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A retrospective study on potential drug–drug interactions in patients with severe asthma receiving biological therapy: a single-center experience

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Abstract

Background Prevalence of potential drug-drug interactions (pDDIs) in adult patients with severe asthma on biological therapy and their clinical significance have not been fully addressed, thus the aim of this study was to investigate them.

Methods In this retrospective observational study, patients who were diagnosed with severe asthma and to whom biological therapy was prescribed between September 2015 and December 2020, were enrolled. The study was conducted at the Department of Allergic and Obstructive Pulmonary Diseases, Clinic for Lung Diseases Jordanovac, Clinical Hospital Center Zagreb. Data on demographic characteristics as well as concomitant medication were collected. The analysis of pDDIs was conducted via Lexicomp® online software. Interactions of significance levels A and B were only recorded, while those of levels C, D and X were further analysed. The collected data was processed via Microsoft Excel 365 software.

Results 60 adult patients, 60% female and 40% male, with median age of 56.2 years, were enrolled. The incidence of pDDIs was 86.67%. Total number of pDDIs detected was 518, out of which 43.24%, 45%, 4.44% and 7.3% of clinical significance B, C, D and X. Interactions of level C, D and X were recorded in, as follows: 83.33%, 25% and 33.33% patients with an average of 4.66, 1.53 and 1.9 interactions per patient. Only 13.33% of the patients had none of the potential clinically significant DDI. Most drug pairs contained at least one antiasthmatic drug. Muscarinic receptor antagonists, oral corticosteroids, β2 agonists and methylxanthines showed potential of entering into clinically significant DDIs, while leukotriene antagonists and biologicals showed no potential for the above.

Conclusion Prevalence of potential drug-drug interactions in patients with severe asthma on biological therapy is high. The majority of identified interactions have moderate to high level of clinical significance. Their identification, prevention and resolution could contribute to optimizing therapy, maximizing its therapeutic effect and avoiding undesirable adverse events.

Keywords Severe asthma, Biological therapy, Drug-drug interactions

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Background

Severe asthma (SA), according to the European Respiratory Society (ERS) and the American Thoracic Society (ATS), is defined as asthma that requires treatment with high-dose inhaled corticosteroids (ICS) and a second controller and/or oral corticosteroids (OCSs) to prevent it from becoming uncontrolled or remaining uncontrolled despite this therapy [1]. The estimated prevalence of SA is approximately 3.7% [2]. The Global Initiative for Asthma (GINA) recommends treatment for severe asthma per Steps 4 and 5 of the GINA guidelines. Step 4 involves using medium doses of ICS-formoterol as the preferred controller and low-dose ICS-formoterol as the preferred reliever. Alternative controllers within Step 4 are medium/high doses of ICS-long-acting β2 agonists (LABAs) with alternative reliever as-needed ICS-short-acting β2 agonists (ICS-SABA) or as-needed SABAs. Other controller options include the addition of long-acting muscarinic antagonist (LAMA) or leukotriene receptor antagonist (LTRA) or the switch to high doses of ICS. Step 5 implies adding biological therapy to preferred/alternative controllers within Step 4, with the same preferred and alternative relievers. As the last resort, Step 5 implies the addition of low doses of OCS [2].

Drug–drug interactions (DDIs) are defined as changes in the effect of one drug due to the simultaneous or prior administration of another drug [3]. DDIs may cause an increased or decreased effect of one or both drugs or no impact on the drug's effect. DDIs are typically classified by mechanism into pharmaceutical, pharmacokinetic and pharmacodynamic [4]. Some of these methods might be beneficial, but most of them are undesirable. DDI detection can be performed manually, through monographs of drugs or summary of product characteristics (SmPC), or through digital clinical resources. There is no single widely accepted grading scale for DDIs, so many clinical resources have developed their own risk rating systems that indicate the clinical significance of DDIs and the corresponding recommendation (none, therapy modification or drug discontinuation). It is important to distinguish *potential DDIs* (pDDIs) (drug pairs known to interact that are concurrently prescribed) from *clinically relevant pDDIs* (drug pairs known to interact that are concurrently prescribed and could cause measurable clinical effects on patients, taking into account an individual patient's profile) and *DDIs that resulted in actual harm* (drug pairs that interacted and resulted in harm to the patient, on the basis of clinical evidence and confirmed by symptoms, laboratory tests, monitoring of patients or interviews with patients) [5]. Potential DDIs inevitably precede actual DDIs [6].

The probability of detecting at least one pDDI increases with the number of prescribed medications [7–9] and is expected to be 50% with 5–9 drugs, 81% with 10–14, 92% with 15–19 and 100% with 20 drugs or more [6]. The prevalence of pDDIs varies across the literature, depending on the study design, studied population, number and types of drugs used, healthcare settings and methods used to identify interactions, making comparisons of results across studies difficult. In the general population, the prevalence of pDDIs ranges from 2.8 to 63% [10]. The prevalence can be relatively high in hospital settings, ranging from 5.3 to 83.9% [11–14]. Elderly patients are considered a high–risk population [15], with a prevalence ranging from 25.1 to 100% [13]. Patients with chronic conditions and long-term medication regimens also have a higher prevalence of pDDIs. The transition from potential to clinically relevant DDIs can lead to an increase in the frequency and/or severity of adverse drug effects (ADEs), which consequently leads to an increase in the frequency of emergency department visits, hospitalizations, or prolonged hospitalizations, generating harm for patients and increased healthcare costs. ADE-related hospital admissions ranged from 0.37 to 27.4%. DDIs are responsible for 6–30% of all ADEs [10].

