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Review

Unraveling the Impact of Salbutamol Polytherapy: Clinically Relevant Drug Interactions

Lara Marques [1,2,3] and Nuno Vale [1,3,4,*]

[1] OncoPharma Research Group, Center for Health Technology and Services Research (CINTESIS), Rua Doutor Plácido da Costa, 4200-450 Porto, Portugal
[2] Faculty of Medicine, University of Coimbra, Azinhaga de Santa Comba, Celas, 3000-548 Coimbra, Portugal
[3] CINTESIS@RISE, Faculty of Medicine, University of Porto, Alameda Professor Hernâni Monteiro, 4200-319 Porto, Portugal
[4] Department of Community Medicine, Health Information and Decision (MEDCIDS), Faculty of Medicine, University of Porto, Rua Doutor Plácido da Costa, 4200-450 Porto, Portugal
* Correspondence: nunovale@med.up.pt; Tel.: +351-220-426-537

Abstract: The proper drug choice determines the treatment quality for a disease. The pharmacotherapeutic strategy for respiratory diseases often involves the combination of different drugs with different mechanisms of action. Salbutamol is a short-acting β2-agonist (SABA) used as a reliever in the treatment of asthma and is frequently paired with inhaled corticosteroids (ICS). Indeed, drug–drug interactions (DDI) receive special attention as they are some of the most common causes of adverse effects and can lead to increased morbidity and mortality. DDIs can occur in patients undergoing polytherapy at the pharmacokinetic (PK) or pharmacodynamic (PD) level. Given this, the interaction of salbutamol with other drugs has been extensively explored in terms of PD and PK since its introduction into the pharmaceutical market. To date, more than a thousand salbutamol interactions have been reported. Here, we propose to review some interactions of salbutamol with other drugs such as beta-blockers, anticholinergics, other classes of bronchodilators, corticosteroids, and others, and point out significant gaps in the knowledge of DDI.

Keywords: salbutamol; drug–drug interactions; pharmacokinetics; safety; adverse reactions; asthma; COPD; respiratory disorders

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1. Introduction

The process of prescribing a drug significantly impacts the effectiveness and quality of treatment. Clinicians are faced with factors such as dosage, administration route, contraindications, and adverse reactions. An ideal pharmacotherapeutic strategy must evaluate each of these elements, but it should also consider drug–drug interactions (DDIs), particularly in patients with a wide spectrum of comorbidities.

A DDI is defined as the interaction that occurs when two or more drugs interact with one other, influencing their effectiveness and/or toxicity. This interaction can be of a pharmacokinetic (PK) nature, resulting in an altered absorption, distribution, metabolization, or elimination, and, as a result, its bioavailability. The interaction can also be of a pharmacodynamic (PD) nature, which occurs when one drug produces agonistic or antagonistic effects on the other, altering the drugs' pharmacological effects [1,2]. The altered function of hepatic CYP P450 enzymes or drug transporters (for example, P-glycoproteins or anionic organic transporters) is the most commonly documented PK interaction, whereas PD drug combinations are frequently recognized in modifying the therapeutic outcome or amplifying unpleasant effects [3–6]. PD interactions, on the other hand, can also be classified according to the effect produced: synergistic, antagonistic, or additive [7,8]. The major criterion to distinguish them is the quantification of the additive effect through validated in vitro methods, such as the Bliss independence equation and the Unified Theory [9].

Remarkably, the management of respiratory disorders usually involves the administration of more than one drug, with different mechanisms of action [8]. For instance, salbutamol is one of the most often used medications for the relief and prevention of bronchoconstriction symptoms (Figure 1), which occurs in diseases such as asthma and chronic obstructive pulmonary disease (COPD). It is a short-acting β_2-agonist (SABA) with unique properties, and its kinetics vary depending on the formulation and the administration route.

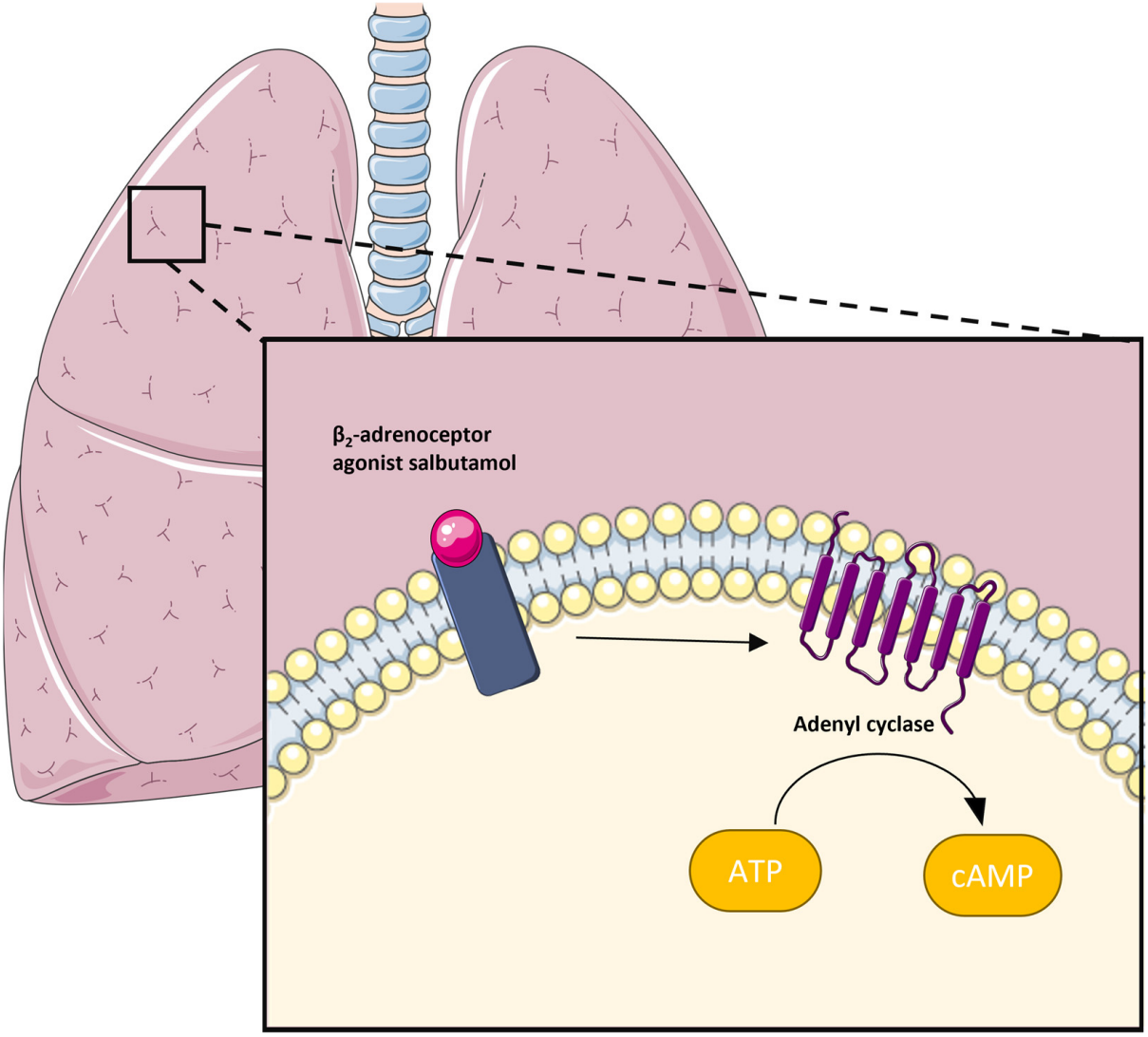
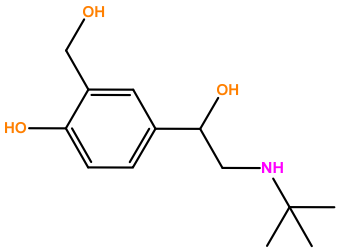


