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Are there any potential drug-drug interactions with oral inhaler medications?: A retrospective study

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ABSTRACT

Background: Oral inhaler medications (OIMs) are widely used for many respiratory diseases. Although OIMs have minimal systemic effects, they may cause potential drug-drug interactions (pDDIs).
Objectives: This study aims to evaluate drug interactions in patients using OIMs.
Methods: This retrospective, and descriptive study was conducted in a community pharmacy in Istanbul (Turkey) between January 1, andMay 312,021. Prescriptions of all asthma and COPD patients aged 18 and over on the specified date were included in the study. Data were collected from the pharmacy information system. Socio-demograhic characteristics were recorded. pDDIs were analyzed via Medscape and Lexicomp drug interaction checker databases. Significant (monitor closely), Serious (use alternative), Contraindicated categories in the Medscape database and D (consider treatment modification) and X (avoid combination) categories in the Lexi-Interact™ database were evaluated as pDDIs. SPSS analysis was performed.
Results: A total of 54 asthma and 42 chronic obstructive pulmonary disease (COPD) patients were included in the study. Most asthma (76%) and COPD (83%) patients were found to have at least one comorbid disease. A total of81 pDDIs were identified in the Medscape database in asthma patients, and 86.5% of them were classified as "monitor closely". A total of 12 drug interactions were detected in the Lexicomp database, with 75% of them were "D" category for asthma patients. In the prescriptions of COPD patients, a total of 162 drug interactions were determined via the Medscape database, with 94.4% classified as "monitor closely". A total of 13 drug interactions were detected in the Lexicomp database, with 61.5% of them falling into the "X" category for COPD patients.
Conclusions: According to the results of this study COPD patients who may be at a high risk of experiencing pDDIs. Healthcare providers should consider the individual patient's clinical profile, including comorbidities and medication regimen, to minimize the risk of pDDIs and optimize treatment outcomes. Further research is needed to elucidate the mechanisms underlying these findings and develop tailored strategies to diminish the risks associated with pDDIs in respiratory disease management.

1. Introduction

Oral inhaled medications (OIMs) are the cornerstone of treating asthma and chronic obstructive pulmonary disease (COPD).[1–3] OIMs provide fewer systemic side effects, no first-pass metabolism, and concentrated drug amounts at the site of the disease, making it an ideal route for the treatment of pulmonary diseases.[4] Owing to the thin alveolar-capillary barrier, and large surface area that facilitates rapid absorption to the bloodstream in the lung, systemic delivery can be achieved as well.[5] Although OIMs primarily affect the lungs, they may cause some systemic effects when their pharmacokinetic properties are examined.[6,7] For example, metabolic side effects of inhaled corticosteroids.[8–10] Corticosteroids, beta 2 agonists and anticholinergic medications are widely given as inhalers in several pulmonary diseases[3,4] and are associated with clinically significant drug interactions.[6]

Drug interactions should be evaluated in a broad spectrum such as drug-food, drug-disease, drug-laboratory and drug-drug interactions.[6] Drug-drug interactions are classified as pharmacodynamic or pharmacokinetic interactions, and the results of these interactions may occur as synergists, antagonists, and increases/decreases in the incidence of side effects.[7] This situation is also encountered outside of systemic drug administration (e.g. inhaled drugs). One of the drug interactions of OIMs

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is an increased risk of hypokalemia caused by the combined use of thiazide diuretic and inhaled salbutamol.[11] The number of comorbidities and the excess of drugs used in asthma patients using OIMs, especially COPD, may cause drug-drug interactions. Evaluating the disease and medication profile and potential drug interactions (pDDIs) in different patient groups using oral inhaler drugs will contribute to the literature. Therefore, this study aimed to determine the medication profile of the patients using OIMs and to evaluate pDDIs.

2. Materials and methods

This study was approved by Marmara University Faculty of Medicine Ethics Committee (Protocol no: 07.12.2020.1340). The Principles of the Declaration of Helsinki were carried out in our study.