Severe asthma patients receiving biologics represent a particularly vulnerable group, compared to the general asthma population. These patients often have multiple comorbidities, resulting in a high medication burden. Polypharmacy in this group increases the likelihood of clinically significant pDDIs, which may compromise treatment efficacy and safety. Additionally, biologics are often added to already complex therapeutic regimens, further increasing the risk of pDDIs. Understanding and managing pDDIs in this population is critical to preventing adverse events, optimizing therapeutic outcomes and reducing healthcare costs associated with SA management.

Given the rising use of biologics in severe asthma therapy and the complexity of these patients' medication regimens, the aim of this study was to determine the prevalence and clinical significance of pDDIs in adult patients diagnosed with SA.

Materials and methods

Study participants

We retrieved the medical records of adult patients (>18 years old), both sexes, who were diagnosed with SA (ICD-10 J45), treated at the Department for Allergic and Obstructive Pulmonary Diseases, Clinic for Pulmonary Diseases Jordanovac, University Hospital Centre Zagreb (UHC Zagreb), and who used biological therapy (omalizumab, mepolizumab, benralizumab, reslizumab). All patients were part of the SHARP Registry (Severe Heterogeneous Asthma Research collaboration, patient-centered), which was initiated by the SHARP team, ERS and expert respiratory clinicians from 28 European countries. A total of 60 patients were enrolled in this study.

Medical records were retrospectively obtained digitally from the hospital information system and manually from the archive of the Department. The obtained data do not reveal the identities of individual patients. The research was conducted in accordance with all applicable guidelines for proper research, safety and protection of individuals whose data were processed, including the Declaration of Helsinki, Good Clinical Practice guidelines, the Health Care Act of the Republic of Croatia (NN121/03) and the Patients' Rights Act of the Republic of Croatia (NN169/04). All patients included in the SHARP registry provided signed informed consent. The study was approved by the Ethics Committee of the UHC Zagreb.

Study design

This retrospective, observational, single-center study aimed to determine the prevalence and clinical significance of pDDIs in adult patients diagnosed with SA.

Methods

We collected data for all patients diagnosed with SA at the Department, to whom biological therapy has been prescribed. The timeframe of the study was from September 2015, when biological drugs first became available for use in Croatia, until December 2020.

For each patient, the following data were collected: sex, age, height, weight, body mass index (BMI), smoking status, pack-years, asthma severity according to the GINA guidelines (GINA Step 4 or 5), dominant asthma phenotype, age at which the patient was diagnosed with asthma, duration of the disease, comorbidities (atopic dermatitis, allergic rhinoconjunctivitis, chronic rhinosinusitis, nasal polyps, depression, osteoporosis) and concomitant medication.

The analysis of pDDIs was conducted via Lexicomp® online software, which focuses on interactions of significance levels C, D and X, whereas those of levels A and B were only recorded and not specifically analyzed (Table 1).

Statistical analysis

The general characteristics of the participants are described via descriptive statistics and are presented as the mean values (± SD). The collected data were processed via Microsoft Excel 365 software.

Results

Overall, 60 patients were included in this study. The clinical and sociodemographic characteristics of the participants are summarized in Table 2.

Medication

The average number of antiasthmatic medications per patient, including biologics, was 6.78 ± 1.25 (Table 3). In the pharmacological groups, OCS (prednisone or methylprednisolone) was used by 55 (91.7%) of the patients, whereas only 5 (8.4%) had no OCS prescribed. All of the patients used ICSs. Budesonide was used the most often, in 29 (48.33%) patients, followed by beclomethasone in 16 (48.33%), fluticasone in 14 (23.3%) and ciclesonide in 1 (1.67%) patient. This was the number of medication/s used at the time of the introduction of biological therapy.

The average number of total medications per patient, including the medications for asthma as well as for the other comorbidities, was 10.42 ± 3.06 (Table 3., Fig. 1.).

Drug interactions

The total number of pDDIs was 518. The distribution by the level of clinical significance is shown in Fig. 3.

At least one pDDI of level X was detected in 20 (33.33%) patients, with an average of 1.9 ± 0.83 (1–4) interactions per patient. There were 10 different interactions in total (Table 4.). The most prevalent interaction was between tiotropium and ipratropium.

