Anti-hiperlipidemik ilaçlara bağlı DDI'ların genellikle orta düzeyde olduğu*

* **Corresponding Author / Sorumlu Yazar:** Miray Arslan
e-mail / e-posta: mirayarslan@yyu.edu.tr, **Phone / Tel.:** +904324445065

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belirlenmiştir. Ancak, çalışmada kullanılan üç DDI kontrol programının DDI'ları tespit etmede farklı sonuçlar verdiği görülmüştür.

Anahtar Kelimeler: *Antihiperlipidemikler, gözlemsel çalışma, ilaç-ilaç etkileşimleri, serbest eczane*

INTRODUCTION

Dyslipidemia is one of the most frequently encountered clinical conditions in Türkiye and worldwide. It is also among the most critical risk factors for cardiovascular diseases [1,2]. According to "Cardiovascular diseases: A handbook for pharmacists," published by the International Pharmaceutical Organization (FIP) in 2022, the incidence of cardiovascular diseases in Middle Eastern countries is 10.1% and the most important risk factor leading to cardiovascular diseases in these regions is dyslipidemia, with a rate of 43% [3].

Pharmacological treatment of dyslipidemia primarily utilizes statins, bile acid sequestrants, cholesterol absorption inhibitors, protein convertase subtilisin/kexin type 9 (PCSK9) inhibitors, nicotinic acid, fibrates, n-3 fatty acids, and cholesteryl ester transfer protein inhibitors [4]. Currently, statins are the most commonly used antihyperlipidemic agents in clinical practice due to their high efficacy and low side effect profile [5]. However, clinically significant drug interactions are known to occur between many drugs, particularly those in this group [6]. When statins are used with other drugs metabolized by cytochrome P450 (CYP) enzymes, they may interact with each other's metabolism [7,8].

A "drug-drug interaction (DDI)" is defined as the phenomenon that occurs when two medications are used together, with the pharmacological effect of one drug being altered by the presence of the other. The most common reason for drug interactions is the simultaneous use of multiple medications (polypharmacy) [9]. While polypharmacy can sometimes cause serious health problems due to interactions, it can also lead to the disease intended to be treated going untreated due to the loss of effect of one of the medications due to the interaction [10]. As stated by Özkaya and Özçelikay, polypharmacy may increase the potential of DDIs [11]. Similarly, Lalatovic et al. pointed out polypharmacy as one of the risk factors that increases the potential of encountering DDIs in patients with dyslipidemia [12]. At this point, online DDI checkers offer support to healthcare professionals.

It is known that several health agencies have published guidelines for assessing DDIs, which generally apply to in vitro studies. However, the number of studies addressing and managing DDIs caused by drug groups used in dyslipidemia is limited. To the best of the author's knowledge, there is a gap in the literature about detecting DDIs induced by antihyperlipidemics at the community pharmacy level in Türkiye. In this regard, this study aims to detect DDIs induced by antihyperlipidemics with the help of three national and international electronic databases, and compare these databases in terms of frequency and severity of DDIs.

MATERIAL AND METHOD

This study was designed as a single-center observational study. Prescriptions filled in a community pharmacy in Van were investigated in terms of DDIs between November 2022 and April 2023. Firstly, ethical permission was obtained from the Van Yüzüncü Yıl University Non-interventional Research Ethics Committee, and subsequently, consent was obtained from the Van-Bitlis-Hakkari Pharmacists' Chamber. Following this process, a random selection was made among community pharmacies located in the city centre that frequently fill prescriptions for dyslipidemia, and written permission for the data collection process was obtained from the pharmacists. Prescriptions matching the inclusion criteria were recorded in compliance with the Turkish Personal Data Protection Law (KVKK). Before prescriptions were included in the study, patients were informed about the study, and written informed consent was taken from each patient. All prescriptions were depersonalized before the assessment. Information about the physician, patients' age and gender, diagnosis (as classified by the International Classification of Diseases, Tenth Revision (ICD-10) codes), and the number of prescribed medications was obtained from the prescriptions. Then, drug pairs in the prescriptions were manually entered into selected DDI checker programs to evaluate possible DDIs. "Medscape", "Drugs.com," and

“RxMediaPharma® Interactive Drug Information Resource” were selected. Medscape is a free online international program that classifies DDIs as contraindicated, serious-use alternative (major), monitor closely (moderate), and minor. Similarly, Drugs.com is a free online international program that divides the level of DDIs as major, moderate (recommended for use only in special cases), minor, and unknown. Lastly, RxMediaPharma is a national (Turkish) program that categorizes DDIs as Level 1 (major interaction) to 3 (minor interaction). If any DDI was found by at least one of the programs, these drug pairs were included in the analysis.