Figure 1. Mechanism of action of salbutamol in the relief and prevention of bronchoconstriction. Salbutamol reversibly binds to β_2-receptors, resulting in the conversion of cyclic AMP (cAMP). This then triggers a cascade of intracellular events, leading to inhibition of bronchial smooth muscle contraction, thereby promoting bronchodilation. Created with SMART—Servier Medical ART. Available online: https://smart.servier.com (accessed on 16 January 2023).

Overall, the mean peak plasma concentration is reached at 0.42 h and is approximately 3 ng/mL (Table 1) [10]. In the context of metabolism, this drug is mostly metabolized in the liver by sulfotransferase enzymes, although its metabolization has also been evidenced in the gastrointestinal tract and in the CYP P450 enzyme system [11–13]. This, in particular, is of relevance to the study of PK DDIs since, as previously stated, the interaction occurs by metabolizing enzyme alterations.

Table 1. ADME (Absorption, Distribution, Metabolism, and Excretion) profile and chemical structure of salbutamol.

	Absorption	Systemic levels are initially undetectable; after 2–3 h, a low plasma concentration is observed (C_{max}: 3 ng/mL and T_{max}: 0.42 h).
	Distribution	The volume of distribution is 156 ± 38 L.
	Metabolism	Mainly metabolized by sulfate conjugation (by sulfotransferase enzymes), but cytochrome P450 (CYP) enzymes are also involved in metabolism.
	Excretion	Salbutamol is excreted in the urine within 24 h ($t_{1/2}$: 2.7—5 h and CL: 272 ± 38 mL/min).

DDIs are some of the most prevalent causes of adverse reactions (ADRs) and are associated with increased mortality and hospitalization rates [14–19]. Polytherapy, in turn, is a major contributor to the occurrence of DDIs. Furthermore, the risk of DDIs increases with age owing to the greater debility of the organs to drugs. In addition, interestingly, polytherapy is very recurrent in elderly people. With this, we believe this topic is of extreme relevance for good clinical practice, which ensures the quality of patient care. It is imperative to have in-depth knowledge about potential DDIs, especially in conditions that require the administration of several drugs, such as respiratory diseases. Here, we review some of the significant DDIs of salbutamol and highlight the gaps that must be filled.

2. DDIs of Salbutamol

2.1. Interaction with Other SABAs/LABAs

SABA monotherapy, namely with salbutamol, is no longer recommended due to recent evidence of higher exacerbation risk and misuse. In 2019, the Global Initiative for Asthma (GINA) [20] reiterated that SABA-only treatment should not be prescribed to adults and adolescents, although its usage remains common among the asthma community [21]. Therefore, following GINA guidelines, salbutamol should be combined with other drugs. In fact, medium or low doses of inhaled corticosteroids with long-acting β_2-agonists (ICS-LABA) combined with as-needed SABA are an alternative therapy in the initial treatment of asthma. This therapeutic approach is indicated when patients experience troublesome asthma symptoms most days and maintenance and reliever therapy (MART) with ICS-formoterol (low dose) is not possible, or when patients reach disease stability and no exacerbations are recorded [20]. Additionally, these drugs, along with long-acting muscarinic antagonists (LAMAs), are also prescribed for the treatment of COPD. For this reason, the interaction between LABA, LAMA, and SABA, as well as their clinical benefit, has been discussed by a great number of authors in the literature. In a randomized double-blind crossover study of 12 patients with mild asthma, Smyth et al. [22] examined the pharmacological interaction of salmeterol and salbutamol and concluded that this combination benefited from an additive effect. In a combination between a partial agonist and a full agonist, the effectiveness of the full agonist may be reduced as the partial one occupies the receptors and acts as an antagonist. Although the reduction in the effectiveness of salbutamol was expected due to salmeterol's partial activity, the present clinical trial did not prove this theory. Thus, the fact that this interaction was not strong enough may be one of the reasons for not causing a significant reduction in the clinical effects of salbutamol. However, the authors argue that this theory should not be discarded in severe asthma events. Similar conclusions were drawn by Blom and Sommers [23]. Further, formoterol interacts with salbutamol by inducing a tolerance to the bronchodilating effect of salbutamol in asthmatic children [24].

Indacaterol, a novel ultra-LABA, is commonly used in COPD and asthma management. In specific circumstances, salbutamol may be combined with indacaterol. In contrast to other information that reports an increased risk of adverse effects when these two drugs are paired [25], Cazzola et al. [26], in a double-blinded, crossover, randomised, and controlled pilot trial, demonstrated that salbutamol can be used as a recue medication for bronchospasm relief, even when COPD patients are under regular treatment with indacaterol. The combination of salbutamol and tiotropium bromide (LAMA) results in a positive interaction. According to Jiang et al. [27], in patients with an acute exacerbation of COPD, this treatment improves their clinical condition and does not increase the risk of ADRs.