Table 1 Categorization of drug–drug interactions by the level of clinical significance. (adapted from Lexicomp® Online [16])

Level of clinical significance (risk rating)	Explanation	Patient management
A	No interactions between drugs.	No need for intervention.
B	Selected drugs may enter into interaction, but there is little or no evidence of its clinical significance.	No need for intervention.
C	Selected drugs may enter into clinically significant interaction, but the benefit of their use overweight the risk.	Monitor the patients. The dose modification may be needed in some patients.
D	Selected drugs may enter into clinically significant interaction.	Consider therapy modification (alternative drug or dose modification). Assess whether the benefit of simultaneous use outweighs the risk. Monitor the patient during the treatment.
X	Selected drugs may enter into clinically significant interaction. In most cases, the risk of their use outweighs the benefits. The combination is usually considered contraindicated.	Avoid combination.

Table 2 Clinical and sociodemographic characteristics of the participants

Age (years)	**Mean ± SD**	**56.2 ± 12.89**
Gender	Female: n (%)	36 (60)
	Male: n (%)	24 (40)
BMI (kg/m^2)	Mean ± SD	26.47 ± 4.23
Smoking status	Nonsmokers: n (%)	33 (55)
	Former smokers: n (%)	25 (41.7)
	Smokers: n (%)	2 (3.3)
Pack-years	Mean ± SD	11.08 ± 17.30
GINA Step	4: n (%)	54 (90%)
	5: n (%)	5 (8.3%)
Diagnosis of asthma (age)	Mean ± SD	31 ± 15.3
Duration of asthma (years)	Mean ± SD	25 ± 15.27
Dominant phenotype of asthma	Allergic: n (%)	28 (47)
	Allergic-eosinophilic: n (%)	16 (26.7)
	Eosinophilic: n (%)	16 (26.7)
Biological therapy	Omalizumab: n (%)	25 (41.7)
	Reslizumab: n (%)	10 (16.7)
	Benralizumab: n (%)	10 (16.7)
	Mepolizumab: n (%)	15 (25)
Comorbidities	Atopic dermatitis: n (%)	6 (10)
	Allergic rhinoconjuctivitis: n (%)	29 (48.3)
	Chronis rhinosinusitis: n (%)	36 (60)
	Nasal polyposis: n (%)	22 (36.7)
	Diabetes: n (%)	12 (20)
	Depression: n (%)	7 (11.7)
	Osteoporosis: n (%)	17 (28.3)

BMI: body mass index; GINA: Global Initiative for Asthma

Table 3 Distribution of participants according to number of concurrently used medications for the treatment of severe asthma and total medications

n **(antiasthmatic medications)**	***n*** **(%)** **(participants)**	***n*** **(total medications)**	***n*** **(%)** **(participants)**
5	7 (11.67)	5–9	28 (46.67)
6	22 (36.67)	10–15	25 (41.67)
7	17 (28.33)	> 15	4 (6.67)
8	7 (11.67)		
9	5 (8.33)		
10	2 (3.33)		

At least one pDDI of level D was detected in 15 (25%) patients, with an average of 1.53 ± 0.62 (1–3) interactions per patient. There were 13 different interactions in total (Table 5.). The most prevalent interaction was between OCS (prednisone or methylprednisolone) and calcium salts.

At least one pDDI of level C was detected in 50 (83.33%) patients, with an average of 4.66 ± 4.37 (1–25) interactions per patient. There were 115 different interactions in total (Supplement 1.). The most prevalent interactions were those between formoterol and salbutamol; between cholecalciferol and calcium; between salbutamol and theophylline; between formoterol and theophylline; between antidiabetic drugs and OCSs; and between diuretics and OCSs.

Only 8 (13.33%) patients had no drugs with potential interactions equal to or greater than level C of clinical significance, which indicates that 86.67% of the potential clinically significant DDIs in this group occurred.

Not a single DDI involving biologicals or LTRAs for SA was detected.

Discussion

In this study, a large number of medications were recorded, averaging 10.42 per patient. The treatment of asthma, with the exception of the mildest forms of the disease, consists of multiple medications. Additionally, patients suffering from asthma are at increased risk of developing other conditions that also require pharmacological treatment. The chronic nature of asthma explains its prevalence in older patients, who are also likely to have other comorbidities and, consequently, a greater number of medications per patient. The probability of detecting at least one pDDI increases with the

