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Research Article

Utilization of SuperCYPsPred Software for Predicting Drug Interactions Mediated by Cytochrome P450 Isoenzymes in Elderly Patients Receiving Polypharmacy

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Abstract

Background: Increasing polypharmacy and complicated prescription regimens raise the likelihood of CYP-mediated drug-drug interactions (DDIs) in older people. ***Objective***: To assess the incidence of CYP-mediated DDIs in older people with polypharmacy and examine the correlation between medication dispensation and the likelihood of these interactions in this high-risk group. ***Methods***: A cross-sectional 17-week analysis was performed, including consecutive new patients aged 65 years and over who were undergoing polypharmacy (defined as the use of more than five medications) at a community pharmacy. The medication profiles of these individuals were evaluated using SuperCYPsPred software and UpToDate® Lexidrug. The frequency of possible CYP-mediated interactions was evaluated. The pharmacists' judgments to suggest prescription adjustments based on the likelihood of CYP-mediated interactions were documented. ***Results***: The prevalence of possible CYP-mediated drug-drug interactions identified among 220 older persons with polypharmacy was 84.5%. Moderate severity DDIs were the predominant and significant kind of interaction (2.70±3.157). A linear regression analysis was performed to predict the frequency of drug interactions based on the number of drugs. A significant association has been identified ($F(1,14)= 67.789$, $p<0.001$). The predominant CYP isoenzyme was CYP3A4 at 34.6%, followed by CYP2C9 at 21.4% and CYP2D6 at 15.7%, with no notable gender differences. ***Conclusion***: The older patients have at least one DDI. Elderly adults taking five or more medicines require frequent care owing to a fourfold greater chance of drug interactions.

Keywords: Elderly, Isoenzymes, Interactions, Prevalence, Polypharmacy.

استخدام برنامج SuperCYPsPred للتنبؤ بالتفاعلات الدوائية بوساطة متشابهات السيتوكروم P450 في المرضى المسنين الذين يتلقون الأدوية المتعددة

الخلاصة

الخلفية: تزيد زيادة تعدد الأدوية وأنظمة الوصفات الطبية المعقدة من احتمالية حدوث تفاعلات دوائية دوائية بوساطة CYP (DDIs) لدى كبار السن. **الهدف**: تقييم وقوع DDIs بوساطة CYP لدى كبار السن من مستخدمي ادوية متعددة وفحص العلاقة بين صرف الأدوية واحتمالية حدوث هذه التفاعلات في هذه المجموعة عالية الخطورة.**الطرائق**: تم إجراء تحليل مقطعي لمدة 17 أسبوعا، بما في ذلك المرضى الجدد المتتاليين الذين تتراوح أعمارهم بين 65 عاما وما فوق والذين كانوا يخضعون لعلاج بالأدوية المتعددة (يعرف بأنه استخدام أكثر من خمسة أدوية) في صيدلية مجتمعية. تم تقييم ملفات تعريف الأدوية لهؤلاء الأفراد باستخدام برنامج SuperCYPsPred و UpToDate® Lexidrug. تم تقييم تواتر التفاعلات المحتملة بوساطة CYP. تم توثيق أحكام الصيادلة لاقتراح تعديلات الوصفات الطبية بناء على احتمالية التفاعلات بوساطة CYP. **النتائج**: كان انتشار التفاعلات الدوائية المحتملة بوساطة CYP التي تم تحديدها بين 220 من كبار السن المصابين بتعدد الأدوية 84.5٪. كانت DDIs متوسطة الخطورة هي النوع السائد والهام من التفاعل (2.70±3.157). تم إجراء تحليل الانحدار الخطي للتنبؤ بتواتر التفاعلات الدوائية بناء على عدد الأدوية. تم تحديد ارتباط كبير ($F (1،14) = 67.789$ ، p <0.001). كان متشادر إنزيم CYP السائد هو CYP3A4 بنسبة 34.6٪ ، يليه CYP2C9 بنسبة 21.4٪ و CYP2D6 بنسبة 15.7٪ ، مع عدم وجود اختلافات ملحوظة بين الجنسين. **الأستنتاجات**: المرضى الأكبر سنا لديهم DDI واحد على الأقل. يحتاج كبار السن الذين يستخدمون خمسة أدوية أو أكثر إلى رعاية متكررة بسبب فرصة أكبر أربعة أضعاف للتفاعلات الدوائية.