2.2. Interaction with Anticholinergics

Shortly after salbutamol was introduced to the pharmaceutical market, several studies evaluating the PDs of salbutamol combined with ipratropium bromide (IB) have emerged. For instance, Ducharme et al. [28] compared the effectiveness and safety of salbutamol paired with IB. The authors conducted a blind-randomized controlled trial in which the 298 participants were assigned to one of two interventional groups: nebulized salbutamol in frequent low doses or IB and salbutamol in hourly high doses. Among other conclusions, their findings do not support the addition of IB to salbutamol in children with mild or moderate asthma when compared to hourly doses of salbutamol. Pulmonary function was also not improved [28]. Similarly, the results of a clinical study conducted at the National Institute of Child Health, Karachi showed that polytherapy (IB + salbutamol nebulization) was not superior to monotherapy (salbutamol nebulization) in terms of clinical score improvements [28]. Nevertheless, the literature was initially not consistent on this issue. Other results from efficacy and safety comparison studies have revealed that when IB is combined with salbutamol at the onset of treatment, bronchodilation is maximized as much as 20 min earlier than if salbutamol is used alone [29,30]. The immediate peak flow rate (PFR) response to a mixture of salbutamol and IB has also been found to be improved [31–33], as well as lung function [34].

IB is an anticholinergic drug that inhibits the parasympathetic nervous system at the level of the airway, which then produces bronchodilation. Currently, this drug is paired with SABAs to treat children and adolescents with acute asthma exacerbation [20,35–37]. A single administration of IB is also a possible treatment option despite its slower onset of action and weaker bronchodilating effect [38]. Therefore, the combination of inhaled anticholinergics with SABAs may yield enhanced and prolonged bronchodilation and provide more effective treatment for acute asthma exacerbations.

A meta-analysis was conducted to assess the efficacy and safety of IB, in combination with salbutamol, in the treatment of asthma in children and adolescents [39]. Among 55 studies, it was concluded that this therapy combination significantly reduced the risk of hospital admission compared with salbutamol alone. Further, no significant differences in the risk of adverse events were observed between the IB and salbutamol group and the salbutamol alone group. According to the authors, this combination may be more effective than salbutamol alone for asthma treatment, especially in those suffering from severe and moderate asthma exacerbation. These findings strengthen GINA guidelines: there are more effective treatments than salbutamol monotherapy [20].

A large number of existing studies in the broader literature have examined the interaction of SABAs with IB [38,40]. For instance, a systematic investigation and meta-analysis on the efficacy of combination therapy and monotherapy in adults admitted to the emergency department with asthma exacerbations [40] demonstrated that the combination of drugs has advantages, as it reduces the number of hospitalizations and improves patients' lung functions. In addition, it was also found to be more effective in preventing hospitalizations in adults with severe asthma. On the other hand, patients undergoing polytherapy were more likely to experience adverse effects such as tremors and palpitations compared to

patients receiving SABA monotherapy. Evidently, these data allow us to conclude that such a combination is advantageous in the management of asthma.

Combination therapy of salbutamol and IB is also an option to treat COPD patients. However, the scientific community's position is ambiguous. A study aimed to investigate the potential of combining salbutamol with IB was performed on 103 patients with acute airflow obstruction (56 with asthma and 47 with COPD) [33]. In COPD patients, the two treatments were of equal benefit. Additionally, Moayyedi et al. [41] have drawn the same conclusions: no significant differences in the treatment duration and PD parameters were observed between polytherapy and monotherapy. On the other hand, Shrestha et al. [42] proved that the addition of IB to a standard beta-agonist COPD treatment decreased the required treatment time. The group of patients treated with salbutamol and IB were discharged from the emergency department (ED) an average of 91 min sooner than the control group. Likewise, following their run-through of this combination therapy features, Gordon et al. [42] report this therapeutic approach to be clinically beneficial.

Oxitropium bromide (OB) is another anticholinergic that is combined with salbutamol. However, there is no evidence that it remains a recurrent drug combination in clinical practice. Only a few studies were found in the 1980s. In a randomized, controlled, single-dose study of 12 asthmatic patients, Tukiainen and Salorinne [42] compared three treatments: salbutamol and OB in monotherapy, and the combination of the two drugs. With regard to the interaction of these drugs, a better response was observed. In acute severe asthma, these two paired drugs are also reported to produce improvements in lung function and reduce the need for hospitalizations [43].

2.3. Interaction with Corticosteroids

Since SABA monotherapy is contraindicated in asthma treatment, these drugs, including salbutamol, are now coupled with ICS. Their mechanism of action on airflow obstruction and airway hyperresponsiveness are different [44]. Whereas ICS, anti-inflammatory medications, inhibits the inflammatory response in the airways by reducing the release of eosinophils and macrophages, salbutamol acts on smooth muscle relaxation. In fact, this combination seeks to address the major limitation of bronchodilators since they do not act on chronic obstructive disease-associated inflammation. Thus, their co-administration allows the control of both bronchodilation and inflammation.

In addition, another goal of the SABAs/ICS combination is to circumvent the airway hyperresponsiveness to allergens and tolerance to the bronchoprotective effect promoted by regular treatment with salbutamol. Cockcroft et al. [44] have previously found that 2-week salbutamol treatment produced tolerance to the acute bronchoprotective effect of salbutamol against methacholine, a non-selective muscarinic receptor agonist that induces bronchoconstriction [45], and allergen. Due to this evidence, they have designed a study to evaluate the interaction of ICS and SABAs on the airway response to methacholine and allergens, where participants underwent treatment with salbutamol paired with budesonide. They have demonstrated that ICS produces beneficial effects on airway responsiveness to methacholine but fails to protect against the adverse effects of regular use of SABAs.

Salbutamol-budesonide constitutes one of the therapy modalities most advised by clinicians and, for this reason, has recently been the subject of extensive research. Phase 3 of MANDALA study [46] determined the efficacy of salbutamol in combination with budesonide in patients with moderate-to-severe asthma. Participants were randomly assigned to three groups: a fixed combination dose of 180 μg of salbutamol and 160 μg of budesonide (the highest dose group), a fixed combination dose of 180 μg of salbutamol and 80 μg of budesonide (the lowest dose group), and 180 μg of salbutamol as monotherapy. The results showed that the risk of severe asthma exacerbation was significantly lower in patients who received the high-dose combination than in the salbutamol-alone group. Nevertheless, the incidence of adverse effects was similar in the three experimental study groups [47]. Thus, based on the clinical outcomes, this combination is considered to be a good therapeutic approach in terms of preventing exacerbations, which is a problem associ-

ated with monotherapy with SABAs, as we recently reported. This is further confirmed by another study [48] whose authors evaluated the effect of salbutamol-budesonide treatment in patients with acute attack bronchial asthma, where the results [forced expiratory volume in the first second (FEV1), forced vital capacity (FVC), and peak expiratory flow (PEF)] demonstrated effectiveness in improving asthma symptoms and pulmonary function.