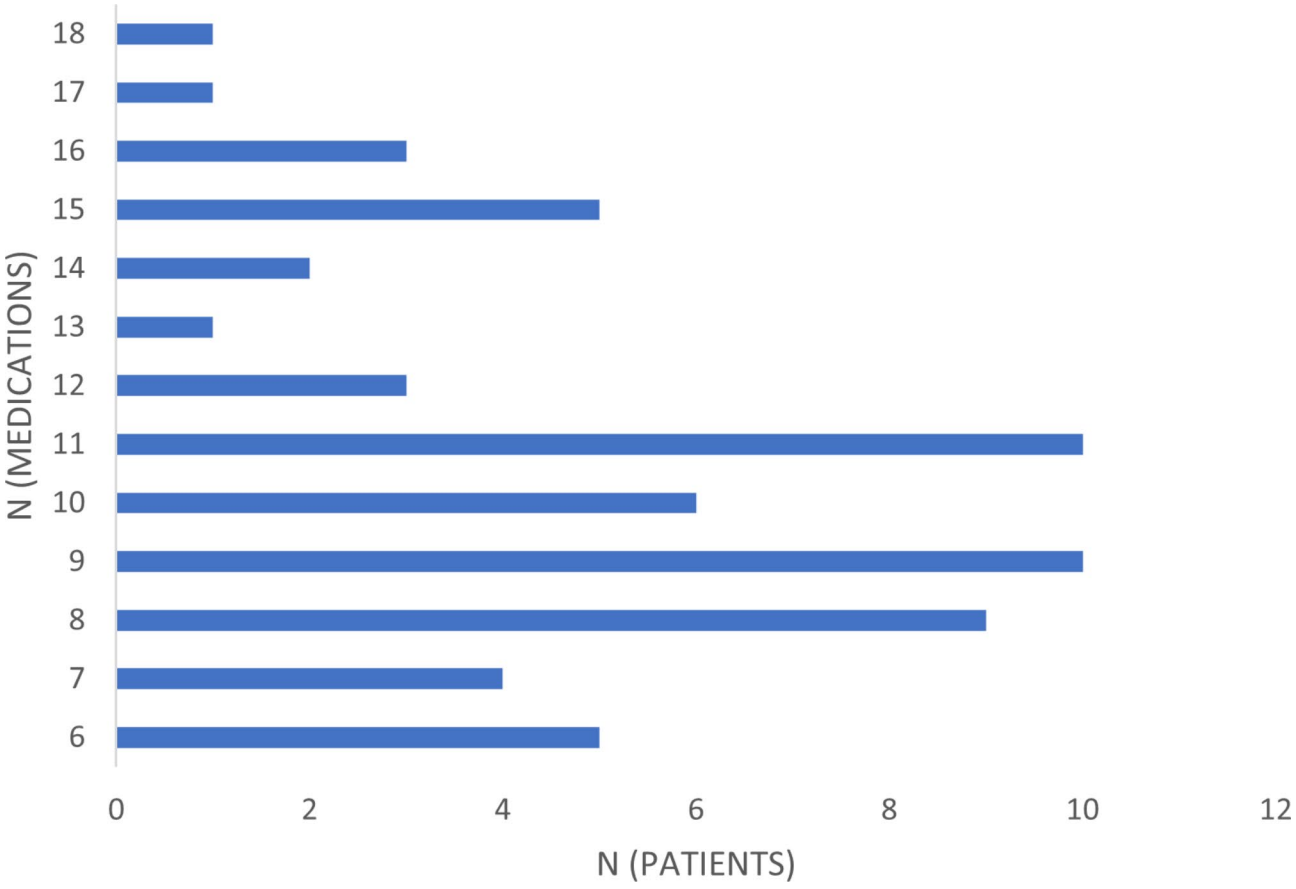

Fig. 1 Distribution of participants according to number of concurently used medications.

number of medications [7–9]. It is expected to be 50% for patients taking 5–9 drugs, 81% with 10–14 drugs, 92% with 15–19 drugs and 100% with 20 drugs or more [6]. The prevalence of pDDIs in this study was 86.67%. The total number of recorded pDDIs in 60 participants was 518. The prevalence of pDDIs varies across different studies, depending on several factors, such as the population being studied, the number and types of drugs used, and healthcare settings. Research on PubMed and Google Shoolar with the key words "drug–drug interactions" and "asthma" provides very little data on the prevalence of pDDIs in patients with asthma. One prospective, observational study, carried out at a tertiary care hospital in India, assessed pDDIs in asthma patients. A total of 516 pDDIs were identified in 229 patients [17]. In contrast to our study, this study had exclusion criteria for all the other comorbidities except asthma, so the average number of medications per patient was only 4–5, two times less than that used in our study. PDDI analysis was performed via software other than those used in our study. In another retrospective study carried out in a community pharmacy in Turkey, pDDIs with oral inhaler medications for asthma and chronic obstructive pulmonary disease (COPD) patients were assessed. PDDIs were detected in 48.1% of asthma patients and 82.9% of COPD patients [18]. Another prospective, observational study from Pakistan assessed pDDIs in hospitalized patients with asthma. The prevalence of potentially clinically relevant DDIs was 74.2% [19]. Even though the prevalence is similar to that in our study, the difference in the study population should be acknowledged. In that study, all asthma patients, regardless of disease severity, were included, whereas we included only SA patients. In addition, pDDI analysis was performed via different software programs than those used in our study.

