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Review Article

Why use long acting bronchodilators in chronic obstructive lung diseases? An extensive review on formoterol and salmeterol

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ABSTRACT

Long-acting β_2-adrenoceptor agonists, formoterol and salmeterol, represent a milestone in the treatments of chronic obstructive lung diseases. Although no specific indications concerning the choice of one molecule rather than another are provided by asthma and COPD guidelines, they present different pharmacological properties resulting in distinct clinical employment possibilities. In particular, salmeterol has a low intrinsic efficacy working as a partial receptor agonist, while formoterol is a full agonist with high intrinsic efficacy. From a clinical perspective, in the presence of low β_2-adrenoceptors availability, like in inflamed airways, a full agonist can maintain its bronchodilatory and non-smooth muscle activities while a partial agonist may be less effective. Furthermore, formoterol presents a faster onset of action than salmeterol. This phenomenon, combined with the molecule safety profile, leads to a prompt amelioration of the symptoms, and allows using this drug in asthma as an "as needed" treatment in patients already on regular treatment. The fast onset of action and the full agonism of formoterol need to be considered in order to select the best pharmacological treatment of asthma and COPD.

1. Introduction

Since the 1990s, Long-Acting β_2-adrenoceptor Agonists (LABAs) have been considered as milestones in the treatment of Chronic Obstructive Pulmonary Disease (COPD) and asthma. In COPD, LABAs, formoterol and salmeterol, reduce airways obstruction, lung hyperinflation and exacerbations, improve exercise tolerance, ameliorate symptoms, enhance health-related quality of life [1–4] and offer a potential survival advantage [5]. In asthma, where LABAs are strictly recommended to be used in association with inhaled corticosteroids (ICS) [6], as results of the above mentioned effects, LABAs increase the probability of achieving disease control with a lower concomitant exposure to ICS as compared to ICS alone [7,8]. Although no specific indications concerning the choice between salmeterol or formoterol are provided by COPD and asthma guidelines [4,9], these drugs differ in pharmacokinetics (what the body does to the drug) and pharmacodynamics (what the drug does to the body).

The aim of this paper is to review formoterol and salmeterol pharmacological properties and related different clinical employment possibilities.

2. Formoterol and salmeterol: differences in pharmacokinetics

A great advantage of inhalation drug therapy is the possibility to reach directly the target organ, reducing the systemic drug exposure and related adverse effects. LABAs have well-known pharmacological and clinical profiles with a few but essential differences [10,11] (Table 1).

The bronchodilatory effect of a LABA is a function of drug concentration at the bronchial smooth muscle cells and the degree of activation of the β_2-adrenoceptor. The onset and duration of bronchodilation are influenced by the time it takes for an inhaled LABA to achieve and maintain effective concentration at the receptor site [11]; both of these are related to physicochemical characteristics of the LABAs. Differences in physicochemical properties between formoterol and salmeterol may explain faster onset of action of formoterol [12]. Relatively high water solubility and moderate lipophilicity ensure rapid access of inhaled formoterol to the β_2-adrenoceptor on bronchial smooth muscle cells and rapid

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Table 1
Effects of LABAs.

	Stimulating effect	Inhibitory effect
Airway smooth muscle		
Relaxation	+	
Proliferation		+
Mucociliary clearance	+	
Ciliary beat frequency	+	
Alveolar fluid clearance	+	
Neutrophil adhesion		+
Neutrophil chemotaxis		+
Neutrophil apoptosis	+	
Eosinophil apoptosis		+
Neutrophil activation		+
Neutrophil ROS production		+
Eosinophil ROS production		+
Mast cell mediator release		+
Eosinophil mediator release		+
T-lymphocyte cytokine release		+

bronchodilation. In contrast, low water solubility and high lipophilicity of salmeterol results in its slower onset of action [12]. Additionally, the uptake of formoterol by airway smooth muscle cells is dependent on organic cation transporter 3 (OCT3); in contrast, the uptake of non-charged lipophilic salmeterol is independent of OCTs transporters. Importantly, corticosteroids inhibit OCT3 and by that may increase the presence of formoterol at cell membrane β_2-adrenoceptor thus potentiating formoterol effect [13,14].