Despite considerable therapeutic outcomes, the interaction of salbutamol with budesonide results in changes in drug PK, namely in the alteration of several metabolic pathways. Quan–Jun et al. [49] developed research on this topic. Their purpose was to determine the distinct metabolic profile upon administration of these two drugs through metabolomic analysis.

Another pharmacotherapeutic alternative includes the combination of salbutamol and beclomethasone dipropionate, with significant improvements in lung function [50,51]. An in vitro study [52] in human bronchial fibroblast cultures to investigate the effects of beclomethasone dipropionate in combination with salbutamol determined that this interaction has an additive effect on the lung cells, as an increase in anti-remodeling activity was observed.

Several in vitro studies report a potential anti-inflammatory activity of β2-agonists, which may exert a complementary or synergistic effect on corticosteroids. It has been shown that in lung cells, β2-agonists promote glucocorticoid receptor (GR) translocation [52], suggesting an increase in the therapeutic effect of corticosteroids when administered concomitantly with β2-agonists. However, most of these findings have been obtained using airway cell lines stimulated with inflammatory stimuli. Otherwise, Profita et al. [52] conducted an ex vivo study to evaluate the ability of beclomethasone dipropionate and salbutamol to exert enhanced anti-inflammatory activity by using induced sputum cells (ISC) isolated from mild-to-moderate asthmatic patients. Their results showed a synergistic effect of salbutamol combined with ICS, supporting the strong value of combined therapy in asthma.

Co-administration of salbutamol and fluticasone is frequently used in the emergency treatment of children with moderate acute asthma since symptom relief is better experienced. However, PD parameters, such as PEF and pulse oximetry, are similar when salbutamol is given as monotherapy or in combination with this corticosteroid [53].

In addition, interaction with methylprednisolone, prednisolone, and prednisone have also been investigated. Taking salbutamol-methylprednisolone as a prophylactic medication improves lung function and prevents life-threatening bronchospasm after intubation, according to a randomized, prospective, placebo-controlled study involving 31 patients with partially reversible airway obstruction performed by Silvanius et al. [54]. Furthermore, data have also emerged suggesting that high doses of salbutamol and prednisolone may be beneficial in treating a rhinovirus-induced wheezing episode in children. Hurme et al. [55] aimed to study the short-term efficacy of SABAs with and without oral corticosteroids in the first acute rhinovirus-induced severe wheezing episode. This study enrolled patients from two clinical trials who received different treatments: regular treatment with high-dose nebulized salbutamol and treatment with inhaled salbutamol on-demand, and the outcomes analysed were the duration of hospitalization and later occurrence. The conclusions drawn from this study are based on a potential positive interaction between salbutamol and prednisolone, although this is not reflected in the duration of hospitalization (only in the occurrence of, and time to, relapse). However, as encouraged by the authors, prospective clinical studies should be done to confirm the beneficial effects of this mixture, as this study has some limitations.

Although it is a widely used therapeutic strategy, there are some ICS that should be prescribed with caution. Prednisone, for example, when concomitantly administered to salbutamol, potentiates the acute biochemical and cardiovascular effects that are reported by SABAs. This is highlighted in the study by Taylor et al. [56] where an increase in plasma potassium and glucose has been demonstrated. This, therefore, represents a concern about

the clinical significance of hypokalaemia caused by the interaction of these drugs. However, at the cardiovascular level, no changes were experienced.

2.4. Interaction with Magnesium Sulfate

Several studies suggest magnesium sulfate ($MgSO_4$) as an additional treatment option in asthmatic patients resistant to standard therapy [56]. Magnesium is recognized for its ability to inhibit smooth muscle contraction and the release of acetylcholine and histamine [57]. A double-blind randomized controlled study developed by Sarhan et al. [58] enrolled 30 patients with an acute attack of bronchial asthma. Evaluation of PD properties led to the conclusion that co-administration of salbutamol with nebulized $MgSO_4$ is beneficial in the treatment of asthma. In contrast, another clinical trial covering a larger number of patients concluded that the use of nebulized $MgSO_4$ with salbutamol is not advised in children with refractory acute asthma [59]. Schuh et al. [59] set out to investigate the effect of nebulized $MgSO_4$ in children with acute asthma. To this end, they developed an 8-year randomized double-blind parallel-group clinical trial in which participants were assigned to three groups with different treatments of salbutamol, either with $MgSO_4$ or placebo. After the clinical intervention, the expected decrease in hospitalization rate was not observed.

It can be stated that the beneficial effects of salbutamol-$MgSO_4$ interaction depend mainly on the route of administration. Another interesting study [60] aiming to analyse the effects of an intravenous infusion of salbutamol, combined with $MgSO_4$, in the treatment of paediatric asthma obtained satisfactory results in terms of improved therapeutic effects. There is evidence that relates paediatric asthma and immune system dysfunction, in particular, to the disturbance of the Th1/Th2 balance (with decreased Th1 and increased Th2) [61–63]. In this study, it was acknowledged that the interaction of these two drugs significantly decreases the levels of IL-4 and IL-6 (secreted by Th2) while contributing to the increase of IL-2 and IFN-γ levels (secreted by Th1), readjusting the Th1/Th2 balance. This inevitably leads to an improvement in the patients' clinical status and, therefore, the salbutamol-$MgSO_4$ combination is considered to offer therapeutic promise in asthma sufferers.

In moderate acute bronchiolitis, this medication shows satisfactory clinical outcomes as well, with an additive effect in improving the short-term effects, as reported by Kose et al. [57]. Further studies should be conducted on this subject.

2.5. Interaction with Xanthines

Numerous studies associating the use of salbutamol with several drugs from the xanthines pharmacological class first emerged in the 1980s. Theophylline is one such drug, whose mechanism of action is based on the relaxation of the muscles in the airways, and for this reason, its combination with salbutamol, a bronchodilator, is quite useful in the management of asthma as well as other respiratory diseases. Although synergism between these two agents has been shown to affect cyclic AMP concentrations in vitro, only additive effects have been demonstrated in vivo. In fact, the combined therapy with inhaled salbutamol and orally administered theophylline seems to cause beneficial effects in asthmatic patients. Research showed that in patients undergoing this type of therapy, symptom recurrence was rare and even PD parameters, such as FEV1 and FVC, were significantly improved [64].

As far as the management of COPD is concerned, a study [65] carried out on patients with stable COPD to determine the additive effect of oral theophylline demonstrated that, despite its bronchodilator effect, it does not promote the improvement of symptoms and, therefore, the authors consider that the usefulness of this therapeutic approach is questionable. These findings do not corroborate what was presented by Thomas et al. [66]. In their study, patients with stable COPD underwent a combination therapy of oral theophylline and inhaled salbutamol, where the two agents were found to interact in an additive manner

and, therefore, this translated into a significant increase in lung function compared to therapies with single drugs.

