J. Fac. Pharm. Ankara / Ankara Ecz. Fak. Derg., 48(3): 1011-1020, 2024
Doi: 10.33483/jfpau.1460173

ORIGINAL ARTICLE / ÖZGÜN MAKALE

COMPARATIVE EVALUATION OF ARTIFICIAL INTELLIGENCE AND DRUG INTERACTION TOOLS: A PERSPECTIVE WITH THE EXAMPLE OF CLOPIDOGREL

YAPAY ZEKA VE İLAÇ ETKİLEŞİM ARAÇLARININ KARŞILAŞTIRMALI DEĞERLENDİRİLMESİ: KLOPİDOGREL ÖRNEĞİ İLE BİR BAKIŞ AÇISI

Zinnet Şevval AKSOYALP[1]*, Betül Rabia ERDOĞAN[1]

[1]Izmir Katip Celebi University, Faculty of Pharmacy, Department of Pharmacology, 35620, Izmir, Türkiye

ABSTRACT

Objective: *The study aims to compare the ability of free artificial intelligence (AI) chatbots to detect drug interactions with freely available drug interaction tools, using clopidogrel as an example.*
Material and Method: *The Lexicomp database was used as a reference to determine drug interactions with clopidogrel. ChatGPT-3.5 AI and Bing AI were selected as the free AI chatbots. Medscape Drug Interaction Checker, DrugBank Drug Interaction Checker and Epocrates Interaction Check were selected as free drug interaction tools. Accuracy score and comprehensiveness score were calculated for each drug interaction tool and AI chatbots. The kappa coefficient was calculated to assess inter-source agreement for interaction severity.*
Result and Discussion: *The results most similar to those of Lexicomp were obtained from the DrugBank and the ChatGPT-3.5 AI chatbot. The ChatGPT-3.5 AI chatbot performed best, with 69 correct results and an accuracy score of 307. ChatGPT-3.5 AI has the highest overall score of 387 points for accuracy and comprehensiveness. In addition, the highest kappa coefficient with Lexicomp was found for ChatGPT-3.5 AI chatbot (0.201, fair agreement). However, some of the results obtained by ChatGPT-3.5 AI need to be improved as they are incorrect/inadequate. Therefore, information obtained using AI tools should not be used as a reference for clinical applications by healthcare professionals and patients should not change their treatment without consulting doctor.*
Keywords: *Artificial intelligence, clopidogrel, drug interactions, patient safety, pharmaceutical databases*

ÖZ

Amaç: *Çalışmanın amacı, klopidogrel örneğini kullanarak ücretsiz yapay zekâ (AI) sohbet robotlarının ilaç etkileşimlerini saptama yeteneklerini ücretsiz olarak erişilebilen ilaç etkileşim araçları ile karşılaştırmaktır.*
Gereç ve Yöntem: *Klopidogrel ile ilaç etkileşimlerini belirlemek için referans veri tabanı olarak Lexicomp kullanılmıştır. Ücretsiz yapay zekâ sohbet robotları olarak ChatGPT-3.5 AI ve Bing AI, ücretsiz ilaç etkileşim araçları olarak ise Medscape Drug Interaction Checker, DrugBank Drug Interaction Checker ve Epocrates Interaction Check seçilmiştir. Her bir ilaç etkileşim aracı ve yapay zekâ sohbet robotu için doğruluk puanı ve kapsamlılık puanı hesaplanmıştır. Etkileşim şiddeti açısından kaynaklar arası uyumu değerlendirmek için kappa katsayısı hesaplanmıştır.*
Sonuç ve Tartışma: *Lexicomp veri tabanına en benzer sonuçlar Drugbank ve ChatGPT-3.5 AI*

* **Corresponding Author / Sorumlu Yazar:** Zinnet Şevval Aksoyalp
e-mail / e-posta: zinnetsevval.aksoyalp@ikcu.edu.tr, **Phone / Tel.:** +902323293535

Submitted / Gönderilme : 28.03.2024
Accepted / Kabul : 17.07.2024
Published / Yayınlanma : 10.09.2024

sohbet robotundan elde edilmiştir. ChatGPT-3.5 AI sohbet robotunun 69 doğru sonuç ve 307 doğruluk puanı ile en yüksek sonuçlara sahip olduğu bulunmuştur. Doğruluk ve kapsamlılık açısından 387 puanla en yüksek toplam puan ChatGPT-3.5 AI sohbet robotu sonuçları ile elde edilmiştir. Ayrıca Lexicomp ile en yüksek kappa skoru (0.201, orta düzey uyum) ChatGPT-3.5 AI chatbot için bulunmuştur. Ancak ChatGPT-3.5 AI ile elde edilen sonuçlardan bazılarının yanlış/yetersiz bulunması nedeniyle iyileştirilmesine ihtiyaç vardır. Sonuç olarak yapay zekâ araçlarından yararlanılarak elde edilen bilgiler sağlık profesyonelleri tarafından klinik uygulamalar için referans olarak kullanılmamalı ve hastalar doktora danışmadan tedavilerini değiştirmemelidir.