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INTRODUCTION

While the implementation of a medication is typically clinically important and intended to enhance the wellness of the individual, it may also elevate the patient's risk of possible interactions between drugs (DDIs) and drug-disease interactions [1]. Clinically significant drug-drug interactions are characterized by a reduction in the therapeutic efficacy of a medication, an elevated incidence of side effects, and diminished

therapeutic effects. Serious potential drug-drug interactions are those that pose a serious risk and need medical therapy or response to mitigate or avert significant adverse effects [2]. Polypharmacy, the simultaneous use of numerous drugs, is often encountered in older persons owing to various chronic health issues and remains an area of concern [3]. Polypharmacy is often described as the simultaneous use of ≥ 5 drugs. The incidence of polypharmacy differs across various groups and expands with age [4,5]. A comprehensive survey of 1,742,336 older individuals revealed a polypharmacy prevalence of 44% [6]. A Scottish Polypharmacy Advisory indicated that up to 11% of unexpected hospitalizations were attributable to damage caused by polypharmacy, with around 50% of these cases deemed avoidable [7,8]. A prospective study including 5052 older persons in Spain indicated that polypharmacy elevated the mortality risk by about 1.8 times [9]. Multiple enzyme systems participate in drug-drug interactions, with the cytochrome P450 (CYP) system being the most prevalent. The inhibition or stimulation of CYP metabolism has been described as a critical mechanism of drug-drug interactions, despite the fact that DDIs involving CYP isoenzymes represent only a minor fraction of adverse drug reactions (ADRs) [10,11]. Drug-drug interactions gain importance due to their predictability, making them typically preventable [12]. The CYP family comprises over 1,000 isoenzymes, with five (CYP3A4, CYP2D6, CYP2C9, CYP2C19, and CYP1A2) responsible for the metabolism of 90% of all pharmaceuticals. Analysis of the 200 most frequently prescribed medications in the US indicates that over 73% undergo metabolism, with around 75% of these pharmaceuticals processed by CYP enzymes. The CYP3A isoenzyme is responsible for the metabolism of forty-six percent of pharmaceuticals, while the CYP2C9 isoenzyme metabolizes sixteen percent of drugs. The CYP2C19 and CYP2D6 isozymes each account for the metabolism of twelve percent of medications, the CYP1A isoenzyme metabolizes nine percent, and both the CYP2B6 and CYP2E1 isozymes are involved in the metabolism of two percent of pharmaceuticals [13]. The primary aim of this research was to assess the frequency and risk of putative CYP-mediated drug-drug interactions among a sample of older persons undertaking polypharmacy in a general community pharmacy. The secondary goals were to examine the correlation between the quantity of drugs given and the risk of possible CYP-mediated drug-drug interactions, as well as to compare the number of potential CYP-mediated DDIs identified by the multidrug software.

METHODS

Study design

This research employed a cross-sectional methodology situated within community pharmacies and was conducted from July 1, 2023, to May 11, 2024. The data were collected utilizing a systematically structured data page, which was provided voluntarily, without any incentives to promote participation. The researchers provided a comprehensive outline of the study's scope and objectives. The research components were designed to guarantee confidentiality and anonymity.

Inclusion criteria

Participants aged 65 years or older, who were taking prescriptions at home, were classified as experiencing polypharmacy if they were concurrently using five or more medications.

Exclusion criteria

The people excluded were individuals with incomplete data at the time of collection or individuals with substantial cognitive impairment (impede patient thinking, communication, understanding, and memory) and patients with malignancy.

Data collection procedure

Drug interactions identified in the research were recorded in a spreadsheet with the subsequent information: Drug name, drug interactions, Severity of drug interaction: a) mild—minimally meaningful. mitigate risk; evaluate risk and explore an alternate medication; implement measures to avoid interaction risk; and/or establish a monitoring protocol. Moderate: Clinically significant to a modest degree. Generally, refrain from combinations; use them just in exceptional situations. serious: Extremely clinically significant. Avoiding combinations: the potential risks of interaction exceed the advantages.

Software for prediction of cytochrome P450 activity

An updated version of the SuperCYPsPred web server prioritizes five major CYP isoforms: 1A2, 2C9, 2C19, 2D6, and 3A4, and other isoforms that account for about 90% of clinical drug metabolism. In addition to projections, the web server offers filtered literature on the established cytochrome interaction networks of authorized medications.