This therapy is even extended to the treatment of chronic bronchitis. Barclay et al. [67] performed a study to determine the effect of the interaction of salbutamol with theophylline at a maximum effective dose. They concluded that pulmonary function was improved after the administration of both drugs. However, we believe that the reduced number of patients (this study enrolled 12 patients) treated may bias these results.

Nevertheless, this interaction does not always result in beneficial effects. In fact, there is evidence that the co-administration of theophylline and salbutamol leads to the potentiation of salbutamol-induced hypokalaemia [68,69], as well as the enhancement of heart rate and supraventricular extrasystoles [70].

Theophylline-induced improvement in lung function when it is co-administered with salbutamol is well-reported in several studies. However, there are theories about the potential of theophylline to inhibit the pro-inflammatory activity of salbutamol and trigger its anti-inflammatory activity. The purpose of these studies was to achieve a similar effect observed in the interaction of SABAs and steroids. Charles et al. [71] investigated the in vitro interaction between theophylline and salbutamol on cytokine generation from human monocytes in order to clarify their anti-inflammatory effects. The combination of both drugs has shown interesting results. Thus, the effect of single administration of salbutamol on monocytes was based on the significant inhibition of TNF-α and, on the other hand, on the enhancement of IL-6 release. In turn, theophylline alone inhibited both TNF-α and IL-6 production. When these agents were combined, the inhibitory effect on TNF-α release was additive, as expected. However, theophylline was able to counteract the salbutamol-induced IL-6 release. In other words, this xanthine demonstrates a potential to suppress the undesirable pro-inflammatory effects of SABAs, at least in in vitro studies. Clinical confirmation could be the lever for the asthma management future, as it is universally recognized, currently, SABAs conjugated with ICS is the most common therapy in asthmatic patients.

With regard to PK interaction, salbutamol appears to alter the clearance of theophylline [71], which means that clinicians when prescribing this combined therapy should consider a dose readjustment of theophylline so as not to alter its pharmacological effect. These findings were previously reported in a study conducted by Amitai et al. [71] in which 10 subjects underwent a concomitant administration of theophylline and salbutamol. The results have demonstrated that such clearance is increased when intravenous (IV) salbutamol is administered simultaneously. Although no data support any of these theories, this phenomenon may be explained by the induction of microsomal oxidative enzymes (theophylline-metabolizing enzymes) or by increased hepatic blood flow [72]. However, interestingly, inhaled salbutamol does not alter theophylline kinetics.

Uniphyl, known as sustained-release theophylline, also has interactions with salbutamol. According to Rivington et al. [73], the addition of uniphyl to asthma therapy with salbutamol significantly improves pulmonary function and, consequently, asthma symptoms. In their study, it has been demonstrated that the co-administration of theophylline with inhaled salbutamol provides disease symptomatology stabilization for patients who have been prescribed high doses of ICS and use as-needed inhaled salbutamol. In addition, the authors claimed that theophylline and as-needed salbutamol or theophylline, as well as regular salbutamol therapy, provide superior clinical benefits than ICS-salbutamol therapy, supporting the settled idea that theophylline is an effective alternative add-on treatment for patients with moderate-to-severe asthma.

2.6. Interaction with Mucolytics

Mucolytics are drugs used to manage mucus hypersecretion, exerting their effect on the mucus layer lining the respiratory tract with the motive of enhancing its clearance [74]. Ambroxol belongs to the mucolytic drug class and has recently been under investigation for potential DDIs. Regarding ambroxol, there are no reported PK DDIs with salbutamol. In an open-label, single-dose, four-treatment, four-period crossover study, Wang et al. [75] aimed to investigate the potential DDI between salbutamol and ambroxol and the safety and tolerability of a new fixed-dose combination formulation (salbutamol 4 mg and ambroxol 15 mg) in healthy Chinese volunteers. Their results found no differences in salbutamol and ambroxol kinetics, and no serious adverse events were reported, with this new formulation being safe and well-tolerated. Later, in another clinical trial [76], the authors examined the PK and tolerability of salbutamol/ambroxol fixed-dose combination granules following single and multiple doses in healthy Chinese subjects. Once again, the authors proved ambroxol does not alter any PK parameters of salbutamol, or the other way around.

2.7. Interaction with β-Blockers

Salbutamol as a beta-agonist is more likely to interact with β-blockers due to their mechanisms of action [77]. In fact, this interaction has been widely explored in recent years despite agents' safety and risks not being clearly defined [78]. The first generation of non-selective β-blockers raised serious concerns about the increase in the number of severe bronchospasms and fatalities, which led to β-blockers being absolutely contraindicated in patients with respiratory problems [79].

In fact, in the 1980s, β-blockers such as propranolol and atenolol were used to antagonize the effects of salbutamol, mainly as antidotes for the toxicity caused by β-agonist overdosage [80]. Several studies have shown that labetalol, another β-blocker, significantly reduces FEV_1 and FVC [81], making it possible to associate this drug with the bronchoconstrictor effect.

Minton et al. [80] evaluated the interaction of propranolol and atenolol on the PD of salbutamol, concluding that both salbutamol-induced hypokalemic effects and cardiovascular effects were more effectively reversed by propranolol than by atenolol. The authors have explained these results based on the non-selectivity of propranolol, which is capable of acting on all types of adrenoceptors. This is unlike atenolol, which is cardioselective and acts preferentially on β_1 receptors. To be specific, selective β_1-blockers were developed to act preferentially on β_1-adrenoceptors, found predominantly in the heart [82]. However, its selectivity is not complete, so there is activity, albeit minimal, on β_2-adrenoceptors, which are found in the bronchial smooth muscle and are the main target of β-agonists [77].

In a meta-analysis conducted by Salpeter et al. [83], randomized blinded placebo-controlled trials that studied the effects of cardioselective β-blockers on FEV1, symptoms, and the use of inhaled β_2-agonists were selected. The authors concluded that cardioselective β-blockers do not produce significant adverse respiratory effects in patients with airway obstruction diseases. In particular, esmolol, a cardioselective β-blocker drug, does not produce detrimental effects on pulmonary function [83]. Indeed, esmolol may be preferred over propranolol in patients with asthma who require β-blocker treatment due to its short duration of action and relative lack of effect on airway resistance [78,84].

As far as COPD is concerned, the concomitant treatment of β-agonists and β-blockers does not pose severe risks [85]. However, there is not much consensus regarding the use of β-blockers in patients with COPD. The order of preference for beta-blocker drugs in the management of hypertension in patients with COPD would be labetalol, atenolol, metoprolol, and then propranolol [86].