Anahtar Kelimeler: *Hasta güvenliği, ilaç etkileşimleri, ilaç veri tabanları, klopidogrel, yapay zekâ*

INTRODUCTION

Clopidogrel is an irreversible P2Y12 adenosine diphosphate receptor antagonist used to inhibit platelet activation and aggregation in patients with coronary artery disease, peripheral vascular disease, and cerebrovascular disease. These patients are often prescribed clopidogrel along with antihypertensive, antihyperlipidemic, and antidiabetic medications to reduce the risk of cardiovascular events [1]. Clopidogrel is a prodrug and is dependent on hepatic cytochrome P450 (CYP) metabolism for conversion to its active metabolite [2]; the therapeutic effect of clopidogrel may be increased or decreased by co-administration with other drugs that affect the CYP enzyme. The clinical outcomes of potential drug-drug interactions can be crucial in patients with coronary artery disease. Studies on the interaction of clopidogrel with other drugs have been conducted based on reviewing previous studies [1,3,4]. A paper on the evaluation of drug interactions with clopidogrel focused on studies of the interaction between clopidogrel with atorvastatin and omeprazole [1]. The interaction of clopidogrel with other drugs that induce and inhibit the CYP enzyme is also briefly discussed [1]. In another paper, the researchers reviewed studies of different drugs that interact with clopidogrel, including statins and proton pump inhibitors [3]. Several pharmacoepidemiological studies have been conducted to evaluate drug interactions with clopidogrel [5-9]; however, to our knowledge, studies have yet to compare these interactions using drug-drug interaction databases. Therefore, this study examined drug-drug interaction databases to introduce an assessment of the use of AIs in clinical practice, using the example of clopidogrel's interaction with other drugs.

Several databases and resources are available to help healthcare professionals and patients check for interactions in clinical practice and daily life. Some databases are free-accesible (Drugs.com, Epocrates, Medscape, RxList, and WebMD), and some are subscription-based (Lexicomp, Micromedex, and PEPID). However, these databases may vary in their information about drug-drug interactions [10-12]. The accessibility of these databases and the diversity of their content complicates the decision-making process for health professionals. There is a need to identify the most comprehensive, reliable, and freely accessible drug interaction database. Recently, there has been growing interest in using artificial intelligence (AI) to detect drug interactions [13-15]. As the use of AI chatbots becomes widespread, they are also becoming an increasingly popular source of information in healthcare. ChatGPT, Google Bard (now known as Gemine), and Microsoft Bing are the most popular AI chatbots. ChatGPT has both free version (ChatGPT-3.5) and commercial version (ChatGPT-4). This study aims to evaluate possible drug interactions with clopidogrel using both freely available drug interaction tools (Medscape, DrugBank, and Epocrates) and AI chatbots (ChatGPT-3.5 and Bing) and to compare the results obtained to test the capability of free AI chatbots.

MATERIAL AND METHOD

Data Collection

This study was conducted from April 25 to May 10, 2023. The list of drug interactions with clopidogrel was accessed from the UpToDate database [16], and a total of 84 cases of interaction with clopidogrel were identified. Interactions between clopidogrel and dietary supplements, nutrients, vitamins, and herbs, and repeated drug interactions were excluded from the analysis and were shown in yellow boxes in Figure 1. In addition, interactions of two drug classes (antiplatelet properties drugs and

calcium channel blockers) with clopidogrel were identified in the UpToDate database. Four drugs from antiplatelet properties drugs and two drugs from calcium channel blockers were selected and these drugs were shown in blue boxes in Figure 1. A total of 78 drugs were included in this study (Table 1).

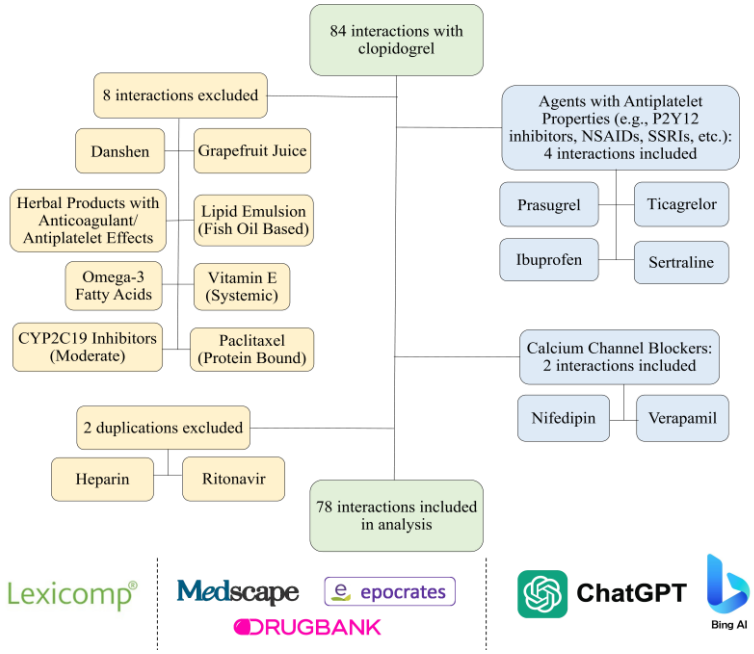

Figure 1. Flowchart for the inclusion/exclusion of drugs that interact with clopidogrel. Eighty-four cases of interaction with clopidogrel were identified in the UpToDate database. Interactions between clopidogrel and dietary supplements, nutrients, vitamins, and herbs, and repeated drug interactions were excluded from the analysis and were shown in yellow boxes. For the interactions of two drug classes (antiplatelet properties drugs and calcium channel blockers) with clopidogrel, selected drugs were shown in blue boxes. The interactions of clopidogrel with 78 selected medications were analyzed using Lexicomp, Medscape, Drugbank, Epocrates, ChatGPT-3.5 AI and Bing AI