On the basis of these findings, the literature data concerning the prevalence of pDDIs in asthma patients are very limited. Owing to different study designs, it is difficult to compare existing studies. To our knowledge, there are no literature data on the prevalence of DDIs in SA to date. Given the average number of 10.42 medications per patient, the high prevalence of pDDIs in our study was expected. Although not all DDIs are clinically significant, it is estimated that approximately 5–10% of all reported interactions lead to clinically significant adverse effects or therapeutic failures. Stated can impact treatment efficacy and safety, highlighting the importance of careful medication management and regular review of patients'

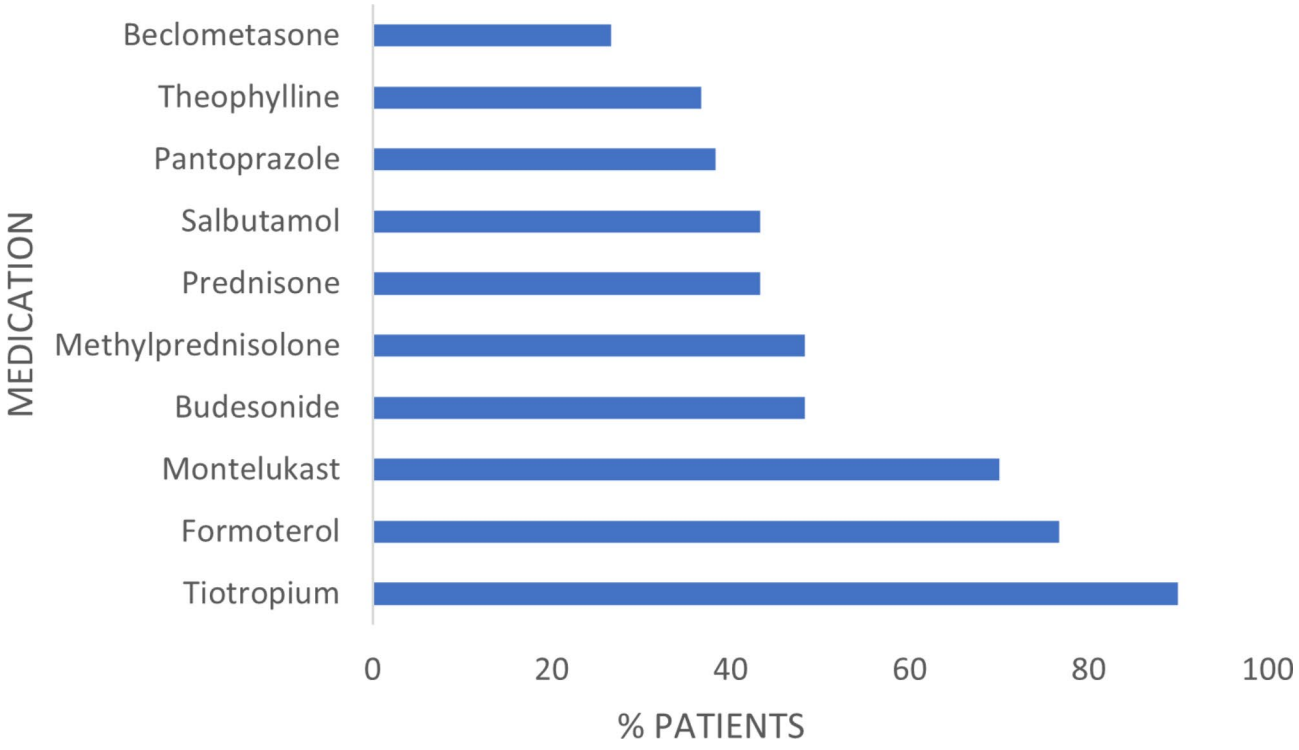

Fig. 2 Frequency of use of medications (other than biologicals) within patients.