This retrospective and descriptive study was conducted in a community pharmacy (Kocaeli/Turkey) between January 1, and May 31, 2021. The sample size was not calculated. Prescriptions of patients with asthma or COPD in the first 6-month period of 2021 were examined. Prescriptions of all asthma and COPD patients aged 18 and over on the specified date were included in the study. Data was collected from the pharmacy information system.

Information on prescriptions (such as patient age and gender, medications, and ICD codes) was recorded. pDDIs were evaluated using Medscape and Lexicomp databases. Significant (monitor closely), Serious (use alternative), Contraindicated categories in the Medscape database and D (consider treatment modification) and X (avoid combination) categories in the Lexi-Interact™ database were evaluated as pDDIs.

2.1. Statistical analysis

Descriptive statistics were used to illustrate the sociodemographic characteristics of patients. Continuous variables, including age and number of comorbid diseases, were expressed as mean values with standard deviation(sd), whereas categorical variables included gender, number of medications, and comorbidities with a percentage. The chi-square test was used to examine the association of demographic characteristics of the 2 groups. The factors that were associated with pDDIs were assessed using correlation analysis. All statistical analyses were conducted using Statistical Package for the Social Sciences (SPSS) version 15.0. The level of statistical significance of the study was $p < 0.05$.

3. Results

3.1. Evaluation of prescriptions for COPD patients

A total of 42 COPD patients were included in the study, with a mean age of 68.5 ± 11.5 years, 74% ($n = 31$) were male and 26% ($n = 11$) were female. It was observed that 40.5% of the COPD patients included in the study received COPD treatment for more than five years and less than ten years, and 38.1% received COPD treatment for more than one year and less than five years (Table 1).

Table 1
Evaluation of Duration of Medication Use of COPD Patients.

Duration of Medication Use	n[a]	%
<1 month	3	7.1
1–3 months	1	2.4
3–6 months	–	0
6–9 months	2	4.8
9–12 months	1	2.4
1–5 years	16	38.1
5–10 years	17	40.5
>10 years	2	4.8

[a] : number of the patients.

When the comorbidities of the COPD patients included in the study were evaluated, it was determined that 61.9% ($n = 26$) of the patients had two or more comorbidities. Essential (primary hypertension) and chronic ischemic heart disease were among the most common comorbidities of the patients included in the study (Fig. 1).

Antihypertensive medications were used in 95.2% and oral antidiabetic drugs were used in 47.6% of the patients (Table 2).

Fluticasone, one of the medications used in the treatment of COPD, was prescribed in 54.8% (n = 23) of the patients (Table 3).

3.2. Evaluation of prescriptions for asthma patients

A total of 54 asthma patients were included in the study, with a mean age of 53.5 ± 16.4 years, 61% ($n = 33$) were female and 39% ($n = 21$) were male. It was found that 33.3% of asthma patients were diagnosed with more than five years and less than ten years (Table 4).

When the comorbidities of the asthma patients included in the study were evaluated, it was determined that 42.6% ($n = 23$) of the patients had two or more comorbidities. It was found that vasomotor and allergic rhinitis ($n = 19$), and essential (primary hypertension) ($n = 17$) were the most common diseases, and all comorbidities are shown in Fig. 2.

Antihypertensive medications were used in 88.9% and oral antidiabetic drugs were used in 53.7% of the patients (Table 5).

Among the medications used in the treatment of asthma, montelukast was prescribed for 53.7% ($n = 29$) of the patients (Table 6).

3.3. Evaluation of potential drug-drug interactions (pDDIs)

The pDDIs between the drugs used by COPD and asthma patients included in the study were evaluated in two separate databases, Medscape and Lexicomp. Statistically, a higher medication usage was observed in COPD patients compared to asthma patients (mean 6.0 vs. 4.5, $p = 0.011$). In the Medscape database, pDDIs were detected in 48.1% of asthma patients and 82.9% of COPD patients ($p < 0.001$). Similarly, in the Uptodate database, more pDDIs were detected in COPD patients than in asthma patients (36.6% vs. 16.7%) ($p < 0.001$) (Table 7).

pDDIs related to OIMs drugs in both databases are exemplified in Table 8.