Table 1. A list of 78 drugs that interact with clopidogrel was retrieved from the UpToDate database and included in the study

Abrocitinib	Cladribine	Enzalutamide	Lansoprazole	Pentoxifylline	Sodium Zirconium Cyclosilicate
Acalabrutinib	Cobicistat	Epoprostenol	Lecanemab	Pioglitazone	Talazoparib
Acetylsalicylic Acid	Collagenase	Erythromycin	Limaprost	Pirtobrutinib	Ticagrelor
Alpelisib	Dabigatran Etexilate	Esomeprazole	Morphine	Prasugrel	Tipranavir
Alteplase	Dabrafenib	Etravirine	Nifedipine	Repaglinide	Topotecan
Amodiaquine	Daprodustat	Fentanyl	Nirmatrelvir and Ritonavir	Rifampin	Treprostinil
Apixaban	Dasabuvir	Fluconazole	Obinutuzumab	Ritonavir	Tucatinib
Bemiparin	Dasatinib	Heparin	Omeprazole	Rivaroxaban	Ubrogepant
Berotralstat	Deoxycholic Acid	Ibritumomab Tiuxetan	Ozanimod	Rosuvastatin	Urokinase
Bupropion	Desloratadine	Ibrutinib	Paclitaxel	Selexipag	Verapamil
Cangrelor	Diamorphine	Icosapent Ethyl	Pantoprazole	Selumetinib	Vonoprazan
Caplacizumab	Edoxaban	Inotersen	Pazopanib	Sertraline	Warfarin
Cephalothin	Enoxaparin	Ibuprofen	Pentosan Polysulfate Sodium	Sibutramine	Zanubrutinib

Lexicomp (Wolters Kluwer, USA), a subscription-based drug interaction screening tool, was selected as the reference database and accessed through the library of Izmir Katip Celebi University. Firstly, drug interactions with clopidogrel were screened by the Lexicomp database. Then, three free software programs, Medscape (WebMD, USA), DrugBank (University of Alberta, USA), and Epocrates (Epocrates Inc., USA), were used to check the capability of ChatGPT-3.5 AI and Bing AI. These databases were chosen because they are available to the public free of charge. In this study, we focused on the free-accesible version of chatbots, which people more widely use due to their free access, so we included ChatGPT-3.5 AI and Microsoft Bing AI. Google Bard was excluded as it was used for testing during the study period. Free accounts were created on ChatGPT-3.5 AI and Bing AI and interacted with the AI-based language model to collect data. As both free AI chatbots have a maximum question limit of 24 hours, the drug interaction screening with AI chatbots was completed between 8 and 10 May 2023. A new conversation was started for each drug interaction question. Five questions were prepared based on information from Lexicomp, the reference database for drug interactions. Each pair of drug interactions was searched with five questions, and the answers were recorded for further analysis. The following questions were used:

"Can I take clopidogrel and X together?"
''What happens if I take clopidogrel and X together?''
''How should I take clopidogrel and X together?''
"What is the risk rating of interaction between clopidogrel and X?" and
"What is the severity of interaction between clopidogrel and X?".

In Lexicomp, the severity of the interaction is categorized as major, moderate, and minor. The results of the free drug interaction checkers and AI chatbots are also standardized as in Lexicomp. Drugs that were unavailable to these tools and AI chatbots were assumed not to interact. The true positive (TP), true negative (TN), false positive (FP), and false negative (FN) values of these databases and the AI chatbots assessing clopidogrel interactions were determined. A drug interaction defined as a major/moderate interaction in Lexicomp is defined as a TP if it is also a major/moderate interaction in other databases and is defined as an FN if it is a minor/no interaction in other databases. On the other hand, a minor interaction identified in Lexicomp is defined as TN if it is a minor/no interaction in other databases, while it is defined as FP if it is a major/moderate in other databases [11].

Statistical Analysis

The data were analyzed using descriptive statistics. The ability of the database to accurately detect major/moderate drug interactions is defined as the sensitivity, while the ability to ignore minor interactions is defined as the specificity [10]. Positive predictive value (PPV) is the probability that an interaction detected by the database is a significant interaction. The probability that interactions not detected by the database are insignificant is reported as negative predictive value (NPV). The sensitivity, specificity, PPV and NPV of these databases were calculated using the following equations [11]:

$$\text{Sensitivity} = TP / (TP + FN)$$
$$\text{Specificity} = TN / (FP + TN)$$
$$PPV = TP / (TP + FP)$$
$$NPV = TN / (TN + FN)$$

The accuracy score was calculated by multiplying the sum of the sensitivity, specificity, PPV and NPV values by 100, and the maximum accuracy score was 400 [10].

The results of drug interaction checkers and AI chatbots were also evaluated for severity level, onset, mechanism, risk rating, management, discussion, documentation level, references, clinical manifestations, and related drugs. Subsequently, the comprehensiveness score was calculated by multiplying the number of these items found in drug interaction checkers and AI chatbots by 13.4 [10]. As ten items are to be assessed, the maximum comprehensiveness score is 134.

