A SURVEY ON DRUG INTERACTIONS AND DETERMINANT FACTORS IN OUTPATIENT PRESCRIPTIONS FOR COPD PATIENTS AT CHO RAY HOSPITAL IN 2023

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ABSTRACT

This study aimed to characterize the prevalence, clinical features, and associated risk factors of clinically significant drug-drug interactions (DDIs) among outpatients with chronic obstructive pulmonary disease (COPD). A retrospective cross-sectional analysis was performed on 500 outpatient prescriptions collected from July to December 2023 at Cho Ray Hospital. DDIs were identified using the Drugs.com and Medscape.com databases and categorized based on severity: major, moderate, or minor. Patient characteristics, including age, sex, number of comorbidities, and total number of prescribed medications, were analyzed as potential risk factors. Statistical analysis was conducted using SPSS 22.0, with logistic regression modeling employed to ascertain significant associations.

The prevalence of DDIs was found to be 48.6% according to Drugs.com and 44.2% based on Medscape. Clinically significant DDIs, defined as major or moderate interactions, were present in 21.8% of all prescriptions, with major and moderate interactions accounting for 6.4% and 15.4%, respectively. Multivariate logistic regression revealed that polypharmacy, defined as the use of five or more medications, was associated with a 3.2-fold increased risk of clinically significant DDIs ($p<0.001$). Furthermore, patients aged 65 years or older demonstrated a 2.0-fold higher risk ($p=0.012$). These findings indicate a considerable prevalence of clinically significant DDIs in this patient population, particularly among older adults and those receiving multiple medications. The results underscore the need for enhanced DDI prevention strategies, such as integrating clinical pharmacists into the prescription monitoring process, to improve patient safety.

Keywords: *Chronic Obstructive Pulmonary Disease (COPD); Outpatients; Drug–Drug Interactions; Cho Ray Hospital*

I. INTRODUCTION

Chronic obstructive pulmonary disease (COPD) is the third leading cause of death worldwide, with an escalating global disease burden. Patients with COPD frequently present with multiple comorbidities such as hypertension, cardiovascular disease, diabetes, and osteoporosis [1]. The presence of these co-existing conditions often necessitates complex treatment regimens, leading to polypharmacy. As a result, the risk of drug–drug interactions (DDIs) is significantly increased.

While some DDIs are merely theoretical (in vitro), others can be clinically significant, potentially leading to increased adverse effects, reduced therapeutic efficacy, or serious adverse events [2]. Numerous international and domestic studies have highlighted a high frequency of DDIs in COPD prescriptions. However, research in Vietnam often has a small sample size and lacks a comprehensive analysis of associated risk factors, particularly in tertiary care hospitals like Cho Ray Hospital.

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Therefore, this study aims to investigate the prevalence of clinically significant DDIs in outpatient prescriptions for COPD patients at Cho Ray Hospital in 2023 and analyze factors associated with the occurrence of these DDIs.

II. OBJECT AND METHOD

2.1. Study Population

This study retrospectively analyzed outpatient prescriptions for COPD patients at Cho Ray Hospital from July to December 2023.

Inclusion Criteria:

- Outpatient prescriptions with a confirmed COPD diagnosis from July to December 2023.
- Prescriptions containing two or more medications.

Exclusion Criteria:

- Repeat prescriptions for the same patient within the study period if the medication regimen was identical to a previously collected sample.
- Prescriptions containing only two medications, one of which was for external use.

2.2. Study Design and Data Collection

Design: A retrospective, cross-sectional study.

Sample Size: The sample size was calculated using the formula for a single proportion:

$$n = \frac{Z^2_{(1-\alpha/2)} * p(1-p)}{d^2}$$

Where:

- n = required sample size
- Z = 1.96 (confidence coefficient for a 95% confidence level, α=0.05)
- d = 0.05 (margin of error)
- p = 0.42 (the prevalence of prescriptions with DDIs, based on the study by Tram Cao Tri [8])

A total of 500 outpatient COPD prescriptions were collected from July to December 2023, meeting the predefined inclusion criteria.

Sampling Method: A random sampling approach was used to select prescriptions chronologically over the study period, ensuring the sample size met the estimated requirement.

Associated Factors: The following factors were analyzed for their association with DDIs:

- Age
- Gender
- Comorbidities
- Number of comorbidities
- Number of prescribed drugs

DDI Analysis Tools:

- Drugs.com (Drug Interactions Checker)
- Medscape.com

Note: Only major and moderate interactions were considered clinically significant for the purpose of this study, consistent with established guidelines.