A statistically significant correlation was found between the number of comorbid diseases and medications in asthma patients and the total pDDIs detected in the Medscape database (Spearman's rho: 0.561, $p < 0.0001$; Spearman's rho: 0.632, $p < 0.0001$). Similarly, it was observed in the Lexicomp database (Spearman's rho: 0.288, $p = 0.034$; Spearman's rho: 0.443, $p = 0.001$).

In COPD patients, a statistically significant correlation was found between the number of comorbid diseases and medications and the total pDDIs detected in the Medscape database (Spearman's rho: 0.419, $p = 0.006$; Spearman's rho: 0.667, $p < 0.0001$). However, in the UpToDate database, a significant correlation was found only between the number of medications and pDDIs (Spearman's rho: 0.350, $p = 0.025$).

4. Discussion

OIMs are widely used in the acute and chronic treatment of various respiratory diseases and the main advantage of OIMs is significant drug accumulation at the site of action (lungs) with minimal systemic effects. These drugs may interact with systemic drugs by being metabolized as a result of tracheobronchial absorption [10]. Since there is relatively limited clinical data on the systemic absorption of OIMs, this study retrospectively evaluated the prescriptions of patients using these drugs and analyzed drug interactions in two drug interaction databases.

In this study medication usage between COPD and asthma patients was found to be significant with COPD patients exhibiting higher medication usage. This discrepancy may reflect the complexity and severity of COPD, often causing a greater number of medications to

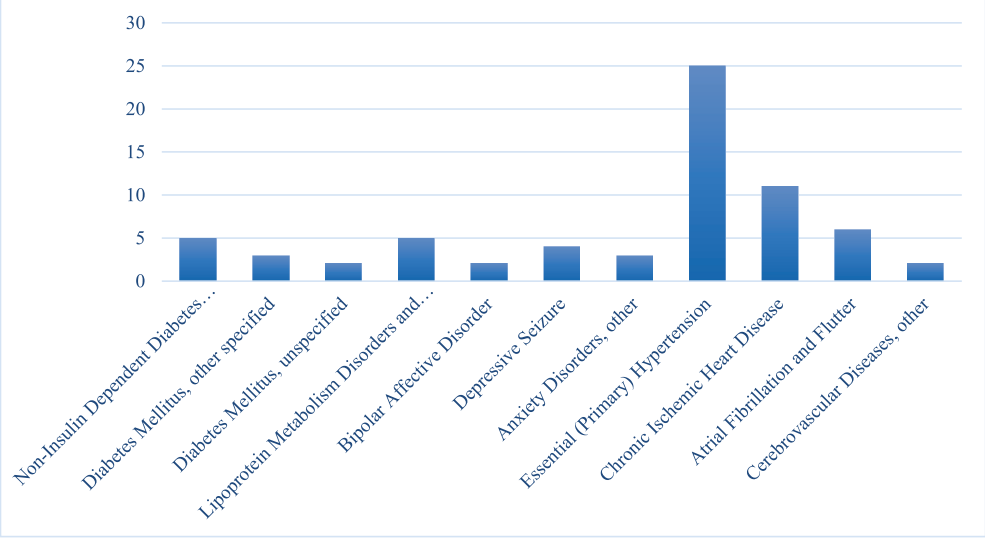

Fig. 1. Comorbidities of the COPD patients.

Table 2
Medications Used in the Treatment of Comorbid Diseases.

	n[a]	%
Antiepileptics	3	7.1
Nootropic Drugs	1	2.4
Oral Antidiabetic Drugs	20	47.6
Insulin Analogues	5	11.9
Antihypertensive Drugs	40	95.2
Antianginals	21	50
Vitamins-Minerals	4	9.5
Antibiotics	1	2.4
Antithrombotic Drugs	21	50
Drugs That Inhibit Uric Acid Production	1	2.4
Antihyperlipidemic Drugs	8	19.1
Expectorant	4	9.5
Analgesics	2	4.8
Urinary Retention Medications	8	19.1
Proton Pump Inhibitors	10	23.8
Antidepressants	11	26.2
Thyroid and Antithyroid Drugs	3	7.1
Antispasmodics	1	2.4
Antineoplastic and Immunomodulatory Drugs	2	4.8
Antivertigo Drugs	2	4.8
Stimulant Laxatives	2	4.8
Vasoprotectors	2	4.8
Alzheimer's Drugs	1	2.4
Antiparkinsonian Drugs	1	2.4
Antiviral Drugs	1	2.4
Antipsychotic Drugs	3	7.1

[a] : number of the patients.