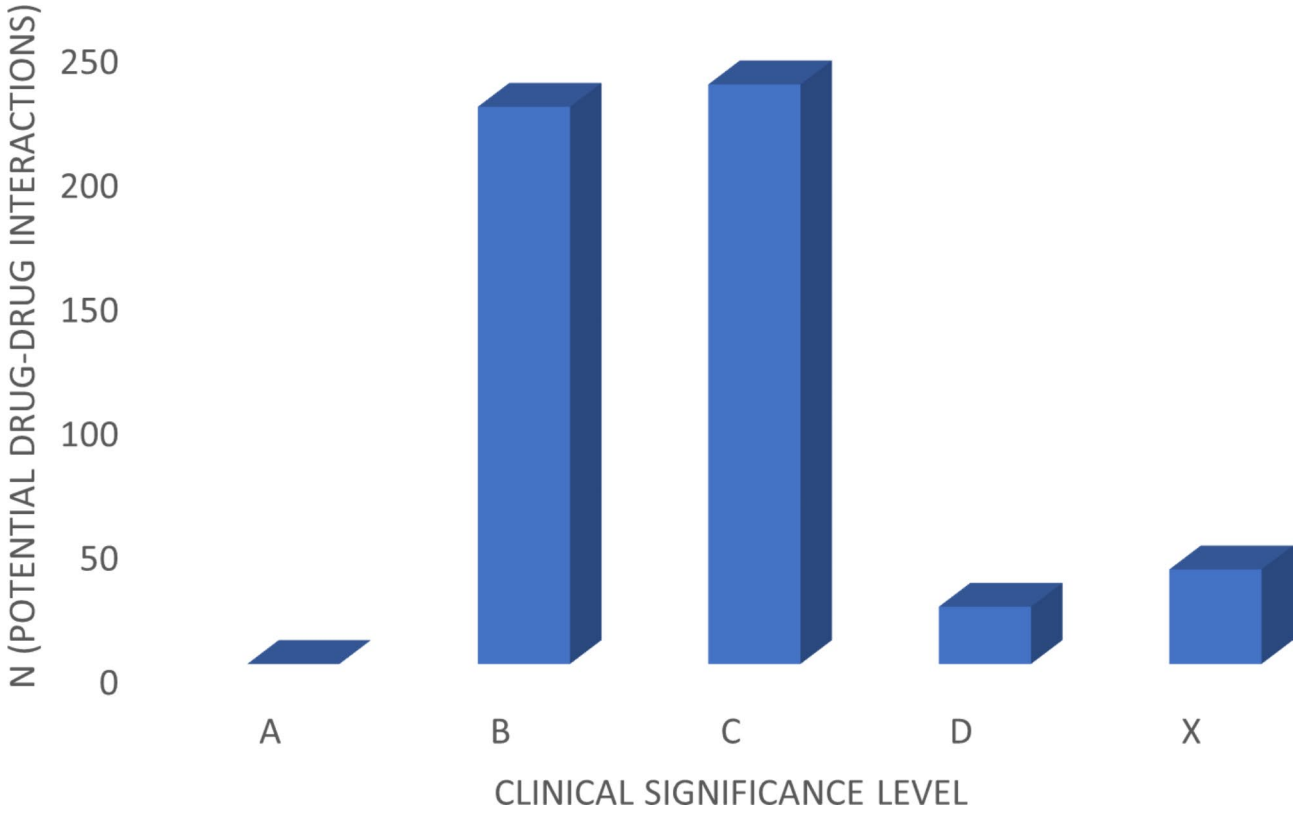

Fig. 3 Number of detected potential drug-drug interactions per each level of clinical signicance (A, B, C, D, X).

Table 4 Potential drug–drug interactions of clinical significance level X

Drug	Interactant	Mechanism	Recommendation of intervention
Tiotropium	Ipratropium	Additive anticholinergic effect	Avoid concurrent use. If such combinations cannot be avoided, monitor patients closely for evidence of anticholinergic-related toxicities (e.g., urinary retention, constipation, tachycardia, dry mouth, etc.)
Tiotropium	Bilastine		
Ipratropium	**Fexofenadine**		
Tiotropium	**Fexofenadine**		
Tiotropium	**Loratadine**		
Ipratropium	**Aclidinium**		
Aclidinium	**Fexofenadine**		
Tiotropium	**Levocetirizine**		
Aclidinium	**Bilastine**		
Bilastine	**Propafenone**	Propafenone may enhance serum concentration of bilastine. This interaction may be of even greater severity in patients with moderate or severe renal insufficiency.	Avoid concurrent use. This combination should be strictly avoided in patients with moderate to severe renal insufficiency.

pharmacological therapy. The significance of DDIs has also been recognized by the GINA guidelines. The guidelines highlight the importance of recognizing and managing DDIs, particularly in patients with complex regimens involving multiple drug classes [2].

In the following text, pDDIs within specific pharmacological groups for SA treatment will be discussed in detail.

Biologicals

No interactions involving biologicals were recorded, which is consistent with current knowledge. According to the literature, benralizumab, reslizumab, mepolizumab, omalizumab, dupilumab and tezepelumab all interact with efgartigimod-alpha and rozanolixizumab (significance level C), which may diminish the therapeutic effects of biologics (Fc receptor-binding agents). Additionally, omalizumab interacts with loxapine (significance level X), which applies exclusively to inhaled products with the brand name Adasuve®. The mechanism of this interaction involves enhancing the adverse effects of loxapine. Dupilumab and tezepelumab additionally interact with live vaccines, increasing their adverse effects. Given the significance of level X, the concurrent use of dupilumab and tezepelumab with live vaccines should be avoided [16]. Egfartigimod-alpha, rozanolixizumab or loxapine, as well as dupilumab and tezepelumab, were not used by any of the subjects in our studies.

β2 agonists

The highest level of pDDIs with β2-agonists was level C. The most common interaction was between the SABAs and LABAs, with an additive sympathomimetic effect. It is recommended to monitor for symptoms of increased sympathetic activity (e.g., elevated blood pressure or pulse). In these interactions, the benefits outweigh the risks. Moreover, β2-agonists interact with β-blockers, bisoprolol, and nebivolol, with mutual antagonism of their effects. This type of interaction is more significant with nonselective β-blockers. Cardioselective β-blockers can sometimes cause bronchospasm in patients with asthma but generally do not antagonize the effects of β2-agonists. A meta-analysis of 29 randomized trials studied the effects of cardioselective β-blockers on patients with reactive airway disease and revealed no clinically significant effects in patients with mild to moderate airway disease [20]. The effects on patients with more severe airway diseases are not known.

Furthermore, β2-agonists interact with diuretics, with an additive hypokalaemic effect. This has also been documented in the literature, where the use of bendrofluazide augmented the hypokalaemic effect of high-dose salbutamol, with visible changes on the ECG [21]. The hypokalaemic effect, as well as hypoxia, can be intensified by the concurrent use of corticosteroids and theophylline, thus requiring special caution in patients with SA. Potassium-sparing diuretics may be added if necessary. It is essential to monitor the serum potassium concentration and ECG changes carefully to reduce the risk of arrhythmias, especially in patients with ischemic heart disease.