Software used to find drug-drug interactions

The UpToDate® Lexidrug ™ (Wolters Kluwer, Hudson, OH) was used to ascertain DDIs. This program was selected due to its excellent sensitivity and specificity in identifying and analyzing potential drug-drug interactions (pDDIs). The program categorized the interactions into five classifications: A (No known interactions), B (No action required), C (Monitor treatment), D (Consider therapy adjustment), and X (Avoid combination). Each interaction was categorized by the intensity of the response into four levels: serious, moderate, minor, and N/A. The interaction description included a paragraph outlining the hypothesized process, which, for the article's purposes, emphasized the various levels of pDDIs.

Sample size calculation

A cohort of 220 elderly individuals was analyzed. The sample size was calculated using a method for estimating a single proportion.

$$n = \frac{z^2 \times \hat{p}(1-\hat{p})}{\varepsilon^2}$$

Z represents the standard normal variable at a 95% confidence level (1.96), p is the estimated prevalence of the old population proportion at 17, according to World Health Organization estimates [14], with an infinite population size, and a margin of error of 5%.

Ethical approval

On January 2, 2024, the scientific and ethical committee of Al-Rasheed University evaluated and approved the research proposal outlining the objectives of the current study and the expected methodologies for data collection (ethics board permission code: RUCPD30112501).

Statistical analysis

Data was extracted from patient records using a standardized data-collecting approach and analyzed using SPSS version 23. Chart abstraction was performed by one clinical pharmacist and then checked by others to minimize errors. The data obtained included demographic information, medical conditions, and home medicines. Data are expressed as mean and standard deviation for continuous variables and as counts (percentages) for categorical variables. An unpaired t-test, or independent t-test, is used to compare the means of two separate groups to ascertain if a significant difference exists between them. One-way ANOVA is used to assess the statistical differences among the means of two or more groups. A Pearson correlation coefficient was computed to assess the correlation between the number of medications taken by participants and the number of interactions experienced. A simple linear regression analysis was conducted to predict the frequency of drug interactions depending on the quantity of medications. A p-value less than 0.05 was deemed statistically significant.

RESULTS

During the research timeframe, a total of 220 patients were included in the final analysis, considering 208 individuals were excluded: 98 due to missing data, 95 aged under 65, and 15 using less than 3 chronic drugs (Figure 1). The mean age of the participants was 68±4.36 years, with about 50.9% of the patients being female. The most used class of medication was antidiabetic (22.5%), followed by antihypertensive (20.9%) and antiplatelet (16.3%). 51.4% of patients take 5 drugs daily, while 45.5 percent take 6-9 drugs daily. The mean number of medications supplied per patient in this research was 5.9±1.3. Drug-drug interactions were prevalent among the research participants, with 84.5% of individuals experiencing these interactions as presented in Table 1.

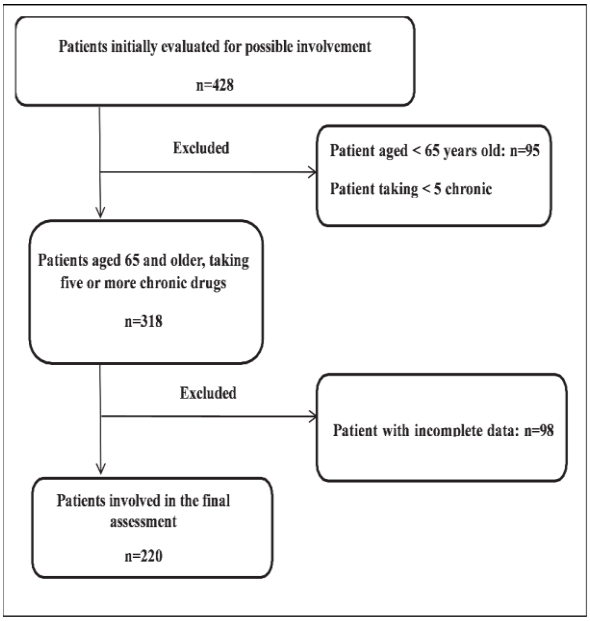

Figure 1: Flowchart of the study.