Table 3
Medications Used in the Treatment of COPD Patients.

	n[a]	%
Acetylcysteine	4	9.5
Beclomethasone	2	4.8
Budesonide	8	19.1
Fluticasone	23	54.8
Formoterol	9	21.4
Glycopyrronium	2	4.8
Indacaterol	1	2.4
Ipratropium	16	38.1
Levosalbutamol	5	11.9
Methylprednisolone	1	2.4
Salbutamol	18	42.9
Salmeterol	15	35.7
Theophylline	2	4.8
Tiotropium	19	45.2
Umeclidinium	6	14.3
Vilanterol	6	14.3

[a] : number of the patients.

Table 4
Evaluation of Duration of Medication Use of Asthma Patients.

Duration of Medication Use	n[a]	%
<1 month	7	13
1–3 months	3	5.6
3–6 months	–	0
6–9 months	–	0
9–12 months	1	1.9
1–5 years	16	29.6
5–10 years	18	33.3
>10 years	9	16.7

[a] : number of the patients.

manage symptoms and comorbidities.

The analysis of pDDIs in the Medscape database revealed a substantially higher prevalence among COPD patients compared to asthma patients. This suggests that COPD patients may be at a high risk of experiencing adverse drug interactions, which might impact treatment efficacy and safety. Similarly, findings from the UpToDate database highlighting the increased vulnerability of COPD patients to pDDIs.

The prevalence of the category 'monitor closely' in the Medscape drug interaction database in the prescriptions of asthma was found to be 86.5%, and 75% of the prescriptions were found to be in category D drug interactions in the Lexicomp database. Similarly, Bibi et al.[12]found that 95% of the prescriptions of asthma patients had at least one pDDIs and 74% of them were classified as major drug interactions.

The prevalence of the pDDIs for COPD patients in the category "monitor closely" in the Medscape was found as 94.4% and 61.5% was found as category X in the Lexicomp database. Seçkin et al.[13] analyzed the drug interactions in 169 prescriptions they retrospectively examined with the Lexicomp database and found drug interactions in category C at a rate to our study (77%). In another study conducted in Iran, because of a total of 2796 prescription examinations of inpatients and outpatients, an interaction in category C was detected with a rate of 66% in the Lexicomp database.[14] In the study conducted in a community pharmacy, according to the data obtained as a result of the retrospective prescription review, 70% of interactions were detected in category C in the Lexicomp database.[15] A total of 801 patients' prescriptions were