Approximately 100-200 prescriptions were considered sufficient in such studies [13,14]. Additionally, as stated by Donner and Eliasziw, with 80% power and a 5% margin of error, at least 123 prescriptions were needed [15]. Therefore, to increase generalizability, prescriptions that included at least one antihyperlipidemic drug and a drug from a different pharmacological group were examined among all prescriptions filled at the corresponding community pharmacy. Descriptive statistical analysis was presented. To assess the agreement for detecting DDIs between DDI checking programs, the kappa coefficient was used. According to Landis and Koch (1977) agreement classification were done as follows: (i) No agreement (<0.00), (ii) Slight agreement (0.00-0.20), (iii) Fair agreement (0.21-0.40), Moderate agreement (0.41-0.60), (iv) Substantial agreement (0.61-0.80), and (iv) Almost perfect agreement (0.81-1.00) [16]. Analyses were conducted via Microsoft Excel for Mac, version 16.17. Microsoft 365 subscription.

RESULT AND DISCUSSION

One thousand eight hundred and seven prescriptions were filled at the corresponding community pharmacy during the research period; 250 of them met the study's inclusion criteria.

Prescriptions are first evaluated based on the patients' and prescribers' demographics (Table 1).

Table 1. Demographics of patients and physicians

Patient		Physicians	
Gender	n (%)	Specialization	n (%)
Female	120 (48.0)	Cardiologist	79 (32.0)
Male	130 (52.0)	Practitioner	79 (32.0)
Age	n (%)	Internal medicine specialist	54 (21.0)
Under 46	39 (16.0)	Family medicine specialist	22 (9.0)
46-65	103 (41.0)	Neurologist	10 (4.0)
Over 65	108 (43.0)	Other	6 (2.0)

As seen in Table 1, antihyperlipidemics were mostly prescribed by cardiologists and practitioners for patients older than 46. Prescriptions were evaluated based on the ICD-10 codes corresponding to the diagnoses. The evaluation results are presented in Table 2.

Table 2. Evaluation of diagnosis

Diagnosis	
ICD-10 codes	Frequency
E78 (0-2-4-5) (Disorders of lipoprotein metabolism and other lipidemias)	165
E13 (Other specified diabetes mellitus)	85
I10 (Essential (primary) hypertension)	58
I25.0 (Atherosclerotic cardiovascular disease)	41
I24.1 (Dressler's syndrome)	13
Others	68

According to Table 2, antihyperlipidemic drugs were most commonly prescribed for diagnoses E13 (Other specified diabetes mellitus) and E78.4 (Other hyperlipidemias). Concerning the number of medications, 70 of the prescriptions contained two, 146 contained 3-5, and 34 contained more than five.

115 of the 250 prescriptions were identified as having DDIs. The prevalence of DDIs was 46.00%. A total of 151 potential DDIs were detected between the 38 different drug pairs. Out of 38 different drug pairs, only 7 of the three online DDI checkers found a typical interaction. RxMediaPharma identified 20 DDIs, Medscape 17, and Drugs.com 20. When examining the interaction levels, all of the interactions identified by RxMediaPharma were Level 1. Of the interactions identified by Medscape, 15 were classified as "Monitor Closely (Moderate)," and two as "Serious (Major)." Drugs.com identified 15 as "Moderate," four as "Major," and one as "Minor."

When the antihyperlipidemics included in the prescriptions were evaluated, it was seen that the most prescribed (n=129) antihyperlipidemic was atorvastatin. Atorvastatin accounted for 85% of identified DDIs. The frequency of DDIs induced by atorvastatin is presented in Table 3.