Lipophilic characteristics of salmeterol and formoterol also explain prolonged duration of bronchodilation by these drugs [12], with a somewhat shorter duration of action for fomoterol than salmeterol in *ex vivo* experiments in small airways [12], however with no difference in duration of effect shown in a clinical study in asthmatic patients [15]. The lipophilicity of both formoterol and salmeterol is sufficient to allow them to easily enter and be stored in cell membranes, making a depot from which drugs are available to β_2-adrenoceptors on bronchial smooth muscle cells for a prolonged period of time [11]. This is in contrast to short-acting β_2-adrenoceptor agonists (such as salbutamol and terbutaline) which after inhalation are cleared from the tissue more rapidly due to their high water solubility. This was clearly demonstrated by Jeppsson et al. who showed that the relaxing effect of formoterol and salmeterol on isolated guinea pig tracheal smooth muscle pre-contracted with carbachol was less readily reversed by washing procedure than that of hydrophilic and short-acting salbutamol [16].

3. Formoterol and salmeterol: differences in pharmacodynamics

3.1. Bronchodilatory effects

The β_2-adrenoceptor agonists are the most effective bronchodilators because they are functional antagonists of airway smooth muscle contraction irrespective of the constricting stimulus. The β_2-adrenoceptors are distributed along the entire bronchial tree, in both large and small airways. Smooth-muscle relaxation results from coupling of the β_2-adrenoceptor, through the stimulatory Gs protein alpha subunit to adenylate cyclase in airway smooth muscle, which in turn increases the concentration of intracellular cyclic adenosine monophosphate (cAMP) [17]. cAMP acts through an intracellular network that is primarily related to protein kinase A (PKA) that leads to a down regulation or an up regulation of different molecular pathways that have smooth muscle relaxation as the principal endpoint. These mechanisms are complex [18,19], and some aspects are not completely understood in airway cells [19]. However, it is known that stimulation of β2-adrenoceptor by structurally different agonists results in stabilisation of different active states of the receptor and this may lead to activation of several different signalling pathways [20], including activation of inhibitory Gi protein which opposes Gs activation [21,22], resulting in decreased cAMP accumulation and the impairment of β2-adrenoceptor-mediated bronchodilation [23]. Thus, the degree of β2-adrenoceptor activation by structurally different agonists may be determined by the extent of Gi activation [22]. The differences in molecular structure of formoterol and salmeterol are responsible for differences in the interaction of these drugs with β_2-adrenoceptor and therefore differences in intrinsic efficacy that is high for formoterol and low for salmeterol (Fig. 1).

Formoterol binds to β_2-adrenoceptor with high affinity and triggers effective signal transduction while salmeterol does not lead to full signal transduction and therefore salmeterol is a partial agonist, i.e. has a lower intrinsic efficacy, compared to formoterol.

This explains higher extent of maximal dilation by formoterol of severely contracted tracheobronchial smooth muscle than that by salmeterol (independent of concentration applied) shown in isolated guinea pig trachea and in human bronchus [23,24]. Significantly, the differences in intrinsic efficacy between formoterol and salmeterol have implications for the bronchodilatory effects of these LABAs under inflammatory conditions. Accordingly, while a full agonist can show a full effect both in normal airway smooth muscles (where there is a reserve of β_2-adrenoceptors) and in inflamed tissues (where the number of fully functioning β_2-adrenoceptors may be limited), partial agonist may be not able to reach full effects in inflamed tissue, disregarded of how high doses are used. Adner et al. [25] showed that the maximal relaxation of carbachol-contracted mouse trachea segment by salmeterol was decreased by 40% by 4-day pretreatment with proinflammatory cytokines (TNFα and IL-1β) while this decrease was only 16% for formoterol. One likely mechanism involved is the cytokine-induced increased expression of cyclooxygenase (COX-2) leading to heterologous desensitisation of β_2-adrenoceptor impairing to a greater extent effects of a partial agonist, salmeterol, than those of full agonist, formoterol. Another possible mechanism is that receptor stimulation by salmeterol activates Gi protein to a greater extent, and that pro-inflammatory cytokines – through the up-regulation of the Gi signalling [26] – attenuate salmeterol responses to a greater extent than responses of formoterol. Interestingly, the concomitant treatment with a glucocorticosteroid, budesonide, blocked the cytokine-induced increased expression of COX-2 and prevented the