In addition, kappa (κ) coefficients were used to assess the consistency of severity between the four drug-drug interaction tools and the two AI chatbots using SPSS (version 29.0, IBM, USA). To harmonize the severity of the interactions classified as major, moderate and minor in the Lexicomp

results with the results from other databases, minor and no interaction results were combined and scored as no interaction. Fleiss' kappa coefficient was calculated to assess the agreement between all drug-drug interaction tools and AI chatbots in terms of the severity of drug interactions with clopidogrel. Cohen's kappa coefficient was calculated to pairwise compare drug interaction tools and AI chatbots. A kappa coefficient of 1 indicates perfect agreement, -1 indicates perfect disagreement, and 0 indicates agreement that would be expected by chance. Kappa coefficient < 0.0 indicates poor agreement, 0.0 - 0.2 slight agreement, 0.21 - 0.40 fair agreement, 0.41 - 0.60 moderate agreement, 0.61 - 0.80 substantial agreement, and 0.81 - 1.00 near perfect agreement [17]. The calculated *p*-value for kappa coefficients is less than 0.05, meaning that the agreement between tools and AI chatbots is unlikely to be due to chance.

RESULT AND DISCUSSION

This study included 78 cases of interaction with clopidogrel; however, some drugs were unavailable in drug interaction checkers tools and AI chatbots (n = 12 for MedScape, n = 1 for Drugbank, n = 9 for Epocrates, and n = 54 for Bing AI) except ChatGPT-3.5 AI. These drugs were assumed to have no interaction with clopidogrel.

Lexicomp Drug Interactions Module, a reference database, has identified 20 major, 53 moderate, and five minor drug interactions with clopidogrel (Table 2). Among the free-accesible databases, Drugbank showed similar results to those of Lexicomp. The DrugBank found 13 major, 49 moderate and six minor interactions with clopidogrel and no interactions with ten other drugs. Epocrates identified 17 major, 35 moderate and two minor interactions with clopidogrel. However, Epocrates did not find interactions with 24 drugs. On the other hand, more than half of these clopidogrel-drug interactions were not found in the MedScape. Interestingly, ChatGPT-3.5 AI found that clopidogrel interacted with all but eight of the drugs that were identified in the UpToDate database. However, some moderate risk interactions in Lexicomp were identified as major interactions in ChatGPT-3.5 AI. In contrast, the Bing AI chatbot found interactions only for 15 drugs.

Table 2. Standardization of the interaction severity ratings of the drug interaction tools and AI chatbots as major, moderate, and minor

Lexicomp		**MedScape**		**Drugbank**		**Epocrates**		**ChatGPT-3.5 AI**		**Bing AI**	
Major	20	Serious/Use alternative Contraindicated	13	Major	13	Avoid/Use alternative	17	High	27	Severe	9
Moderate	53	Monitor closely	23	Moderate	49	Monitor/Modify treatment	35	Moderate	41	Moderate	6
Minor	5	Minor	0	Minor	6	Caution advised	2	Mild	2	Minor	0
		No interaction found	42	No interaction found	10	No interaction found	24	No known interaction	8	No interaction found	63

The highest number of correct answers (TP plus TN) was received by ChatGPT-3.5 AI chatbot (n = 69) and Drugbank (n = 64). However, some of the results were misinterpreted by the AI chatbot, such as the fact that clopidogrel is a prodrug. One of the most common interactions with clopidogrel is with CYP2C19 inhibitors. As clopidogrel is a prodrug, co-administration of clopidogrel with CYP2C19 inhibitors reduces serum levels of the active metabolite of clopidogrel. ChatGPT-3.5 AI and Bing AI chatbot accurately describe the interaction of clopidogrel with proton pump inhibitors, which are CYP2C19 inhibitors, suggesting that it leads to decreased plasma levels of the active metabolite. On the other hand, ChatGPT-3.5 AI chatbot incorrectly explains the interaction of fluconazole, nifedipine, and ritonavir (enzyme inhibitors) [1,18,19] and rifampin (enzyme inducer) [20] with clopidogrel, ignoring that clopidogrel is a prodrug. A similar incorrect result was found for erythromycin (enzyme inhibitor) [1] in the Bing AI.

The highest number of incorrect answers (FN plus FP) was received by the Bing AI chatbot (n = 60) and MedScape (n = 39). A reliable drug-drug interaction checker should be sensitive to detect significant interactions and specific to ignore insignificant interactions. The ChatGPT-3.5 AI chatbot

was the most sensitive, while the Bing AI chatbot was the least sensitive. Among the free drug interaction checkers, the DrugBank had the highest level of sensitivity, while the MedScape had the lowest level of sensitivity. Epocrates was found to have the highest specificity of all the databases, while the Bing AI chatbot was found to have the lowest specificity.

The positive predictive values of Drugbank, Medscape and ChatGPT-3.5 AI were comparable and higher, demonstrating their ability to identify significant interactions. On the other hand, both Drugbank and ChatGPT-3.5 AI showed high negative predictive value, further supporting their reliability. The most accurate database was the ChatGPT-3.5 AI chatbot, with 307 out of 400 accuracy points. On the other hand, Bing AI chatbot was the least accurate database, with 197 points (Table 3). Among the free drug interaction checkers, the most accurate database was Drugbank, with 299, and the least accurate was MedScape, with 244 points (Table 3).