β2-agonists also interact with theophylline, with additive hypokalaemic and sympathomimetic effects, predominantly manifesting as tachycardia. This combination of medications is beneficial in asthma treatment, but careful monitoring of the serum potassium concentration is recommended.

Corticosteroids

Potential DDIs with ICSs are minimal due to their low systemic absorption and low plasma concentration.

Table 5 Potential drug–drug interactions of clinical significance level D

Drug	Interactant	Mechanism	Recommendation of intervention
Torasemide	**Meloxicam**	NSAID may diminish the diuretic effect of loop diuretics. Loop diuretics may enhance nephrotoxic effect of NSAID	Consider therapy modification. Monitor for decreased therapeutic effect of loop diuretics and acute kidney injury. Patients with heart failure or liver cirrhosis may be more sensitive to alterations in fluid balance in which case consideration should be given to avoiding concomitant use.
Methylprednisolone	**Calcium**	Calcium may decrease bioavailability of corticosteroids (oral)	Consider separating doses for 2 or more hours. Monitor for decreased therapeutic effects of OCS.
Ibandronate	**Calcium**	Calcium may decrease serum concentration of bisphosphonate derivates	Consider therapy modification. Avoid administration of calcium within 1 h after oral ibandronate.
Levothyroxine	**Calcium**	Calcium may diminish the therapeutic effect of levothyroxine.	Consider therapy modification. Separate the dose of levothyroxine and calcium by at least 4 h.
Prednisone	**Calcium**	Calcium may decrease bioavailability of corticosteroids (oral)	Consider separating doses for 2 or more hours. Monitor for decreased therapeutic effects of OCS.
Gliclazide	**Linagliptin**	Linagliptin may enhance the hypoglycemic effect of gliclazide.	Consider therapy modification. Consider a decrease in gliclazide dose when initiating linagliptin. Monitor patients for hypoglycemia.
Furosemide	**Naproxen**	NSAID may diminish the diuretic effect of loop diuretics. Loop diuretics may enhance nephrotoxic effect of NSAID	Consider therapy modification. Monitor for decreased therapeutic effect of loop diuretics and acute kidney injury. Patients with heart failure or liver cirrhosis may be more sensitive to alterations in fluid balance in which case consideration should be given to avoiding concomitant use.
Perindopril	**Urapidil**	Urapidil may interact via an unknown mechanism with perindopril	Consider therapy modification. Avoid concomitant use.
Simvastatin	**Amlodipine**	Amlodipine may increase serum concentration of simvastatin	Consider therapy modification. Limit the dose of simvastatin to 20 my daily if coadministering with amlodipine. Close laboratory and clinical monitoring for signs and symptoms of rhabdomyolysis.
Tramadol	**Alprazolam**	Additive CNS depressant effect	Consider therapy modification. Avoid concomitant use when possible. If combined, limit the dosages and duration of each drug to the minimum possible.
Tramadol	**Fexofenadine**	Additive CNS depressant effect	Consider therapy modification. Combine only if alternative options are inadequate.
Loratadine	**Amiodarone**	Amiodarone may increase the serum concentration of loratadine	Consider therapy modification. Due to reported QT interval prolongation and torsades des pointes with this combination, consider using an alternative to loratadine when possible.
Aspart insulin	**Linagliptin**	Linagliptin may enhance hypoglycemic effect of insulins	Consider therapy modification. Consider a decrease in insulin dose when initiating linagliptin. Monitor patients for hypoglycemia.

NSAID: nonsteroidal anti-inflammatory drugs; OCS: oral corticosteroids; CNS: central nervous system

Therefore, most pDDIs, including corticosteroids, are attributed to OCS. The highest level of interactions they encountered was D, with calcium salts, which may reduce the bioavailability of OCS. It is recommended that their application be separated by at least 2 h [16]. OCSs also encountered pDDIs of significance level C with the following medications: diuretics (furosemide, hydrochlorothiazide, and indapamide), antidiabetics (metformin, insulin aspart, gliclazide, linagliptin, and empagliflozin), acetylsalicylic acid, warfarin, NSAIDs (meloxicam, naproxen, and ibuprofen), carbamazepine, phenobarbital, verapamil, and empagliflozin. The mechanisms and recommendations are available in Supplement 1.

Muscarinic receptor antagonists (MRAs)

The highest level of interactions these drugs encounter is X, either between each other or with antihistamines (bilastine, fexofenadine, loratadine, levocetirizine). In both cases, the mechanism of these interactions is an additive anticholinergic effect. This type of interaction is more significant with LAMAs than with short-acting muscarinic antagonists (SAMAs). Although these are inhalation drugs with minimal systemic absorption, they can lead to anticholinergic effects, such as dry mouth, increased intraocular pressure, and urinary retention, especially when combined with other anticholinergics. The additive anticholinergic effect is particularly significant for patients who, in addition to SA, suffer from closed-angle glaucoma, prostate hyperplasia, or bladder neck obstruction. The use of LAMAs with systemic anticholinergic drugs is generally recommended [22]. MRAs also encountered interactions of level C restraint with diuretics and tramadol. The mechanisms and recommendations are available in Supplement 1.