Table 3. Interactions with atorvastatin

Drug pairs	Frequency	RxMediaPharma	Medscape	Drugs.com
Atorvastatin-Pantoprazole	43	Level 1	No interactions	Moderate
Atorvastatin-Clopidogrel	26	No interactions	No interactions	Moderate
Atorvastatin-Amlodipin	12	No interactions	No interactions	Moderate
Atorvastatin-Fenofibrate	9	Level 1	Major	Major
Atorvastatin-Spironolactone	6	Level 1	No interactions	No interactions
Atorvastatin-Ramipril	5	No interactions	No interactions	Moderate
Atorvastatin-Telmisartan	4	No interactions	Monitor closely	No interactions
Atorvastatin-Tikagrelor	3	Level 1	No interactions	Minor
Atorvastatin-Ciprofloxacin	3	No interactions	No interactions	Moderate
Atorvastatin-Esomeprazole	2	Level 1	No interactions	Moderate
Atorvastatin-Lansoprazole	2	Level 1	No interactions	Moderate
Atorvastatin-Calsium Carbonate	2	Level 1	No interactions	No interactions
Atorvastatin-Pioglitazone	2	No interactions	Monitor closely	No interactions
Atorvastatin-Glyburide	1	No interactions	Monitor closely	No interactions
Atorvastatin-Ranolazine	1	No interactions	Monitor closely	Major
Atorvastatin-Silodosin	1	No interactions	Monitor closely	No interactions
Atorvastatin-Digoxin	1	Level 1	Monitor closely	Moderate
Atorvastatin-Prednizolon	1	No interactions	Monitor closely	No interactions
Atorvastatin-Valsartan	1	No interactions	Monitor closely	No interactions
Atorvastatin-Vitamin D ₃	1	Level 1	No interactions	No interactions
Atorvastatin-Tacrolimus	1	No interactions	Monitor closely	Moderate
Atorvastatin-Sitagliptin	1	Level 1	No interactions	No interactions
Atorvastatin-Magnesium Carbonate	1	Level 1	No interactions	No interactions

Table 3 indicates that the active ingredients fenofibrate and digoxin interact with atorvastatin in all three databases. An interaction between atorvastatin and pantoprazole was detected as the most common, which may increase the blood levels and effects of atorvastatin and potentially result in rhabdomyolysis. In assessing the agreement for detecting DDIs based on atorvastatin using the Kappa index in RxMediaPharma and Medscape, no agreement was found (Kappa value = -0.487), slight agreement (Kappa value = 0.045) was found in RxMediaPharma and Drugs.com, and no agreement was found (Kappa value = -0.211) in Drugs.com and Medscape.

Table 4 presents the frequencies of drug-drug interactions encountered based on rosuvastatin. 4.6% of the DDIs were caused by rosuvastatin.

Table 4. Interactions with rosuvastatin

Drug pairs	Frequency	RxMediaPharma	Medscape	Drugs.com
Rosuvastatin-Clopidogrel	5	Level 1	No interactions	Major
Rosuvastatin-Lansoprazole	1	Level 1	No interactions	No interactions
Rosuvastatin-Esomeprazole	1	Level 1	No interactions	No interactions

In assessing the agreement for detecting DDIs based on rosuvastatin using the Kappa index in RxMediaPharma and Medscape, no agreement was found (Kappa value = 0.000). Similarly, no agreement was found in RxMediaPharma and Drugs.com (Kappa value = 0.000), and no agreement was found in Drugs.com and Medscape (Kappa value = 0.000). Table 5 presents the frequencies of drug-drug interactions encountered with pitavastatin.

Table 5. Interactions with pitavastatin

Drug pairs	Frequency	RxMediaPharma	Medscape	Drugs.com
Pitavastatin-Pioglitazon	2	No interactions	Monitor closely	No interactions
Pitavastatin-Fenofibrate	1	Level 1	Major	Major
Pitavastatin-Esomeprazole	1	Level 1	No interactions	No interactions
Pitavastatin-Valsartan	1	No interactions	Monitor closely	No interactions
Pitavastatin-Pantoprazole	1	Level 1	No interactions	No interactions

3.9% of the DDIs were due to pitavastatin. Pitavastatin was recognized as a significant interaction with fenofibrate in all three drug interaction databases. In assessing the agreement for detecting DDIs based on pitavastatin using the Kappa index in RxMediaPharma and Medscape, no agreement was found (Kappa value = -0.667), fair agreement (Kappa value = 0.286) was found in RxMediaPharma and Drugs.com, and fair agreement (Kappa value = 0.286) was found in Drugs.com and Medscape.

Lastly, Table 6 presents the frequencies of DDIs encountered with fenofibrate.