Statistical Analysis: Data were processed and analyzed using Microsoft Excel 2016 and SPSS 22.0. Descriptive statistics, Chi-square tests, and multivariable logistic regression were performed. A p-value of <0.05 was considered statistically significant.

Ethical Considerations: The study protocol received approval from the Biomedical Research Ethics Committee of Hong Bang International University and the Biomedical Research Ethics Committee at Cho Ray Hospital.

III. RESULTS

3.1. General Characteristics of the Study Sample

From July to December 2023, the study collected 500 outpatient COPD prescriptions that met the inclusion criteria. The general characteristics of the patients are presented in Table 1.

Table 1. ***General Patient Characteristics***

Age Group	Male n (%)	Female n (%)	Total n (%)
18–40	2 (0.4)	1 (0.2)	3 (0.6)
>40–59	66 (13.2)	6 (1.2)	72 (14.4)
≥60	387 (77.4)	38 (7.6)	425 (85.0)
Total	455 (91.0)	45 (9.0)	500 (100)
Mean Age ± SD	69.7 ± 10.1	72.8 ± 12.3	70 ± 10.3
Note: Minimum age: 35, Maximum age: 95			

A majority of patients in the study were in the ≥60 age group (85.0%). Males accounted for the primary proportion of the sample, with 455 cases (91.0%), while females comprised 45 cases (9.0%). The mean age for the entire sample was 70 ± 10.3 years, with a range from 35 to 95 years.

3.2. Characteristics of Comorbidities and Prescribed Medications

To clarify the prescribing patterns and comorbidity status, the study analyzed the average number of comorbidities, the proportion of prescriptions with five or more medications, and the mean number of drugs per prescription.

Table 2. Characteristics of Comorbidities and Medications in COPD Patients

Characteristic	Mean Value ± SD
≥3 comorbidities	3.6 ± 0.7
Prescriptions with ≥5 drugs	7.3 ± 1.0
Mean number of drugs per prescription	7.2 ± 2.8

The average number of medications per prescription was notably high (7.2 ± 2.8). A large proportion of prescriptions contained five or more medications (7.3 ± 1.0), and patients typically had multiple comorbidities, with an average of 3.6 ± 0.7 comorbidities.

3.3. Drug–Drug Interactions Based on Databases

To assess the prevalence and severity of DDIs, prescriptions were cross-referenced with three databases: Decision 5948/QD-BYT from the Ministry of Health, Drugs.com, and Medscape.com. The results are shown in Tables 3 and 4.

Table 3. ***Prevalence of Prescriptions with DDIs by Database***

Database	DDI Status	Frequency	Percentage (%)
According to Decision 5948/QD-BYT	Yes	0	0
	No	500	100
According to Drugs.com	Yes	461	92.2
	No	39	7.8
According to Medscape.com	Yes	431	86.2
	No	69	13.8

According to the Ministry of Health's Decision 5948/QD-BYT, no DDIs were found. However, searches on Drugs.com and Medscape.com revealed that 92.2% and 86.2% of prescriptions, respectively, contained DDIs. The frequency of prescriptions without DDIs according to these sources was 39 and 69, respectively, out of 500.

Table 4. ***Distribution of DDI Severity by Database***

Database	Severity Level	Number of Interactions	Percentage (%)
According to Decision 5948/QD-BYT	Contraindicated	0	0
	Total	0	0
According to Drugs.com	Serious	184	21.3
	Moderate	427	49.5
	Minor	252	29.2
	Total	863	100
According to Medscape.com	Contraindicated	3	0.5
	Serious	123	20.9
	Moderate	396	67.4
	Minor	66	11.2
	Total	588	100

The most common level of interaction was moderate according to both Drugs.com (49.5%) and Medscape.com (67.4%). Serious interactions accounted for 21.3% and 20.9% of the interactions, respectively.

Table 5. ***Prevalence of Multiple DDIs per Prescription***

Number of DDIs per Prescription	According to Drugs.com	According to Medscape.com
	Frequency	Percentage (%)
0	39	7.8
1	101	20.2
2	77	15.4
3	46	9.2
≥4	237	47.4
Total	500	100

According to Drugs.com, nearly half of the prescriptions (47.4%) contained four or more DDIs, compared to 28.8% in Medscape.com. The majority of prescriptions contained at least one interaction, with 44.8% having 1–3 DDIs according to Drugs.com and 57.4% according to Medscape.com.