Table 1: Patient characteristics, number and classes of medications

Characters	Frequency (%)
Gender	
Female	112(50.9)
Male	108(49.1)
Classes of medications commonly used	
Antihypertensive	270(20.9)
Antibiotic	41(3.1)
Anticoagulant	102(7.9)
Antiplatelet	210(16.3)
Dyslipidemia	103(7.9)
Antidepressant/anxiolytic	77(6)
Loop diuretics	84(6.5)
Antidiabetic	291(22.5)
Proton pump inhibitors	69(5.3)
Others	42(3.2)
Number of medications per each patient	
5	113(51.4)
6-9	100(45.5)
10-12	6(2.7)
13 and above	1(0.5)
Interaction reported	
Yes	183(84.5)
No	34(15.5)
Age (Mean±SD)	68±4.36

A Pearson correlation coefficient was computed to assess the correlation between the number of medications taken by participants and the number of interactions experienced. A strong positive correlation was identified ($r(14) = 0.487$, $p < 0.001$), indicating a significant linear correlation between the two variables. A simple linear regression analysis was conducted to predict the frequency of drug interactions depending on the quantity of medications. A significant regression formula has been found ($F(1,14) = 67.789$, $p < 0.001$) (Figure 2).

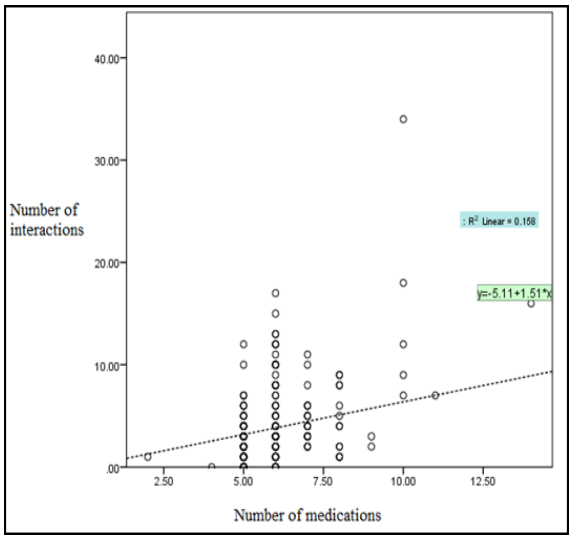

Figure 2: Correlation between number of medications and number of interactions

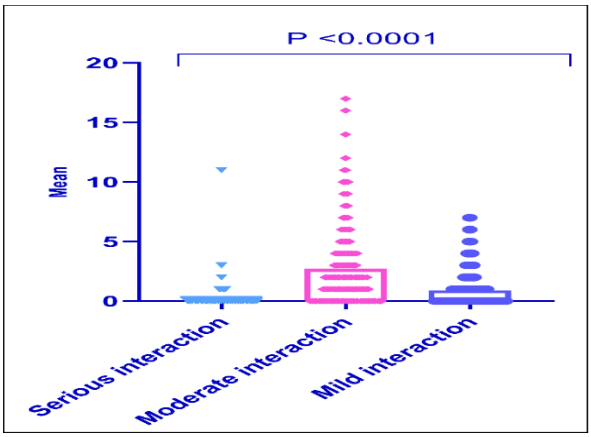

Figure 3: mean differences in interactions severity.

Participants' anticipated drug interactions are represented by the regression formula: [−5.111 + 5.43 (number of medications)]. Moderate severity drug-drug interactions were the most common kind of interaction, with a mean of 2.70 and a standard deviation of 3.157, $p< 0.0001$, as presented in Figure 3. The most dominant CYP isoenzyme was CYP3A4 at 34.6%, followed by CYP2C9 at 21.4% and CYP2D6 at 15.7% with no significant difference between genders as reported in Tables 2 and 3.

Table 2: CYP isoenzymes involved in drug-drug interactions based on an updated version of SuperCYPsPred software

CYP isoenzymes	Frequency (%)
CYP3A4	55(34.6)
CYP2C9	34(21.4)
CYP2D6	25(15.7)
CYP1A2	12(7.5)
CYP2C19	11(6.9)
CYP2C8	7(4.4)
CYP2B6	6(3.8)
CYP3A5	4(2.5)
CYP2C10	3(1.9)
CYP2E1	1(0.6)
CYP7A1	1(0.6)
Total	159

Table 3: Gender distribution of medication interactions classified by severity

Serious																
Frequency	1	2	3	11												*p*-value
Female	12	0	2	1												0.870
Male	11	1	0	0												
Moderate																
Frequency	1	2	3	4	5	6	7	8	9	10	11	12	14	16	17	*p*-value
Female	20	19	10	9	7	4	2	3	4	4	1	1	0	0	1	0.330
Male	19	18	10	11	3	4	3	1	0	1	2	0	1	1	0	
Mild																
Frequency	1	2	3	4	5	6	7									*p*-value
Female	31	8	6	5	2	1	1									0.50
Male	27	10	7	2	1	1	0									

Table 4 includes the most severe drug-drug interactions known, whereby one substance either enhances the effects of the other via pharmacodynamic synergism or diminishes them via pharmacodynamic antagonism, accompanied by rationales and recommendations for each combination.