In addition, β-blocker ophthalmic formulations (e.g., betaxolol and timolol) are also capable of producing adverse effects with regard to the induction of bronchoconstriction. Betaxolol is reported as an agent less likely to cause changes in the PD of patients taking β-agonists, such as salbutamol [87,88].

In short, if the co-administration of β-agonists and β-blockers is required, a cardioselective β-blocker is preferred. Some authors [78] have suggested starting with the lowest possible dosage of β-blocker and using esmolol as the first-line treatment. The patients' heart rate and bronchial reactions should be monitored.

2.8. Interaction with Antiepileptic Drugs

Patients with epilepsy have a greater tendency to develop asthma and, therefore, polytherapy is quite recurrent in these cases [89,90]. Nevertheless, some long-standing beliefs about salbutamol causing seizures in patients with epilepsy taking anti-asthma drugs have emerged as an obstacle in the treatment of these patients [91]. Although it has been proven that there is no direct relationship between the use of SABAs and the increased incidence of seizures [92], salbutamol seems to interact negatively with antiepileptic drugs.

The effect of salbutamol on the anticonvulsant efficacy of antiepileptic drugs (AEDs) (valproate, carbamazepine, phenytoin, and phenobarbital) in vivo was the subject of a study carried out by Swiąder et al. [90]. As a result, the authors observed a change in the antiepileptic activity of phenobarbital, with no effect on the other AEDs. However, the type of interaction was not explicit: the non-alteration of serum concentrations of phenobarbital allows inferring that this is not a PK interaction, but the PD interaction was not yet confirmed. Notwithstanding, AEDs are cytochrome P450 simulators, where the metabolization of several β2-adrenergic agonists, including salbutamol, takes place. So that, although salbutamol does not influence the absorption of AEDs, the latter can influence plasma concentrations of salbutamol. Further studies are needed.

2.9. Interaction with Antidepressant Drugs

Tricyclic antidepressants (TCAs) may interact with salbutamol. This class of drugs, which includes amitriptyline, doxepin, and nortriptyline, is used in the treatment of depression. Its therapeutic effect is based on increasing norepinephrine and serotonin concentrations in the synaptic cleft, contributing to its anti-depressant effect. Concomitant use of TCAs and SABAs, including salbutamol, may potentiate adverse cardiovascular effects, namely hypertension, palpitations, arrhythmias, and chest pain [19,93]. Therefore, a patient with asthma and depression should receive special care when prescribing the appropriate treatment. Another drug combination should be considered. Alternatively, if there is a need to prescribe one of these agents, the patient should undergo a 2-week discontinuation period [94]. Likewise, monoamine oxidase inhibitors (MAOIs), the first type of antidepressant drugs, also alter the PD of salbutamol, in terms of potentiating the adverse effects on the cardiovascular system [19].

2.10. Interaction with Antihistamines

Asthma and allergic rhinitis are interrelated diseases [95], so combining antihistamines and anti-asthmatic is often required. Antihistamines are medicines used to relieve symptoms of allergies by binding them to either H1 or H2 histamine receptors and inhibiting the effects of histamine in the body. As an example of DDI with antihistamines, ketotifen augments the bronchodilator effect of salbutamol by possibly optimizing β-adrenoceptor expressions [96]. In addition, cetirizine, an H1-antihistamine drug, is also reported to potentiate the bronchodilator effect of salbutamol [97]. However, in contrast to what one would expect, to our knowledge, this interaction has not been much explored.

2.11. Interaction with Antidiabetic Drugs

Asthma, as well as other disease conditions, and diabetes mellitus (DM) are often associated due to low-grade systemic inflammation and the use of asthma drugs. In fact, the coexistence of these conditions may favour the worsening of asthma symptoms and the lack of glycaemic control [98]. Salbutamol, by interacting with blood glucose control, results in hyperglycemia. Rosiglitazone, an insulin sensitizer, may positively interact pharmacodynamically with salbutamol, in particular on airway smooth muscle

responsiveness [99,100]. The study conducted by Fogli et al. [99] aimed to investigate whether the peroxisome-proliferator-activated receptor (PPAR)γ agonist rosiglitazone modulated salbutamol-induced β2-adrenoceptor desensitization in vivo and in vitro, and their results support the therapeutic potential of this combination in COPD. Therefore, when these drugs are co-administered, a close clinical monitoring of glycaemic control is recommended [101].

2.12. Interaction with COVID-19 Drugs

With the emergence of the SARS-CoV-2 virus, several issues have been raised about asthmatics' susceptibility to COVID-19. To date, most studies looking for a relationship between the two diseases have found no increased risk of COVID-19 severity in people with asthma [102]. In fact, there are no indications that asthma is a risk factor for the development of COVID-19. Conversely, COVID-19 also does not increase the risk of asthma exacerbations [103].

Therefore, at the beginning of the pandemic, several studies have focused on determining whether COVID-19 medications are safe to use in asthmatic patients infected with SARS-CoV-2. Current guidelines recommend that asthma control medication should be maintained [102]. Regarding salbutamol, most drug interaction studies have found no negative interactions with COVID-19 drugs. For example, Azanza et al. [104] developed a list of drugs that are contraindicated or should be used with or without precautions when Paxlovid, an oral antiviral (nirmatrelvir plus ritonavir), is administered. Salbutamol, like olodaterol and terbutaline, does not pose a risk of interaction with this drug and can therefore be used without any precautions, unlike salmeterol, in which its use is contraindicated. In a similar study, Brandariz–Nuñez et al. [104] characterized potential DDIs in COVID-19 patients treated with lopinavir/ritonavir. The authors recommend salbutamol in place of salmeterol since this drug is contraindicated due to its high risk of cardiovascular toxicity, tachycardia, and ventricular arrhythmia.

Furthermore, another study conducted at the University Hospital of Heraklion in Greece focused on assessing the prevalence and clinical outcome of potential DDIs in patients with COVID-19 [104]. Salbutamol was one of the drugs identified for interacting, at the PD level, with levofloxacin, quetiapine, escitalopram fluoxetine, and bisoprolol. In particular, the salbutamol-bisoprolol combination revealed an increased risk of acute bronchospasm, whereas the other drugs demonstrated an increase in the interval between the contraction and relaxation of the heart. These recent studies are extremely relevant for determining the types of DDIs that exist and helping clinicians to prescribe the most effective polytherapy.