Methylxanthines

The drug from this group used in our study was theophylline. It is important to note that theophylline is no longer recommended by the GINA guidelines for asthma management. However, in our cohort, some chronic patients had been prescribed theophylline in the past due to historical treatment practices and were unwilling to discontinue the therapy because they relied on it. Additionally, a subset of these patients had concomitant COPD, for which theophylline may still be prescribed. The highest level of interaction that theophylline encountered was C, with β2-agonists, β1-antagonists (nebivolol), levothyroxine, amiodarone, and diazepam. Interactions between theophylline and β2-agonists have been previously explained. Nebivolol can antagonize the bronchodilatory effect of theophylline. While nonselective β-blockers have the greatest potential for this interaction, even selective β-blockers can cause this effect, especially when they are administered at higher doses. Additionally, the undesirable cardiovascular and metabolic effects of theophylline, which are mediated by β-receptors, are reduced by the concurrent use of β-blockers [23, 24]. Thyroid status may affect theophylline metabolism, increasing it in hyperthyroidism patients and decreasing it in patients with hypothyroidism. Therefore, increasing the theophylline dose should be considered when initiating levothyroxine therapy. Thyroid status stabilization sometimes takes weeks to months, so theophylline blood concentration should be monitored throughout this period. The mechanism of the interaction between theophylline and amiodarone is not fully understood, but it is believed that amiodarone reduces the liver metabolism of theophylline. Additionally, amiodarone can lead to thyroid dysfunction, affecting the required therapeutic dose of theophylline. An isolated case described an 86-year-old patient on furosemide, digoxin, domperidone, and sustained-release theophylline who developed signs of theophylline toxicity after the amiodarone dose of 600 mg daily was initiated. The serum theophylline concentration nearly doubled from 16.8 to 35 mg/L. The toxicity completely disappeared when amiodarone was excluded from chronic therapy [25].

Leukotriene receptor antagonists

Leukotriene receptor antagonist used in this study was montelukast. No interactions involving montelukast were detected, which is consistent with previous findings. However, due to the reported various neuropsychiatric side effects of LTRAs, which are idiosyncratic in mechanism, special caution and monitoring for these side effects are recommended in clinical practice.

Limitations

This study has several limitations. The major limitation of the study is its retrospective design, which only allowed us to detect pDDIs through medical records, but not to directly identify clinically relevant DDIs or DDIs that resulted in actual patient harm. Another limitations are the small sample size and single-center design, which may limit the generalizability of findings. Additionally, single software used for pDDIs identification may not account for all possible interactions or individual patients factors. A prospective study investigating the correlation of ADEs, unplanned emergency visits and hospitalizations with clinically relevant DDIs in SA patients is currently in progress.

Conclusion

The prevalence of potential drug–drug interactions in patients with severe asthma receiving biological therapy is high. Their identification, prevention and resolution could contribute to optimizing therapy, maximizing its therapeutic effect and avoiding undesirable adverse events. These findings highlight the importance of integrating regular pDDIs assessments into clinical practice for patients with severe asthma. Comprehensive drug interaction software can aid in early detection and mitigation of pDDIs. Furthermore, multidisciplinary collaboration between pulmonologists, clinical pharmacists, and other healthcare professionals is essential for evaluating and managing complex medication regimens.

Abbreviations

ADE	Adverse Drug Effect
ATS	American Thoracic Society
BMI	Body Mass Index
COPD	Chronic Obstructive Pulmonary Disease
DDI	Drug-Drug Interaction
ECG	Electrocardiogram
ERS	European Respiratory Society
GINA	Global Initiative for Asthma
ICS	Inhaled Corticosteroid
LABA	Long-Acting β2 agonist
LAMA	Long-Acting Muscarinic Antagonist
LTRA	Leukotriene Receptor Antagonist
MRA	Muscarinic Receptor Antagonist
NSAID	Nonsteroidal Anti-Inflammatory Drug
OCS	Oral Corticosteroid
pDDIs	Potential Drug-Drug Interaction
SABA	Short-Acting β2 Agonist
SA	Severe Asthma
SHARP	Severe Heterogeneous Asthma Research Collaboration, Patient-Centered
SmPC	Summary of Product Characteristics
UHC	University Hospital Centre

Supplementary Information

The online version contains supplementary material available at https://doi.org/10.1186/s12890-025-03495-2.

Supplementary Material 1

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Author contributions
P.T. and M.M. designed the study; S.P.G. provided the data; P.T., M.M. and F.B. collected and analyzed the data; M.M. and P.T. wrote the manuscript; S.P.G. supervised the study.

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Data availability
The datasets used and analyzed in the current study are available from the corresponding author upon reasonable request.

Declarations

Ethics approval and consent to participate
This study was approved by the Ethics Committee of University Hospital Centre Zagreb and written informed consent was obtained from all patients.

Consent for publication
Not applicable.

Competing interests
The authors declare no competing interests.

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