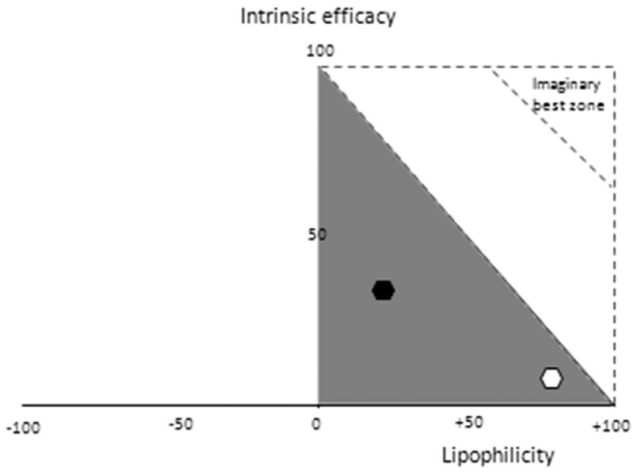

Fig. 1. The bronchodilator gray playing field. The black hexagon represents formoterol and the white hexagon salmeterol. The imaginary zone (upper right triangle) identifies the drugs with high power expressed by intrinsic efficacy and duration of action underline by lipophilicity; of course, the onset of action is related to water solubility which is not presented in this figure. However, it's worth considering that while lipophilicity per se does not guarantee a long duration of action, on the other hand may have several disadvantages too.

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cytokines-induced impairment of tracheal relaxation and β_2 adrenoceptor/cAMP signalling for formoterol but not for salmeterol [25]. This suggests differences between these drugs in coupling/activation of β_2-adrenoceptor and/or signal transduction from this receptor. The possible explanation of no improvement of salmeterol responses by budesonide is a greater involvement of the inhibitory Gi protein signalling from the receptor stimulated with salmeterol than with formoterol and earlier described insensitivity of Gi protein to glucocorticosteroid treatment [27]. From the clinical perspective, these results suggest that the combined treatment with budesonide/formoterol could guarantee an efficient bronchodilation during periods with increased inflammation such as during asthma exacerbations, whereas effects of combination treatment with a glucocorticosteroid and salmeterol may be less efficient during inflammation.

3.2. Non-bronchodilatory effects

3.2.1. Mucociliary clearance

The β_2-adrenoceptor agonists may also have clinically relevant effects not related to bronchodilation per se. It is well known that β_2-adrenoceptor agonists increase ciliary beat frequency and stimulate mucus clearance [28–30]. The ciliary beat frequency was shown to be significantly reduced in nasal epithelium samples from subjects with COPD and subjects with pneumonia compared to healthy subjects while salmeterol applied *ex vivo* in these samples increased ciliary beat frequency in concentration-dependent manner in all subjects [31]. Recently, single inhaled dose of formoterol (12 μg) was shown to enhance mucus clearance in mild/moderate COPD patients compared to placebo and tiotropium (18 μg) or salbutamol (200 μg) [32]. Furthermore, in that study treatment for 14 days with tiotropium retarded mucus clearance while this was not observed with formoterol suggesting that formoterol sustains its mucociliary effect during 14 days treatment. It is clear that to increase the mucociliary clearance by β_2-adrenoceptor agonists may enhance airway clearance of ICS when these drugs are used in combination. This has a greater impact on highly lipophilic ICS such as fluticasone propionate, which requires hours to be dissolved in epithelial lining fluid, as compared to budesonide which dissolves in a few minutes [33,34].