2.13. Interaction with Diuretics

Diuretics are also reported as potential salbutamol interactors, as the concomitant use of both agents may lead to electrocardiographic (ECG) changes and/or hypokalaemia (low-serum potassium levels) [105–108]. In elderly people, this interaction may be potentiated, so caution should be taken when combining salbutamol with potassium-lowering drugs [105]. This interaction may occur due to the antagonism between these drugs since one of the adverse metabolic effects is the enhancement of potassium concentration (hyperkalaemia). According to a 12-month retrospective study of hospitalized paediatric patients [107], and after a total of 1500 prescriptions were reviewed, salbutamol with furosemide presented a moderate interaction, which means that this polytherapy should be monitored in order to identify potential negative effects.

Furthermore, combination therapy of salbutamol with furosemide is considered a promising therapy in COPD treatment. Saba et al. [106] compared the effect of this combined therapy with a single therapy in COPD patients. With the assessment of spirometric parameters (FEV1, FVC), the authors validated the salbutamol–furosemide therapy as a viable option in the treatment of patients with COPD. Further information needs to be elucidated, namely the type of interaction as well as the optimization of drug doses.

2.14. Other Interactions

Additionally, other drugs from other classes can be listed as interactors with salbutamol (Table 2).

Table 2. List of other potential salbutamol interactions recorded: drug, with the respective class, effect, and level of interaction are described.

Drug	Drug Class	Effect	Interaction Level	Reference
Dextromethorphan	Antitussive	More effective antitussive action	L	[109–111]
Sodium cromoglycate	Mast cell stabilizer	Better control of asthma symptoms	M	[111,112]
Nedocromil sodium	Benzopyrone	Decreased excretion rate of salbutamol	M	[111,113,114]
Benazepril	Antiseptic	No interaction	L	[111,115]
Glycyrrhizin	Saponin	Enhancement of anti-inflammatory effects	L	[111,116]
Cilomilast Roflumilast Ensifentrine	Phosphodiesterase inhibitors	No relevant PK interactions	L	[111,117–121]
Nifedipine Tiapamil	Calcium channel blockers	Increased heart rate; normal lung function	L	[111,122,123]
Phenylephrine	Nasal decongestant	Hypokalemia	M	[111,124]
Digoxin	Digitalis glycosides	Decreased digoxin serum levels	M	[111,113]
Gentamicin	Aminoglycoside Antibiotic	QT prolongation	M	[111,125]
Azithromycin	Macrolide antibiotic	QT prolongation	M	[111,125]
Chloroquine	Antimalarial	QT prolongation	M	[111,125]
Promethazine	Phenothiazine		M	[111,126]

Interaction level: L (low)—minimal risk of additional clinical effects; M (moderate)—increased risk of additional clinical effects; the combination should be avoided and only used in specific circumstances, under medical observation.

3. Pharmacogenetics Considerations in DDI of Salbutamol

The success of a treatment is largely pronounced by genetic factors. Clinicians must consider the inter-individual heterogeneity in response to a given drug in order to prescribe a rational strategy that maximizes efficacy with minimal adverse effects [127,128]. The advancement of precision medicine has benefitted from the emerging era of pharmacogenomics, with insights into how our DNA can influence the drug response [129].

Over the past few years, multiple genome-wide association studies (GWASs) and candidate gene studies have reported several polymorphisms in the β_2-adrenergic receptor (ADRB2) gene (chromosome 5q31-q32), as well as others, such as CLOCK, ARG1, and ARG2. As the main target of β_2-agonists, ADRB2 polymorphisms have been widely studied in relation to drug responses, namely their therapeutic effect and adverse reactions [127,130]. Among the numerous recognized genetic variations, this gene is characterized as having two of the most studied non-synonymous variants, rs1042713 and rs1042714, which lead to amino acid substitution at Position 16—from arginine to glycine—and at Position 27—from glutamate to glutamine, respectively [131,132]. The connection between these genetic variants and the decreased bronchodilation response (BDR) is debatable. While some studies do not demonstrate evidence to support a link between polymorphisms and BDR, others have found associations with BDR and even asthma exacerbations [128,133].

Individuals with the Glu-27 form of the receptor yields greater resistance to β_2-agonists-induced downregulation. Therefore, this polymorphism prevents the hypersensitivity associated with the recurrent use of β_2-agonists [132,134]. Further investigations at Locus 16 (Arg-16) [135–138] highlight the contrasts between regular salbutamol and "as-required" therapy. Subjects with an Arg-16 genotype have demonstrated clinical improvements and less risk of exacerbation, with regular salbutamol intake compared with "as-required" therapy. These findings do not apply to the wild-type (Gly-16) group. Conversely, in a retrospective analysis study [139], Arg-16 subjects developed airway hyperresponsiveness to regular fenoterol, which may be extrapolated to salbutamol as well. Based on this evidence, although ADRB2 genotyping cannot be used as a predictor of "responders" or "non-responders" to therapy, Robin Taylor [135] encourages its use as a marker for patients whose asthma symptoms worsen with frequent β_2-agonists treatment. Even so, a recent meta-analysis [130] to scrutinize the associations between salbutamol response and ADRB2 variants underlined that such topics lack sustained scientific basis, owing to the research design, which does not include heterogeneity of subjects.

Studies of other genes in the ADRB2 pathway are limited. Nevertheless, the interaction between ADRB2 and nitrosylation pathway genes has been reported to influence the response to salbutamol therapy in some cohorts. This pathway indirectly regulates ADRB2. S-nitrosoglutathione (GSNO) reductase metabolizes GSNO, which regulates GRK2 by nitrosylation. As intracellular GSNO decreases, so does GRK2 activity, namely at the level of ADRB2 phosphorylation and desentization. Therefore, polymorphisms in intronic regions of GSNO reductase (GNSOR) have been identified. Some authors have shown that intronic polymorphisms in Gly16 subjects lead to a lesser effectiveness of salbutamol [140–142]. For instance, Choudhry et al. [143] investigated the association between GSNOR gene variants and asthma in Puerto Rican and Mexican individuals, as well as the pharmacogenetic interaction between GSNOR and ADRB2. The results revealed that GSNOR gene polymorphisms reduce bronchodilator response, and yet interactions between the genetic variations of both genes influence salbutamol treatment response.

As a result of the prescription of ICS in the treatment of respiratory diseases, some scientists have focused on pharmacogenomics in response to ICS. Cazzola et al. [144] reviewed genetic variants in the corticosteroid pathway, associating them to ICS responsiveness and PK. Likewise, variability in the CRHR1 gene, which encodes the corticotropin-releasing hormone Receptor 1, which then triggers anti-inflammatory processes, which may also be linked [144,145]. Other genetic variants in STIP1 (encoding a heat shock protein that stimulates the glucocorticoid receptor) likely to alter ICS responsiveness [144,146]. Indeed, there are numerous genes with polymorphisms that might impact how an individual responds to treatment. However, difficulties in reproducing pharmacogenomic studies raise concerns regarding the credibility of these findings. ADRB2 polymorphisms may also impact the response to anticholinergic, possibly through intracellular cross-talk [147]. In agreement with these previous findings, Konno et al. [147] conducted a study in which they determined an association between polymorphisms and preferential BDR to β_2-agonists and anticholinergics in patients with COPD.