Table 3. Accuracy score of drug interaction checkers and AI chatbots for assessing clopidogrel interactions with 78 drugs

	TP	FN	TN	FP	Sensitivity	Specificity	PPV	NPV	Accuracy Score*
MedScape	35	38	4	1	0.48	0.90	0.97	0.10	244
Drugbank	60	12	4	2	0.83	0.94	0.97	0.25	299
Epocrates	48	25	1	4	0.66	0.98	0.92	0.04	260
ChatGPT-3.5 AI	67	7	2	2	0.91	0.97	0.97	0.22	307
Bing AI	14	59	4	1	0.19	0.78	0.93	0.06	197

*Maximum accuracy score is 400. Abbreviation; FN, false negative; FP, false positive; TN, true negative; TP, true positive; PPV, positive predictive value; NPV, negative predictive value

The Bing AI and DrugBank are superior to other checkers in providing references for drug interactions with clopidogrel. On the other hand, ChatGPT-3.5 AI has cited the Lexicomp and Epocrates databases for some interactions, but the results are inconsistent (Table 4). Epocrates, ChatGPT-3.5 AI and Bing AI offer management of drug interactions with clopidogrel. The Bing AI chatbot had the highest comprehensiveness score of 107 points (Table 4). On the other hand, the most comprehensive free drug interaction checker was Drugbank, with 80 comprehensiveness scores. The total score was obtained by summing the accuracy and comprehensiveness scores [10]. ChatGPT-3.5 AI had the highest total score, with 387. Among the free interaction checkers, DrugBank had the highest score, with 379 (Table 5).

Fleiss' kappa coefficients were evaluated for interaction severity agreement between drug-drug interaction tools and AI chatbots for clopidogrel and drug interaction pairs (Table 6). The overall Fleiss kappa coefficient was 0.043 (slight agreement; $p = 0.040$). The kappa coefficient was 0.106 (slight agreement; $p < 0.001$) for interaction pairs with the major severity drug interaction category. Pairwise agreement for the severity of interactions between drug interactive tools and/or AI chatbots was assessed using Cohen's kappa coefficient (Table 7). The highest kappa coefficients were found between Epocrates and Medscape ($\kappa = 0.390$; $p < 0.01$) and Lexicomp and ChatGPT-3.5 ($\kappa = 0.201$; $p = 0.020$), both showing fair agreement.

Table 4. Comprehensiveness score of drug interaction checkers and AI chatbots for assessing clopidogrel interactions with 78 drugs

	Risk rating	Onset	Mechanism	Severity level	Management	Discussion	DL	Ref	CM	Related drugs	CS*
MedScape	Yes	No	Yes	Yes	No	No	No	No	Yes	No	54
Drugbank	Yes	No	Yes	Yes	No	Yes	No	Yes	Yes	No	80
Epocrates	Yes	No	Yes	Yes	Yes	No	No	No	Yes	No	67
ChatGPT-3.5 AI	Yes	No	Yes	Yes	Yes	Yes	No	No	Yes	No	80
Bing AI	Yes	No	Yes	Yes	Yes	Yes	Yes	Yes	Yes	No	107

*Maximum comprehensiveness score is 134. Abbreviation; CM, clinical manifestations, CS, comprehensiveness score, DL, documentation level, Ref, references

Table 5. Total score of drug interaction checkers and AI chatbots for assessing clopidogrel interactions with 78 drugs

	Accuracy Score	Comprehensiveness Score	Total Score*
MedScape	244	54	298
Drugbank	299	80	379
Epocrates	260	67	327
ChatGPT-3.5 AI	307	80	387
Bing AI	197	107	304

*Maximum total score (accuracy + comprehensiveness) = 400 + 134 = 534

Table 6. Fleiss' kappa coefficients for the interaction severity agreements of four drug interaction tools and two AI chatbots for clopidogrel and drug interaction pairs

	Kappa coefficient	*p*-value	Strength of agreement
Major	0.106***	< 0.001	Slight
Moderate	0.000	0.990	Slight
No interaction	0.045	0.127	Slight
Overall	0.043*	0.040	Slight

In drug interactions reported as minor or not applicable, it was assumed that there were no drug interactions. *$p < 0.05$, ***$p < 0.001$

Table 7. Cohen's kappa coefficients for the interaction severity agreements of between drug interaction tools and/or AI chatbots for clopidogrel and drug interaction pairs

	Lexicomp	MedScape	Drugbank	Epocrates	ChatGPT-3.5 AI	Bing AI
Lexicomp	-	0.095	0.108	0.004	0.201*	0.009
Medscape	0.095	-	0.071	0.390***	0.090	0.118
DrugBank	0.108	0.071	-	0.101	-0.007	0.030
Epocrates	0.004	0.390***	0.101	-	0.047	0.007
ChatGPT-3.5 AI	0.201*	0.090	-0.007	0.047	-	-0.037
Bing AI	0.009	0.118	0.030	0.007	-0.037	-

In drug interactions reported as minor or not applicable, it was assumed that there were no drug interactions. *$p < 0.05$, ***$p < 0.001$