Table 6. Interactions with Fenofibrate

Drug pairs	Frequency	RxMediaPharma	Medscape	Drugs.com
Fenofibrate-Insulin Aspart	2	No interactions	Monitor closely	Moderate
Fenofibrate-Insulin Glargine	2	No interactions	Monitor closely	Moderate
Fenofibrate-Irbesartan	1	No interactions	No interactions	Moderate
Fenofibrate-Lansoprazole	1	No interactions	No interactions	Moderate
Fenofibrate-Glibenclamide	1	Level 1	Monitor closely	Moderate
Fenofibrate-Gliclazide	1	Level 1	No interactions	No interactions
Fenofibrate-Glimepiride	1	Level 1	Monitor closely	Moderate

5.9% of the interactions identified were due to fenofibrate. The interaction of fenofibrate with glibenclamide and glimepiride was identified in all three databases. In assessing the agreement for detecting DDIs based on fenofibrate using the Kappa index in RxMediaPharma and Medscape, slight agreement was found (Kappa value = 0.160), no agreement (Kappa value = -0.296) was found in RxMediaPharma and Drugs.com, and fair agreement (Kappa value = 0.364) was found in Drugs.com and Medscape.

In addition to the interaction presented in Table 6, it is also revealed that fenofibrate interacts with statins (please see Tables 3 and 5). This interaction occurred as a result of the combined use of these two active substances. Recent studies have generally demonstrated that statins and fenofibrate can be used in combination, and that adverse effects from combined therapy can be mitigated through patient monitoring [17,18]. The fact that the statin-fenofibrate interaction was generally shown to be significant by the online DDI checkers.

The study results show that most prescribed antihyperlipidemic drug is atorvastatin, which also induces most of the detected DDIs. Similarly, a study conducted by Morival et al. found that atorvastatin caused the most interactions [19]. Additionally, when Tables 3, 4, and 5 are examined, it is evident that 51 of the 151 interactions detected in the study involve proton pump inhibitors and statins. The most common DDIs were encountered between atorvastatin and pantoprazole. As stated by Barkas et al., proton pump inhibitors (PPIs) and statins are commonly prescribed together, and PPIs increase the plasma concentrations of statins [20]. Online DDI checkers provide different levels of interaction between these drugs, but they are not at a serious level. As Aykut and Arslan stated, PPIs do not generally cause major interactions [21]. However, further clinical studies are needed to investigate these potential interactions [20].

Another common interaction was between atorvastatin and clopidogrel, which was identified at a "moderate" level in only one database. The metabolism of these two drugs is rooted in CYP 450 activation, and it is known that atorvastatin interferes with clopidogrel metabolism by inhibiting its activation [22].

Finally, when considering the online checkers used to detect DDIs, it was found that the three databases yielded different results, with their agreement being very low. It is also worth noting that previous studies have reported varying results from online DDI checkers [12,13,23]. This situation is thought to be related to the online DDI checkers using different sources or the up-to-dateness of the sources used.

In this regard, the current study emphasizes the necessity for further research on DDIs induced by antihyperlipidemics. Determining DDIs with more precise and consistent data can contribute to the development of safer and more effective treatment strategies. It should be noted that the DDI checkers used in the study also necessitate updating the information sources of the databases.

This study has potential limitations. Prescriptions filled by only one community pharmacy were evaluated in the study. Hence, this may limit generalizability. Additionally, incorporating the outputs of other DDI checking programs or Artificial Intelligence (AI)-driven tools may help improve the generalizability of the results. Even then, using national and international DDI checking programs, as well as the number of prescriptions examined, reveals the study's strengths.

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AUTHOR CONTRIBUTIONS

Concept: Z.B.C., M.A.; Design: Z.B.C M.A.; Control: M.A.; Data Collection and/or Processing: Z.B.C.; Analysis and/or Interpretation: Z.B.C., M.A.; Literature Review: Z.B.C., M.A.; Manuscript Writing: Z.B.C., M.A.; Critical Review: M.A.; Other: -

CONFLICT OF INTEREST

The authors declare that there is no real, potential, or perceived conflict of interest for this article.

ETHICS COMMITTEE APPROVAL

This study was conducted after the Van Yüzüncü Yıl University Non-interventional Research Ethics Committee approved it ethically (Date: 18/11/2022, Decision No: 2022/11-30).

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