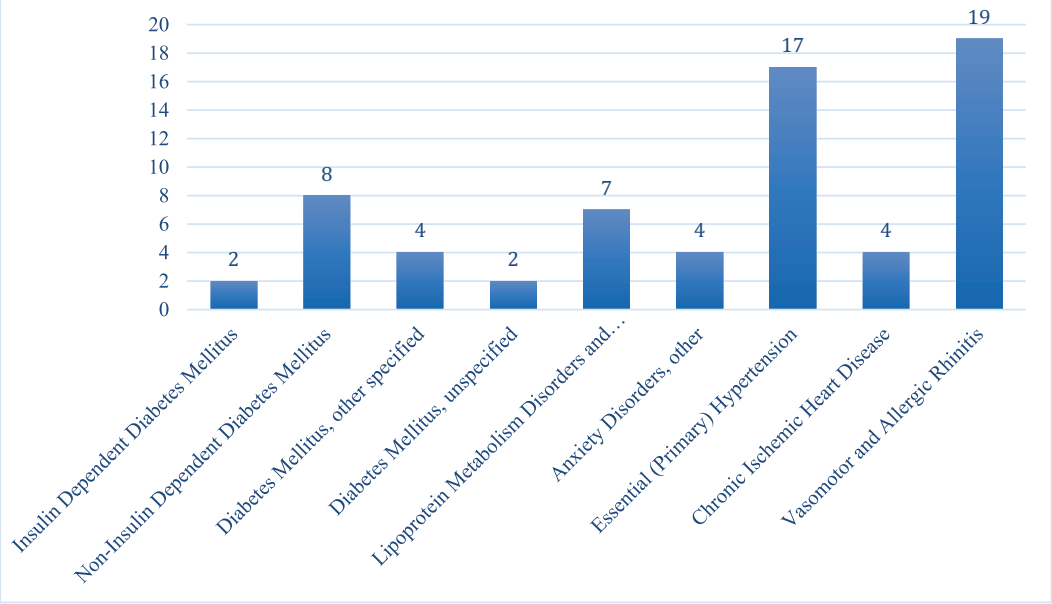

Fig. 2. Comorbidities of asthma patients.

Table 5
Medications Used in the Treatment of Comorbid Diseases in Asthma Patients.

	n[a]	%
Antiepileptics	5	9.3
Nootropic Drugs	3	5.6
Oral Antidiabetic Drugs	29	53.7
Insulin Analogues	8	14.8
Antihypertensive Drugs	48	88.9
Antihistamines	8	14.8
Bisphosphonates	2	3.7
Antianginals	9	16.7
Vitamins-Minerals	5	9.3
Antibiotics	3	5.6
Antithrombotic Drugs	8	14.8
Drugs That Inhibit Uric Acid Production	5	9.3
Drugs That Do Not Affect Uric Acid Metabolism	1	1.9
Antihyperlipidemic Drugs	3	5.6
Expectorants	2	3.7
Analgesics	3	5.6
Urinary Retention Medications	1	1.9
Proton Pump Inhibitors	14	25.9
Antidepressants	7	13
Thyroid and Antithyroid Medications	2	3.7
H2 Receptor Antagonists	2	3.7
Antispasmodics	1	1.9
Nasal Decongestants	1	1.9
Antineoplastic and Immunomodulatory Drugs	1	1.9
Muscle Relaxants	1	1.9

[a] : number of the patients.

examined in various outpatient clinics of 6 different hospitals in Jordan, 3359 drug interactions were detected and 78% of them were found to be in category C.[16,17]

In asthma patients, a significant correlation was identified between the number of comorbid diseases and medications and the total number of pDDIs detected in both the Medscape and Lexicomp databases. This underscores the importance of considering the cumulative burden of comorbidities and medications when assessing the risk of pDDIs in asthma management.

In contrast, COPD patients exhibited a distinct correlation between comorbid diseases, medications, and pDDIs. The analysis revealed a significant relationship between the number of comorbid diseases and medications and the total pDDIs detected in the Medscape database. However, in the UpToDate database, the correlation was predominantly

Table 6
Medications Used in the Treatment of Asthma Patients.

	n[a]	%
Beclomethasone	5	9.3
Budesonide	15	27.8
Fluticasone	27	50
Formoterol	17	31.5
Ipratropium	6	11.1
Levosalbutamol	2	3.7
Mometasone	3	5.6
Montelukast	29	53.7
Salbutamol	19	35.2
Salmeterol	22	40.7
Theophylline	1	1.9
Tiotropium	4	7.4
Vilanterol	1	1.9
Methylprednisolone	5	11.9

[a] : number of the patients.

Table 7
Evaluation of Potential Drug-Drug Interactions (pDDIs).

	Database	Category	Number of pDDIs/%
PRESCRIPTIONS FOR ASTHMA PATIENTS	Medscape ($n = 81$)	Serious	4 (4.5)
		Significant (monitor closely)	77(86.5)
		Contraindicated	0
	Lexicomp ($n = 12$)		
		D	9(7.0)
		X	3 (2.3)
PRESCRIPTIONS FOR COPD PATIENTS	Medscape ($n = 162$)	Serious	9 (5.6)
		Significant (monitor closely)	153 (94.4)
	Lexicomp ($n = 13$)		
		D	5 (38.5)
		X	8(61.5)

n: total number of Potential Drug-Drug Interactions, pDDIs: Potential Drug-Drug Interactions.