3.4. Clinically Significant DDIs by Number of Medications

The study assessed the relationship between the number of drugs per prescription and the severity of DDIs. The results are presented in Table 6.

Table 6. ***Proportion of Clinically Significant DDIs by Number of Drugs per Prescription***

Number of medications per prescription	Drugs.com	Medscape.com
	Serious	Moderate
	Frequency	Percentage (%)
2–4 drugs	4	2.2
5–7 drugs	42	22.8
>7 drugs	138	75.0
Total	184	100

The proportion of serious and moderate DDIs increased with the number of drugs per prescription. The >7 drugs group accounted for the largest percentage of serious (75.0% from Drugs.com, 73.2% from Medscape.com) and moderate (55.3% and 56.1%) interactions.

3.5. Common Clinically Significant DDI Pairs

Table 7 lists the most frequent clinically significant DDI pairs (≥1.5% prevalence) identified by both Drugs.com and Medscape.com, highlighting their potential clinical consequences.

Table 7. ***Common Clinically Significant DDI Pairs***

Number	Interaction Pair	Severity	Main Clinical Consequence	Frequency (%)
1	Ipratropium - tiotropium	Moderate	Increased risk of fluid retention, dry mouth, and increased heart rate	35.71
2	Clopidogrel - rabeprazole	Serious	Reduced antiplatelet effect of clopidogrel	8.86
3	Amlodipine - atorvastatin	Moderate	Increased risk of statin-induced myotoxicity (rhabdomyolysis)	2.37
4	Spironolactone - empagliflozin	Moderate	Increased risk of hyperkalemia, dehydration	2.12
5	Aspirin - valsartan	Moderate	Decreased antihypertensive effect, increased risk of renal damage	1.87
6	Aspirin - budesonide	Moderate	Increased risk of gastrointestinal bleeding	1.75
7	Hydrochlorothiazide - formoterol	Moderate	Increased risk of hypokalemia, arrhythmias	1.62
8	Pantoprazole - clopidogrel	Moderate	Reduced antiplatelet effect of clopidogrel	1.50

The most common DDI pair was ipratropium–tiotropium (35.71%), followed by clopidogrel–rabeprazole (8.86%).

3.6. Mechanism of Clinically Significant DDIs

Classifying DDIs by mechanism clarifies their nature and potential adverse effects. Table 8 presents the distribution of clinically significant DDIs by their primary mechanism.

Table 8. ***Classification of Clinically Significant DDIs by Mechanism***

Interaction Mechanism	Number of DDIs	Percentage (%)	Number of DDI Pairs	Percentage (%)
Pharmacokinetic	107	13.4	18	11.0
Absorption	5	4.7	5	27.8
Distribution	0	0.0	0	0.0
Metabolism	102	95.3	13	72.2
Excretion	0	0.0	0	0.0
Pharmacodynamic	694	86.6	145	89.0
Synergistic	636	91.6	132	91.0
Antagonistic	58	8.4	13	9.0
Total	801	100	163	100

The majority of clinically significant DDI pairs (89.0%) were pharmacodynamic, with synergistic interactions predominating within this group (91.0%). Pharmacokinetic interactions were less common (11.0%) and primarily involved effects on drug metabolism (72.2%) and absorption (27.8%).

3.7. Factors Influencing Drug–Drug Interactions

Identifying factors that influence DDIs helps in recognizing high-risk patient groups. Table 9 presents the relationship between certain clinical characteristics and DDI frequency.

Table 9. Factors Associated with the Occurrence of DDIs

Influencing Factor		Prescriptions with DDI	Frequency (%)	Prescriptions without DDI	Frequency (%)	p-value
Gender	Male	391	78.2	64	12.8	0.893
	Female	39	7.8	6	1.2	
Age Group	18–40 years	2	0.4	1	0.2	0.008
	40–59 years	54	10.8	18	3.6	
	≥60 years	374	74.8	51	10.2	
Number of Comorbidities	1	48	9.6	24	4.8	0.001
	2	75	15.0	8	1.6	
	3	128	25.6	15	3.0	
	4	81	16.2	1	0.2	
	>4	36	7.2	1	0.2	
Number of Drugs per Prescription	2-4	69	13.8	39	7.8	
	5-7	126	25.2	19	3.8	0.001
	>7	236	47.2	11	2.2	

There was no statistically significant difference in DDI frequency based on gender ($p>0.05$). In contrast, age group, number of comorbidities, and number of medications were all significantly associated with DDI frequency ($p<0.05$). The proportion of interactions increased sharply in patients aged ≥60 years, those with ≥3 comorbidities, or those taking >7 drugs per prescription.