3.2.2. Airway inflammation and remodelling

Both formoterol and salmeterol were shown *in vitro* to exert anti-inflammatory effects in airway smooth muscles cells. These effects are additive to, or even synergise with the anti-inflammatory effects of glucocorticosteroids [35–38] and include suppression of inflammatory responses induced by viral exposure [39–41] and anti-remodelling effects. Airway remodelling is an inherent component of asthma and includes increased numbers of airway smooth muscle cells, goblet cell hyperplasia and fibrotic rearrangement of the airway extracellular matrix. The β_2-adrenoceptor agonists have potential to decrease the enhanced proliferation of airway smooth muscle cells via β_2-adrenoceptor-dependent mechanism as shown for salmeterol and salbutamol [42]. Roth et al. [43] demonstrated that even very low concentrations of formoterol (10^{-12}–10^{-8} M) effectively inhibited serum-stimulated proliferation of airway smooth muscle cells *in vitro*. Activation of lung fibroblasts is thought to play a key role in the fibrotic reorganisation of the extracellular matrix in the airways and lung in asthma and COPD. Increased synthesis of specific collagens and proteoglycans by myofibroblats is a part of this process. β_2-adrenoceptor agonists may attenuate these fibrotic alterations [44]. Kelly et al. have shown that in subject with asthma allergen inhalation results in an increase in the numbers of submucosal myofibroblasts but that formoterol in combination with budesonide (but not budesonide monotherapy), significantly counteracted this increase [45]. Todorova et al. [46] demonstrated the synergistic inhibition of serum-stimulated proteoglycan production by formoterol and budesonide in human lung fibroblast cell line. Also the study in primary fibroblasts established from central bronchial biopsies from asthmatic patients, has shown that formoterol in combination with budesonide has a potential to counteract enhanced collagen production and normalise the production of small proteoglycans which may affect collagen structure and deposition [47].

The lung airways harbour a cellular network involved in inflammatory responses during COPD evolution. In particular neutrophils are few in the sub-epithelial area, but largely represented in the epithelium and in the bronchial glands [48,49] as well as in the airway lumen. Bronchoalveolar lavage fluid and induced sputum from patients with COPD contain increased numbers of neutrophils, which correlate with concentrations of the neutrophil chemoattractant, interleukin (IL)-8, and other inflammatory mediators, such as leukotriene B4 (LTB4) which plays a central role in neutrophil activation and migration [48,50,51]. β_2-adrenoceptors are present on neutrophils, [52] and data published indicate that salmeterol and formoterol increase cAMP in neutrophils and therefore inhibit their adhesion, accumulation and activation [53]. This should translate into the reduction of the number of neutrophils and decrease of their activation in the airway tissue and airway lumen. Indeed, formoterol therapy significantly reduced neutrophil numbers and neutrophil chemoattractant IL-8 in sputum of severe asthmatics compared to placebo [54]. Salmeterol was also reported to decrease IL-8 concentration in bronchoalveolar lavage fluid in patients with asthma. These effects of LABA may compensate for relative resistance of neutrophil inflammation to corticosteroids in COPD and severe asthma. On the other hand, corticosteroids may also compensate for shortcomings of LABA. For example, LABAs (and short-acting β_2-adreneoceptor agonists) were shown to induce *in vitro* a prolong survival of eosinophils, inhibiting their apoptosis, a potentially harmful mechanism in asthma, that however, seems to be totally reversed by corticosteroids [55]. Indeed, Kelly et al. [45] have shown that in asthmatic subjects, allergen-induced sputum eosinophilia was reduced by the combination of inhaled budesonide and formoterol treatment even to a greater extent than by budesonide alone.

Both COPD and severe asthma are characterised by enhanced oxidative stress and production of reactive oxygen species (ROS) by inflammatory and structural airway cells, aggravating inflammation and causing airway tissue injury and remodelling. ROS can also decrease the number and function of β_2-adrenoceptors in lung tissue, and impair steroid receptor function. Formoterol and salmeterol were shown to reduce ROS generation in neutrophils and eosinophils *in vitro* and *in vivo* [56–63] and in cooperation with corticosteroids [64]. Principally, leukocytes have a relatively low number of β_2 adrenoceptors which may be further decreased under inflammatory conditions and oxidative stress. Therefore partial agonists, such as salmeterol, may be not effective or may not be able to reach full effects in these cells disregarded of how high doses are used. Indeed, formoterol in a concentration-dependent manner inhibited ROS generation (induced by LTB4) in guinea pig peritoneal eosinophils while salmeterol had no effect at any concentrations and pre-incubation times investigated [56]. Significantly, in that study, salmeterol competitively antagonised inhibition exerted by formoterol; so salmeterol acted as an antagonist in eosinophils. Recently, Rossios et al [68] have shown that oxidative stress reduced the level of β_2-adrenoceptors in the cell membrane of mononuclear cells and decreased salmeterol-induced cAMP production while it did not affect significantly cAMP induced by formoterol. Formoterol also restored corticosteroid sensitivity reduced in these cells by oxidative stress whereas salmeterol was less effective even at 100 times higher concentration. Furthermore, in Rossios et al study, although both formoterol (1 nM) and salmeterol (100 nM) reversed