Table 8
pDDIs with oral inhaler medications (OIMs).

pDDIs	Database /Category	Mechanism	Management
Escitalopram-Umeclidinium Bromide/ Vilanterol İnhaled	Medscape/ Serious	escitalopram increases toxicity of umeclidinium bromide/vilanterol inhaled by QTc interval.	Extreme caution when vilanterol is coadministered with drugs that prolong QTc interval; adrenergic agonist effects on the cardiovascular system may be potentiated.
Ipratropium-Fluticasone/ Umeclidinium Bromide/ Vilanterol Inhaled	Medscape/ Serious	ipratropium, umeclidinium bromide/vilanterol inhaled. Either increase the toxicity of the other by pharmacodynamic synergism.	Concomitant use with other anticholinergic-containing drugs may lead to additive anticholinergic adverse effects.
Ipratropium/ Albuterol–Quetiapine	Lexicomp/ X	Ipratropium (Oral Inhalation) may enhance the anticholinergic effect of Agents with Clinically Relevant Anticholinergic Effects.	Avoid concurrent use of ipratropium with any other drugs that have anticholinergic properties. If such combinations can not be avoided, monitor patients closely for evidence of anticholinergic-related toxicities (e.g., urinary retention, constipation, tachycardia, dry mouth, etc.).
Ipratropium/ Albuterol–Tiotropium	Lexicomp/ X		
Quetiapine–Tiotropium	Lexicomp/ X		
Chlorpromazine–Tiotropium	Lexicomp/ X		
Fluticasone And Salmeterol - Propranolol	Lexicomp/ X	Beta-Blockers (Nonselective) may diminish the bronchodilatory effect of Beta2-Agonists.	Avoid the use of nonselective beta-blockers in patients treated with beta2-agonists. If used concomitantly, monitor closely for diminished bronchodilatory effects of the beta2-agonist.
Carvedilol–Ipratropium And Albuterol	Lexicomp/ X		

pDDIs: potential drug-drug interactions, X: Avoid combination.

driven by the number of medications rather than comorbidities.

5. Conclusions

Due to pDDIs with OIMs, many undesirable effects such as hypokalemia, QT prolongation, an increased risk of arrhythmias, and additional anticholinergic effects may occur.[17] The inhaled drugs with the most documented potential for drug interactions in the literature are corticosteroids. To optimize clinical outcomes, clinicians must have adequate information about all the medications their patients may be taking. The identification, prevention, and resolution of OIMs-drug interactions are the responsibility of a multidisciplinary team. Pharmacists are a crucial resource for the interpretation and management of suspected drug interactions. Patient profiling, assisting in drug selection, communicating drug interactions to other members of the multidisciplinary team, and helping to monitor adverse reactions are their fundamental areas of responsibility. Consequently, we believe that pharmacists will be useful in determining the drug interactions of asthma and COPD patients treated with OIMs.

Limitations: The study was conducted during the COVID-19 pandemic period. Therefore, the number of patients is quite low and the clinical significance of the detected pDDIs was not examined. Since it was conducted in only one community pharmacy, further studies are needed to generalize the results of the study.

Disclosures

We confirm that this work is original. The results of this study were presented as a poster presentation in the 49th ESCP virtual symposium on clinical pharmacy (19.10.2021–21.10.2021). an was published in the International Journal of Clinical Pharmacy as a meeting abstract.

Disclosures

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CRediT authorship contribution statement

Songul Tezcan: Writing – review & editing, Writing – original draft, Supervision, Resources, Investigation, Formal analysis, Conceptualization. **Nurdan Yaban:** Writing – original draft, Resources, Conceptualization.

Declaration of Competing Interest

The authors have no conflicts of interest, financial or otherwise.

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