DISCUSSION

Polypharmacy is common among older people who have numerous diseases. Polypharmacy presents a considerable danger of interactions between drugs and continues to be a critical concern, since consequences may vary from minor health issues to fatality [15]. This study aimed to clarify the prevalence of polypharmacy and the characteristics of significant possible interactions between drugs in elderly individuals. The average number of drugs taken per participant in this study was 5.9, similar to the study conducted in Taiwan, which reported 5.8 [16], but lower than findings from Puducherry [17] and India [18], which reported 7.61 and 9.15, respectively. Various disparities might result from variations in research design, health insurance policies, and variances in the impact of comorbidities and patterns of taking medication in different environments. This research revealed polypharmacy (the use of five or more medications) as a predictor for the incidence of drug-drug interactions (DDI) (p= 0.0001).

Table 4: List of serious drug interactions with their potential risks (UpToDate® Lexidrug ™)

Combination	Recommendation and Rationale	CYP450 isoenzyme
Fenofibrate + Rosuvastatin	Fenofibrate, rosuvastatin. Either increases effects of the other by pharmacodynamic synergism. Serious - use alternative	
Niacin + Rosuvastatin	Niacin with rosuvastatin. Either enhances the toxic effects of the other via pharmacodynamic interaction. Avoid or use an alternative medication	
Aspirin + Perindopril	Aspirin and perindopril exhibit pharmacodynamic antagonistic effects. Combining the administration may lead to a substantial decline in renal function. Refrain from usage or consider alternative medication.	CYP2C9
Aspirin + Lisinopril	Aspirin and lisinopril have a pharmacodynamic antagonistic effect. Coadministration may lead to a substantial decline in renal function. Refrain from usage or consider alternative medication.	
Allopurinol + Captopril	Captopril can raise the risk of allergic or hypersensitive responses to allopurinol. Observe for signs of hypersensitivity if the concurrent administration of both medications is necessary.	
Clarithromycin + Ciprofloxacin	Avoid or Utilize Alternative Medication Clarithromycin and ciprofloxacin both prolong the QTc interval. Refrain from use or consider other medication.	CYP3A4
Aceclofenac + Ketorolac	Aceclofenac will elevate the concentration or efficacy of ketorolac due to competitive inhibition of renal tubular clearance by acidic (anionic) drugs.	
Clopidogrel + Omeprazole	The effectiveness of clopidogrel may be diminished by medications that suppress CYP2C19. The inhibition of platelet aggregation by clopidogrel is solely attributed to an active metabolite.	CYP2C19
Bisoprolol + Digoxin	Bisoprolol enhances the therapeutic effects of digoxin via pharmacodynamic synergism. Exacerbated bradycardia. Both bisoprolol and digoxin raise blood potassium levels. Maintain Caution/Observe.	CYP3A4
Ceftriaxone + Calcium Carbonate	Avoid all calcium-containing therapies, including Ringer and Hartmann solutions, while administering IV ceftriaxone due to the danger of possibly deadly particle precipitation in the lungs and kidneys. Ensure a minimum separation of 48 hours.	
Ciprofloxacin + Theophylline	Ciprofloxacin will elevate the concentration or efficacy of theophylline via influencing the hepatic enzyme CYP1A2 metabolism. Refrain from use or consider other medication.	CYP2C19
Fluphenazine + Trifluoperazine	Fluphenazine and trifluoperazine both prolong the QTc interval. Refrain from use or consider other medication.	
Carbamazepine + Hydrochlorothiazide	One enhances the impact of the other via pharmacodynamic synergism. Refrain from using or using alternative medication.	
Clomipramine + Fluoxetine	Fluoxetine and clomipramine both elevate serotonin levels. Refrain from use or consider other medication.	
Amiodarone + Levofloxacin	Amiodarone and levofloxacin both prolong the QTc interval. Refrain from use or consider other medication.	CYP2D6
Amlodipine + Simvastatin	An increased risk of myopathy or rhabdomyolysis is possible. Restrict the simvastatin dosage to a maximum of 20 mg per day when administered simultaneously.	
Aripiprazole + Azithromycin	Both aripiprazole and zithromax prolong the QTc interval. Refrain from use or consider other medication.	
Ferrous Sulfate + Doxycycline	Ferrous sulfate reduces doxycycline levels by inhibiting intestinal absorption. Refrain from or Utilize an Alternative Medication.	