An increasing number of medicines are coming onto the market, and many new interactions are reported that may interfere with treatment or cause adverse effects [21]. The identification of predictable and preventable drug-drug interactions is essential for patient safety, and healthcare professionals often use drug-drug interaction tools to help them identify all the possible interactions between medicines. There are many drug-drug interaction tools available, but the results from these databases are not always consistent, and several studies have been carried out to compare these databases [10-12,22-29]. Although the drug-drug interaction tools and the drugs compared in these studies were different, the conclusion was that subscription-based tools may be more useful than free tools and that health professionals should use at least two different resources to assess drug interactions. Most of these studies showed that Lexicomp had the highest score among subscription-based drug interaction tools [11,12,26], so we chose Lexicomp as our reference source. Artificial Intelligence (AI) is revolutionizing many fields, including health [30]. In recent years, AI applications in healthcare have been in the spotlight, and the potential for AI tools to provide information about drug use among the public is growing [31,32]. Our study focused on clopidogrel, a drug with significant drug-drug interactions, and compared the performance of drug-drug interaction databases and AI chatbots in identifying these interactions.

Our research, along with two previous studies [13,14], has shed light on the potential of AI chatbots in detecting drug interactions. In the first study, the results of another previous study evaluating 40 drug-drug interactions [10] were compared with the free-accesible version of ChatGPT [14]. ChatGPT is partially effective in detecting drug interactions. Although the information provided by ChatGPT is sometimes insufficient, it may be helpful in detecting drug interactions [14]. Similarly, the ChatGPT-3.5 AI chatbot provided useful information about clopidogrel-drug interactions in our study.

The other study searched ChatGPT-3.5 AI, ChatGPT-4 AI, Microsoft Bing AI and Google Bard for interactions of five drugs selected from the class of SGLT-2 inhibitors and macrolides with the 51 most prescribed drugs [13]. These results were compared with those from Micromedex and Drugs.com [13]. In contrast to our study, it was found that Bing AI had the highest accuracy and specificity [13]. In our research, ChatGPT-3.5 AI and DrugBank had the highest accuracy scores. These resources may be free and reliable for identifying drug interactions with clopidogrel. Although Bing AI has the highest comprehensive score, it appears inadequate as it only includes a few drugs. DrugBank and ChatGPT-3.5 AI had the highest comprehensiveness scores, except for Bing AI. As a result, our study shows that ChatGPT-3.5 AI and DrugBank are the most comprehensive and accurate drug interaction detection tools available to healthcare professionals and patients. On the other hand, the compatibility of Lexicomp-ChatGPT-3.5 AI chatbot results for interaction severity was found to be fair. The fact that clopidogrel is a prodrug leads to different results for interactions with drugs that induce or inhibit CYP3A4/A5, CYP2C19, CYP2C9 and CYP1A2, which are involved in the metabolism of clopidogrel [1]. The interaction between the CYP2C19 inhibitors, proton pump inhibitors [1], and clopidogrel was correctly explained by ChatGPT-3.5 AI. However, the interaction with the CYP3A4/A5 inhibitors nifedipine, fluconazole, ritonavir [1] and the CYP3A4/A5 inducer rifampin [1] was incorrectly explained. Even though ChatGPT-3.5 AI achieved the highest overall (accuracy + comprehensiveness) score, a major weakness of ChatGPT-3.5 AI is that it ignores the fact that clopidogrel is a prodrug in these interactions. In addition, our study has some limitations. One limitation is that the data included in the ChatGPT-3.5 AI is from before September 2021 and may not include the most recent medical data. More accurate results can be obtained with ChatGPT-4 AI, but its cost limits its use.

In conclusion, the main findings of our research are as follows: (a) Drugbank Drug Interaction Checker among free-accesible databases and ChatGPT-3.5 AI among AI chatbots provide the results most similar to Lexicomp, (b) More than half of the drugs are not available in Bing AI chatbot, (c) The ChatGPT-3.5 AI chatbot and the Drugbank database have the highest number of correct answers and accuracy score for drug interactions, (d) The Bing AI chatbot performs excellently on the comprehensiveness score, but the inaccessibility of 80% of medications limits this result, (e) Finally, ChatGPT-3.5 AI performed best when considering the overall score.

ChatGP T-3.5 AI shows promise in predicting drug interactions with clopidogrel but may lead to incorrect conclusions with CYP enzyme inhibitors/inducers, ignoring the properties of the drug compound. ChatGPT-3.5 AI can provide general information about drug therapy but cannot give specific medical advice or recommendations. Also, ChatGPT-3.5 AI emphasizes that other medications or supplements should be avoided without the advice of a healthcare professional while using clopidogrel. The AI chatbots recommend being aware of bleeding symptoms when taking clopidogrel and taking the medications at different times of the day to reduce the risk of bleeding. The AI chatbots also warn that the questioner should consult a healthcare professional, regardless of whether there is data on drug interactions, which is beneficial for patient safety. In the future, AI chatbots could become even more useful by improving their ability to predict the interactions between drugs accurately. However, patients should always consult their healthcare provider before changing or stopping taking their medicines.