IV. DISCUSSION

4.1. General Characteristics of the Study Sample

The demographic analysis revealed that the study population was predominantly male (91%), with a mean age of 70 ± 10.3 years. The majority of patients (85%) were aged 60 years or older. These findings are consistent with the established epidemiology of chronic obstructive pulmonary disease (COPD), which shows a higher prevalence in older age groups and a male predominance, often attributed to factors such as smoking history and occupational exposures. The results align with other studies, including one by Phan Thanh Thuy (2022), which reported a similar patient profile with 85.8% male and a mean age of 66.16 ± 8.1 years [6], as well as a study by Ta Huu Anh (2021) with a mean age of 69.3 ± 9.2 and 59.1% male patients [7]. The advanced age of this cohort is a significant concern, as it is frequently associated with an increased prevalence of comorbidities and polypharmacy. This, in turn, elevates the risk of drug-drug interactions (DDIs) and subsequent adverse drug reactions. As demonstrated by a study from Nguyen Thi Huu Hieu (2023), age ≥ 60 and the number of medications prescribed are strongly associated with a higher incidence of clinically significant DDIs [5]. This underscores the necessity of implementing rigorous prescription monitoring and clinical pharmacy interventions to enhance patient safety within the context of COPD management at Cho Ray Hospital.

4.2. Characteristics of Comorbidities and Number of Medications in Prescriptions

The results of this study indicate that patients with chronic obstructive pulmonary disease (COPD) were frequently exposed to

polypharmacy and multimorbidity. The mean number of medications per prescription was 7.2±2.8, with a significant number of prescriptions (mean of 7.3±1.0 drugs) containing five or more medications. Concurrently, patients presented with a high average of 3.6±0.7 comorbidities.

These findings are consistent with the established literature on COPD, which highlights the high burden of co-existing conditions and complex treatment regimens in this population, particularly among older adults. A study by Nguyen Thi Huu Hieu (2023) supports these results, demonstrating that patients taking 5–7 medications had a significantly higher rate of drug-drug interactions (DDIs), a risk that was particularly elevated in the ≥60 age group [5]. Similarly, Tram Cao Tri (2021) found that the mean number of medications in outpatient prescriptions was 4.53, with some prescriptions containing up to eight drugs, thereby increasing the risk of DDIs [8]. The high average number of prescribed medications observed in our study underscores a significant potential for DDIs and adverse drug events. This necessitates the proactive involvement of clinical pharmacists in medication monitoring and patient counseling to ensure the safety and efficacy of treatment for patients with COPD.

4.3. Drug Interactions in Prescriptions According to Databases

A significant disparity was observed in the detection of drug-drug interactions (DDIs) based on the database used for analysis. The Vietnamese domestic database, Decision 5948/QD-BYT, recorded zero DDIs across all prescriptions. In stark contrast, international databases identified a high prevalence of interactions, with Drugs.com and Medscape.com detecting DDIs in 92.2% and 86.2% of prescriptions, respectively. This finding is consistent with previous research, such as the studies by Dong Be Hai (2023) and Nguyen Huynh Thao Vy (2023), which reported clinical interaction rates of 52.0% and 51.8%, respectively [3,4].

This discrepancy highlights the limitations of the domestic database, which lacks the comprehensive, up-to-date information found in international sources. The high prevalence of DDIs detected by the international databases signals a substantial risk to treatment efficacy and patient safety. For elderly patients with COPD, who are often characterized by multimorbidity and polypharmacy, the use of international lookup tools in conjunction with domestic guidelines is crucial for proactive DDI identification and management.

Furthermore, a notable difference in the severity classification of DDIs was observed among the databases. While the domestic database reported no interactions, Drugs.com identified a distribution of 49.5% moderate, 29.2% minor, and 21.3% serious interactions. Similarly, Medscape.com classified interactions as 67.4% moderate, 20.9% serious, 11.2% minor, and 0.5% contraindicated. This variation underscores the superior detail and classification provided by international databases. The high rates of serious and moderate interactions—exceeding 20% in both international databases-are particularly alarming and emphasize the critical need for close monitoring. These results underscore the vital role of clinical pharmacists in supporting safe prescribing practices to mitigate adverse drug events.