Several more studies have indicated an increased number of medicines as an indicator of drug-drug interactions in the elderly [19]. A Brazilian study indicated that the likelihood of potential drug interactions for those using 2–3, 4–5, and 6–7 medications was 39 percent, 88.8 percent, and 100 percent, respectively [20]. About fifty percent of elderly persons use one or more pharmacological agents that are medically unneeded [21]. In the setting of the older people, polypharmacy does not inherently imply inappropriateness. Several elderly people may be administered a combination of medications to have a synergistic therapeutic effect [22]. The usage of several medicines in the elderly is often unnecessary owing to their illnesses; nonetheless, it is crucial not to eliminate essential prescriptions due to the possible danger of drug interactions. Numerous drug interactions may be mitigated by using alternate drugs; nevertheless, those that cannot need understanding of the interaction to facilitate adequate treatment and suitable dosage modification [23]. In practice, we must possess knowledge not just about drug-drug interactions; a comprehensive awareness of the safe administration of diverse medications to our patients is vital [24]. The DDIs in the present research are theoretical or possible drug-drug interactions. Although the occurrence of actual drug-drug interactions is less frequent than that of prospective DDIs, several investigations have identified clinically significant potential DDIs in the elderly at rates as high as 25–47%. The incidence of clinically significant interactions is contingent upon particular risk variables, including polypharmacy, comorbidities, age, therapeutic range, and medication dose. Research has definitively demonstrated a robust correlation between polypharmacy, resulting in drug-drug interactions (DDI), and worse clinical outcomes [14]. During the COVID-19 pandemic, many older individuals encountered an increased risk of medication interactions owing to the administration of the vaccination and COVID-19 treatments [25]. Consequently, the present research is crucial for raising awareness about the risky possible interactions that may yield adverse clinical

outcomes and for identifying at-risk populations. Fewer than ten percent of the enrolled patients had not less than one serious possible drug-drug interaction. An Italian study of senior individuals indicated that just 16% of participants had not less than one potentially severe drug-drug interaction [26]. Nonetheless, significant prospective drug-drug interactions were delineated using the Italian interaction database. CYP3A4 and CYP2D6 are responsible for the metabolic process of 93 percent of medications experiencing hepatic degradation in the elderly [27]. This research demonstrates that an escalation in the quantity of pharmaceuticals processed by the CYP system is associated with an increased chance of at least two drugs within a multiple prescription having a similar metabolic pathway and interacting. 10% and 5% of Caucasians are categorized as weak metabolizers or ultrarapid metabolizers of CYP2D6. A clinical pharmacist may contribute to determining and evaluating possible drug-drug interactions, therefore facilitating appropriate dose or treatment modifications. A general enhancement has been noted in the quality of prescriptions, together with the right use of polypharmacy, which therefore led to a reduction in possible drug-drug interactions [28,29]. Decision-making tools and data technologies are being utilized to avoid serious interactions among drugs. Even though alert fatigue is acknowledged as a key barrier in the usage of such tools, clinical pharmacist-assisted automated decision support systems were shown to be successful and give another chance for the detection of potential drug-drug interactions. This research analyzes the prevalence of possible drug-drug interactions among the elderly. Furthermore, polypharmacy was identified as a risk factor for the incidence of drug-drug interactions in the elderly, as shown by previous investigations.

Study limitations

The research had several limitations: it was conducted on a limited cohort of older individuals in comparison to previous research. Secondly, as cross-sectional research conducted at a single time point, it couldn't be feasible to observe the outcomes of potential drug-drug interactions or the actual incidence of these interactions from a standpoint of clinical practice. Additional long-term research, including a greater number of subjects, is needed.

Conclusion

The current study revealed that more than three-fourths of elderly patients have no less than one likely interaction. Individuals aged 65 and older taking more than five medications need continuous oversight owing to a fourfold heightened risk of drug-drug interactions. Recognizing and mitigating possibly harmful drug-drug interactions is an essential aspect of a pharmacist's role, necessitating that clinical pharmacist be attentive in monitoring suspected DDIs and implementing suitable dose or therapeutic modifications.

Conflict of interests

No conflict of interest was declared by the authors.

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Data sharing statement

Supplementary data can be shared with the corresponding author upon reasonable request.

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