AUTHOR CONTRIBUTIONS

Concept: Z.S.A.; Design: Z.S.A, B.R.E.; Control: Z.S.A, B.R.E.; Sources: Z.S.A.; Materials: - ; Data Collection and/or Processing: Z.S.A, B.R.E.; Analysis and/or Interpretation: Z.S.A.; Literature Review: Z.S.A, B.R.E.; Manuscript Writing: Z.S.A, B.R.E.; Critical Review: Z.S.A, B.R.E.; Other: -

CONFLICT OF INTEREST

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

ETHICS COMMITTEE APPROVAL

The authors state that ethics committee approval is not required for this study.

REFERENCES

1. Bates, E.R., Lau, W.C., Angiolillo, D.J. (2011). Clopidogrel-drug interactions. Journal of the American College of Cardiology, 57(11), 1251-1263. [CrossRef]
2. Kazui, M., Nishiya, Y., Ishizuka, T., Hagihara, K., Farid, N.A., Okazaki, O., Ikeda, T., Kurihara, A. (2010). Identification of the human cytochrome P450 enzymes involved in the two oxidative steps in the bioactivation of clopidogrel to its pharmacologically active metabolite. Drug Metabolism & Disposition, 38(1), 92-99. [CrossRef]
3. Wang, Z.Y., Chen, M., Zhu, L.L., Yu, L.S., Zeng, S., Xiang, M.X., Zhou, Q. (2015). Pharmacokinetic drug interactions with clopidogrel: Updated review and risk management in combination therapy. Therapeutics and Clinical Risk Management, 11, 449-467. [CrossRef]
4. Lee, C.H., Franchi, F., Angiolillo, D.J. (2020). Clopidogrel drug interactions: A review of the evidence and clinical implications. Expert Opinion on Drug Metabolism & Toxicology, 16(11), 1079-1096. [CrossRef]
5. Agergaard, K., Mau-Sorensen, M., Stage, T.B., Jorgensen, T.L., Hassel, R.E., Steffensen, K.D., Pedersen, J.W., Milo, M., Poulsen, S.H., Pottegard, A., Hallas, J., Brosen, K., Bergmann, T.K. (2017). Clopidogrel-Paclitaxel drug-drug interaction: A pharmacoepidemiologic study. Clinical Pharmacology & Therapeutics, 102(3), 547-553. [CrossRef]
6. Bykov, K., Schneeweiss, S., Donneyong, M.M., Dong, Y.H., Choudhry, N.K., Gagne, J.J. (2017). Impact of an interaction between clopidogrel and selective serotonin reuptake inhibitors. American Journal of Cardiology, 119(4), 651-657. [CrossRef]
7. Cressman, A.M., Macdonald, E.M., Fernandes, K.A., Gomes, T., Paterson, J.M., Mamdani, M.M., Juurlink, D.N. (2015). A population-based study of the drug interaction between clopidogrel and angiotensin converting enzyme inhibitors. British Journal of Clinical Pharmacology, 80(4), 662-669. [CrossRef]
8. Leonard, C.E., Zhou, M., Brensinger, C.M., Bilker, W.B., Soprano, S.E., Pham Nguyen, T.P., Nam, Y.H., Cohen, J.B., Hennessy, S. (2019). Clopidogrel Drug interactions and serious bleeding: Generating real-world evidence via automated high-throughput pharmacoepidemiologic screening. Clinical Pharmacology & Therapeutics, 106(5), 1067-1075. [CrossRef]
9. Suzuki, Y., Suzuki, H., Umetsu, R., Uranishi, H., Abe, J., Nishibata, Y., Sekiya, Y., Miyamura, N., Hara, H., Tsuchiya, T., Kinosada, Y., Nakamura, M. (2015). Analysis of the Interaction between clopidogrel, aspirin, and proton pump inhibitors using the FDA adverse event reporting system database. Biological and Pharmaceutical Bulletin, 38(5), 680-686. [CrossRef]
10. Kheshti, R., Aalipour, M., Namazi, S. (2016). A comparison of five common drug-drug interaction software programs regarding accuracy and comprehensiveness. Journal of Research in Pharmacy Practice, 5(4), 257-263.
11. Marcath, L.A., Xi, J., Hoylman, E.K., Kidwell, K.M., Kraft, S.L., Hertz, D.L. (2018). Comparison of nine tools for screening drug-drug interactions of oral oncolytics. Journal of Oncology Practice, 14(6), e368-e374. [CrossRef]
12. Shariff, A., Belagodu Sridhar, S., Abdullah Basha, N.F., Bin Taleth Alshemeil, S.S.H., Ahmed Aljallaf Alzaabi, N.A. (2021). Assessing Consistency of drug-drug interaction-related information across various drug information resources. Cureus, 13(3), e13766. [CrossRef]
13. Al-Ashwal, F.Y., Zawiah, M., Gharaibeh, L., Abu-Farha, R., Bitar, A.N. (2023). Evaluating the sensitivity, specificity, and accuracy of ChatGPT-3.5, ChatGPT-4, Bing AI, and Bard Against conventional drug-drug interactions clinical tools. Drug, Healthcare and Patient Safety, 15, 137-147. [CrossRef]
14. Juhi, A., Pipil, N., Santra, S., Mondal, S., Behera, J.K., Mondal, H. (2023). The Capability of ChatGPT in predicting and explaining common drug-drug interactions. Cureus, 15(3), e36272. [CrossRef]
15. Akyon, S.H., Akyon, F.C., Yilmaz, T.E. (2023). Artificial intelligence-supported web application design and development for reducing polypharmacy side effects and supporting rational drug use in geriatric patients. Frontiers in Medicine, 10, 1029198. [CrossRef]
16. UpToDate. Clopidogrel drug information 2023 [cited 2023]. Available from: https://www.uptodate.com/contents/clopidogrel-drug information?search=clopidogrel&source=panel_search_result&selectedTitle=1~148&usage_type=panel&kp_tab=drug_general&display_rank=1#F153600. Acess date:14.04.2023.
17. Landis, J.R., Koch, G.G. (1977). The measurement of observer agreement for categorical data. Biometrics, 33(1), 159-174. [CrossRef]
18. Nakagita, K., Wada, K., Terada, Y., Matsuda, S., Terakawa, N., Oita, A., Takada, M. (2018). Effect of fluconazole on the pharmacokinetics of everolimus and tacrolimus in a heart transplant recipient: Case report. International Journal of Clinical Pharmacology Research, 56(6), 270-276. [CrossRef]
19. Zeldin, R.K., Petruschke, R.A. (2004). Pharmacological and therapeutic properties of ritonavir-boosted