One of the inherent problems of these genetic association studies is the lack of heterogeneity. Most studies are conducted in the Caucasian population, expressing concern about the application of these findings to other ethnicities [127].

Therefore, pharmacogenomics proves to be an important tool to guide the patient towards the best treatment. Genetic variants, in particular, may play a more significant role in patients undergoing polytherapy. Hence, it is crucial to conduct complete studies of the human genome, applied to the patients' reality. Co-administration of multiple medicines is the pattern for the majority of patients. These pharmacogenomic studies need to be extended to drugs administered concomitantly.

4. Future Perspectives: The Need of PK DDI Studies

According to our review, the study of salbutamol DDIs is highly diversified and involves multiple drugs from different classes (Figure 2). The greatest interest tends to be in exploring the interaction of SABAs with ICS and anticholinergics, as these medicines are frequently combined. As we previously stated, the GINA guidelines encourage the use of ICS with as-needed SABAs as a feasible choice for asthma therapy. As we observed, in addition to anticholinergics and ICS, β-blockers and xanthines are also the subject of interaction studies with salbutamol.

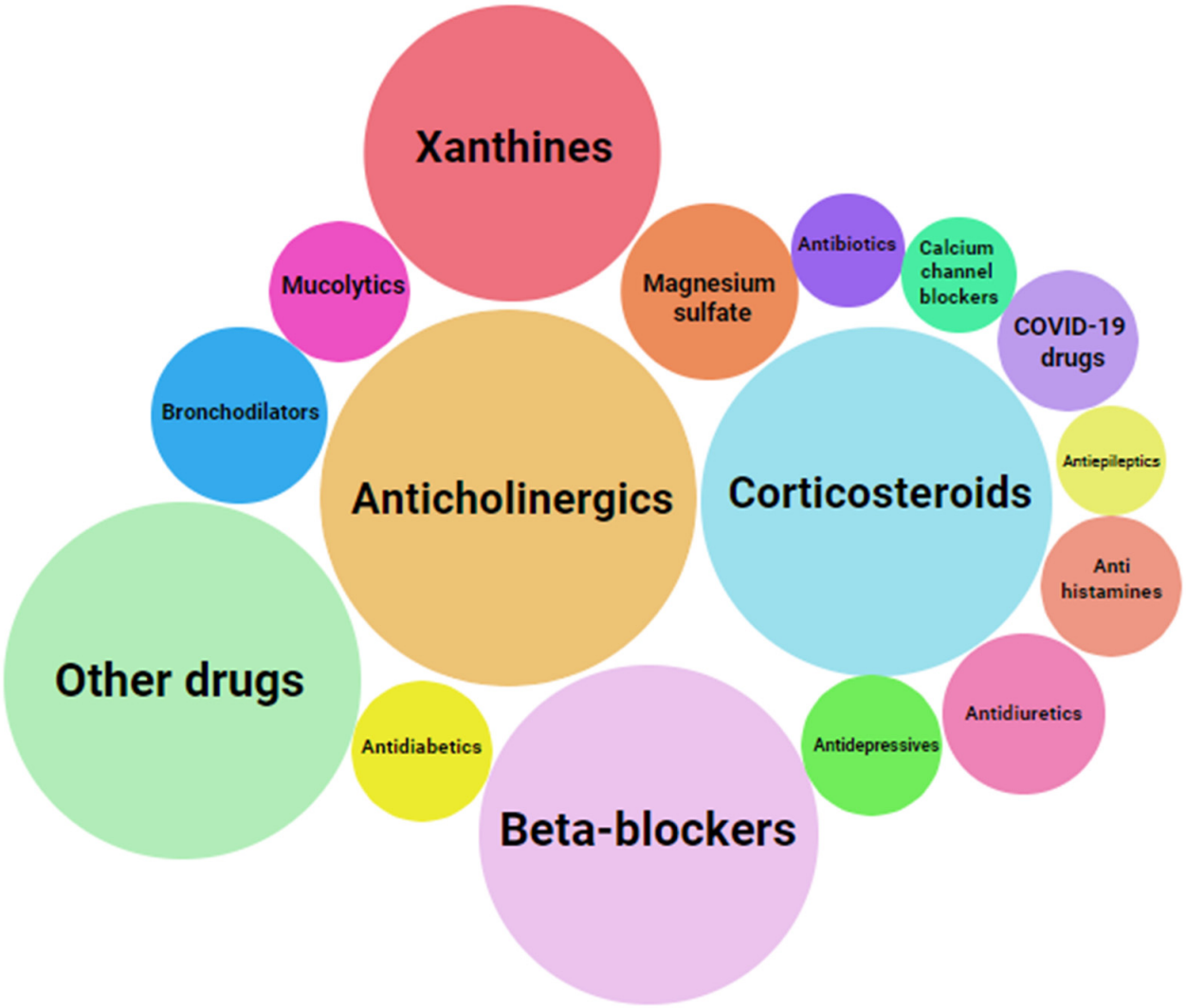


Figure 2. Distribution of DDIs research considering different drug classes. Other drugs such as phosphodiesterase inhibitors, saponins, and anti-tussives, although their interaction with salbutamol has been studied, have all been grouped together.

The study of PD interaction is extremely relevant to the knowledge of the therapeutic and adverse effects that might occur when two or more drugs interact. In fact, clinical practice is focused on the improvement of patients' health status without additional consequences. In other words, the prescription of polytherapy is mostly based on PD interactions.

Nevertheless, more than 50% of the documented drug interactions are due to PK interactions, mainly at the metabolism level. When two or more drugs are co-administered, metabolic pathways may change or are otherwise directed. In addition, the absorption,

distribution, and elimination of the drug may be as well altered. Consequently, the drug's bioavailability is changed, ultimately affecting the therapeutic efficacy.

Very few studies on PK interactions have been reported. The present study highlights the need of a growing corpus of research on this field. Thus, clarifying what happens to the drug in polytherapy regimens helps to determine its efficacy when it is not taken alone and provides insight into whether dose adjustment is required. In short, pharmacometrics can no longer be considered in its classical form. It must, therefore, include the investigation of potential PK DDIs. This is very much the key component in future attempts to obtain an even more complete drug profile.

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