4.4. Clinically Significant Drug Interactions by Severity Level

The study revealed a significant dose-response relationship between the number of medications prescribed and the prevalence of serious and moderate drug-drug interactions (DDIs). In prescriptions with more than seven medications, the proportion of serious

DDIs reached 75.0% on Drugs.com and 73.2% on Medscape.com. Similarly, moderate DDIs were found in 55.3% and 56.1% of these prescriptions, respectively.

In stark contrast, prescriptions containing only 2–4 medications showed considerably lower DDI rates. Serious interactions ranged from 2.2% to 7.3%, and moderate interactions were between 14.6% and 15.9%.

These findings align with previous research by Nguyen Thi Huu Hieu (2023) and Dong Be Hai (2023), both of whom identified the number of drugs in a prescription as a key factor in increasing DDI risk [3,5]. This underscores the critical need for meticulous prescribing practices and the use of DDI lookup tools, especially for patients with COPD who require complex, multi-drug regimens to manage their disease and comorbidities.

4.5. Analysis of Clinically Significant Drug Interaction Pairs

The analysis of clinically significant drug-drug interaction (DDI) pairs revealed that most common interactions were of moderate severity. The most frequent DDI pair was ipratropium–tiotropium, occurring in 35.7% of prescriptions. This was followed by clopidogrel–rabeprazole (8.9%) and amlodipine–atorvastatin (2.4%). These interactions predominantly involve cardiovascular and respiratory medications, a finding consistent with studies by Nguyen Thi Huu Hieu (2023) and Dong Be Hai (2023) [3,5].

Some of these interactions have direct clinical consequences. For instance, the ipratropium–tiotropium interaction can increase the risk of fluid retention and arrhythmias. The interaction between clopidogrel and rabeprazole may reduce the antiplatelet efficacy of clopidogrel, while spironolactone–empagliflozin is associated with an elevated risk of hypokalemia.

The identification of these high-frequency DDI pairs provides a valuable tool for clinicians. Proactive monitoring and timely adjustment of treatment protocols based on this information can improve therapeutic outcomes and reduce the incidence of adverse drug events in the management of COPD.

4.6. Clinically Significant Drug Interactions by Mechanism

Analysis of the mechanisms behind clinically significant drug-drug interactions (DDIs) revealed that pharmacodynamic interactions were predominant, accounting for 89.0% of all interactions. Within this group, synergistic interactions were the most common, making up 91.0% of the total. In contrast, pharmacokinetic interactions constituted a smaller proportion (11.0%), primarily affecting the drug metabolism phase (72.2%).

These findings are consistent with previous research, including studies by Nguyen Thi Huu Hieu (2023) and Dong Be Hai (2023), which also observed a high rate of synergistic interactions, particularly among cardiovascular and respiratory medications [3,5]. The prevalence of pharmacodynamic interactions poses a significant challenge for prediction and management, as they directly impact treatment responses. Unlike pharmacokinetic interactions, which can sometimes be managed by dose adjustments, pharmacodynamic interactions often necessitate changes to the medication regimen. This highlights the importance of understanding the mechanism of interaction to effectively mitigate risks and improve therapeutic outcomes in multimorbid COPD patients.

4.7. Factors Influencing Drug Interactions

The analysis demonstrated that gender did not significantly influence the risk of DDIs

(p>0.05). However, age, the number of comorbidities, and the number of medications in a prescription were all strongly correlated with the occurrence of DDIs.

Patients aged ≥ 60 years had the highest rate of interactions, which aligns with the fact that this demographic typically presents with multiple chronic diseases and requires complex medication regimens. Furthermore, the results showed that having ≥ 3 comorbidities and prescriptions containing > 7 types of drugs significantly increased the risk of DDIs (p<0.05). These findings are corroborated by studies from Nguyen Thi Huu Hieu (2023) and Dong Be Hai (2023), both of which noted a clear link between multimorbidity, polypharmacy, and the frequency of DDIs [3,5]. This underscores the need to proactively identify these risk factors, especially in elderly patients, to develop rational prescribing strategies that minimize interactions and optimize the effectiveness of COPD treatment.

V. CONCLUSION

This study found a high prevalence of clinically significant drug interactions in outpatient COPD prescriptions at Cho Ray Hospital in 2023. Interactions were most common in patients aged ≥ 60 with multimorbidity and polypharmacy. The predominant mechanism was pharmacodynamic, particularly involving cardiovascular and respiratory drugs, which can compromise treatment efficacy and patient safety. Regression analysis identified the number of medications and older age as independent risk factors. These findings highlight the need for tailored drug selection and proactive clinical pharmacy interventions in tertiary care settings to mitigate adverse events and optimize outcomes for COPD patients.

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