protease inhibitor therapy in HIV-infected patients. The Journal of Antimicrobial Chemotherapy, 53(1), 4-9. [CrossRef]
20. Niemi, M., Backman, J.T., Fromm, M.F., Neuvonen, P.J., Kivisto, K.T. (2003). Pharmacokinetic interactions with rifampicin: Clinical relevance. Clinical Pharmacokinetics, 42(9), 819-850. [CrossRef]
21. McQuade, B.M., Campbell, A. (2021). Drug prescribing: Drug-drug interactions. FP Essentials, 508, 25-32.
22. Drwiega, E.N., Badowski, M.E., Michienzi, S. (2022). Antiretroviral drug-drug interactions: A comparison of online drug interaction databases. Journal of Clinical Pharmacy and Therapeutics., 47(10), 1720-1724. [CrossRef]
23. Alkhalid, Z.N., Birand, N. (2022). Determination and comparison of potential drug-drug interactions using three different databases in northern cyprus community pharmacies. Nigerian Journal of Clinical Practice, 25(12), 2005-2009. [CrossRef]
24. Hecker, M., Frahm, N., Bachmann, P., Debus, J.L., Haker, M.C., Mashhadiakbar, P., Langhorst, S.E., Baldt, J., Streckenbach, B., Heidler, F., Zettl, U.K. (2022). Screening for severe drug-drug interactions in patients with multiple sclerosis: A comparison of three drug interaction databases. Frontiers in Pharmacology, 13, 946351. [CrossRef]
25. Suriyapakorn, B., Chairat, P., Boonyoprakarn, S., Rojanarattanangkul, P., Pisetcheep, W., Hunsakunachai, N., Vivithanaporn, P., Wongwiwatthananukit, S., Khemawoot, P. (2019). Comparison of potential drug-drug interactions with metabolic syndrome medications detected by two databases. PLoS One, 14(11), e0225239. [CrossRef]
26. Patel, R.I., Beckett, R.D. (2016). Evaluation of resources for analyzing drug interactions. Journal of the Medical Library Association, 104(4), 290-295. [CrossRef]
27. Pehlivanli, A., Eren-Sadioglu, R., Aktar, M., Eyupoglu, S., Sengul, S., Keven, K., Erturk, S., Basgut, B., Ozcelikay, A.T. (2022). Potential drug-drug interactions of immunosuppressants in kidney transplant recipients: Comparison of drug interaction resources. International Journal of Clinical Pharmacy, 44(3), 651-662. [CrossRef]
28. Martins, M.A., Carlos, P.P., Ribeiro, D.D., Nobre, V.A., Cesar, C.C., Rocha, M.O., Ribeiro, A.L. (2011). Warfarin drug interactions: A comparative evaluation of the lists provided by five information sources. European Journal of Clinical Pharmacology, 67(12), 1301-1308. [CrossRef]
29. Monteith, S., Glenn, T. (2019). A comparison of potential psychiatric drug interactions from six drug interaction database programs. Psychiatry Research, 275, 366-372. [CrossRef]
30. Alowais, S.A., Alghamdi, S.S., Alsuhebany, N., Alqahtani, T., Alshaya, A.I., Almohareb, S.N., Aldairem, A., Alrashed, M., Bin Saleh, K., Badreldin, H.A., Al Yami, M.S., Al Harbi, S., Albekairy, A.M. (2023). Revolutionizing healthcare: The role of artificial intelligence in clinical practice. BMC Medical Education, 23(1), 689. [CrossRef]
31. Younis, H.A., Eisa, T.A.E., Nasser, M., Sahib, T.M., Noor, A.A., Alyasiri, O.M., Salisu, S., Hayder, I.M., Younis, H.A. (2024). A systematic review and meta-analysis of artificial intelligence tools in medicine and healthcare: Applications, considerations, limitations, motivation and challenges. Diagnostics (Basel), 14(1), 109. [CrossRef]
32. Davenport, T., Kalakota, R. (2019). The potential for artificial intelligence in healthcare. Future Healthcare Journal, 6(2), 94-98. [CrossRef]