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insensitivity to corticosteroid treatment in peripheral blood mononuclear cells (PBMCs) from subjects with severe asthma, only formoterol restored corticosteroid sensitivity in PBMCs from COPD subjects and increased significantly cAMP production in these cells. The authors concluded that, under conditions of high oxidative stress such as COPD, formoterol, combined with corticosteroids, should be more effective than salmeterol.

LABAs are often administered with ICS and it is now clear that both drug classes affect airway function at multiple levels, including an integrated effect on several cell types. LABAs and glucocorticosteroids were long thought to act in parallel at different cells, but now it is clear that they also work in concert at the same type of cells, in an additive or synergistic manner, or each alleviating the shortcomings of the other. The interaction between LABA and ICS is often synergistic and may even create a self-enhancing cycle at the level of β_2-adrenoceptor and glucocorticosteroid receptor expression and their signallinig pathways [65,66]. In many cells the effects of β_2-adrenoceptor agonists seem to involve glucocorticosteroid receptor. Eickelberg et al [67] demonstrated that β_2-adrenoceptor agonists are able to translocate glucocorticosteroid receptor to the cell nucleus. This has been observed *in vitro* with both salmeterol and formoterol in various human cells, such as lung fibroblasts [67], vascular smooth muscle cells [67] and airway smooth muscle cells [43]. However, it does not seem to occur in cultured human bronchial epithelial cells where neither formoterol nor salmeterol translocated glucocorticosteroid receptor [68]. On the other hand, Usmani et al [69] reported that in sputum epithelial cells (and macrophages), combination therapy with salmeterol and fluticasone propionate in asthmatics augmented nuclear localisation of glucocorticosteroid receptor compared to fluticasone alone. Essentially, both formoterol and salmeterol synergistically enhance glucocorticosteroid-dependent transcription in human airway epithelial and smooth muscle cells [60] which may be important to counteract insensitivity to glucocorticosteroids in severe asthma and COPD.

4. LABA and clinical management of chronic respiratory diseases

The prompt symptoms relief is one of the principal goals both in asthma and in COPD. In COPD, morning symptoms, including dyspnea and sputum production, affect quality of life and limit the ability to perform even simple activities. It is emerging that these symptoms are associated with increased risk of exacerbations and work absenteeism, suggesting that they have a more profound impact on patients than previously thought [70]. This makes rapid onset of action an essential characteristic for a bronchodilator also in COPD symptoms management. Recently, Cazzola et al evaluated the onset of effect of a single-dose of formoterol (9 μg) versus a single-dose of salmeterol (50 μg) in patients with moderate COPD in a multicentre, double-blind, double-dummy, placebo-controlled, three-way single-dose crossover study [71]. The increase in FEV1 at 5 min post-dose versus pre-dose was 7.2% for formoterol, 4.1% for salmeterol and 0.7% for placebo, and significantly greater for formoterol versus salmeterol (ratio of treatment effects: 1.030; 95% CI 1.008–1.052; $p = 0.009$). Moreover, the proportions of patients with ≥12% increase in FEV1 at 5 min post-dose were 23.1%, 9.2% and 6.4% for formoterol, salmeterol and placebo, respectively; this was significantly larger after formoterol than salmeterol ($p = 0.008$) or placebo ($p < 0.001$). The number of patients with adverse events as well as the frequency of adverse events were low, both with formoterol and salmeterol, and none of the adverse events fulfilled any criteria for a serious adverse event [71]. Another study of Cazzola et al explored whether the acute addition of an ICS influenced the fast bronchodilator response to formoterol in stable COPD [72]. The results demonstrated that over 60 min explored after a single dose of budesonide/formoterol (2 × 160/4.5 μg) or formoterol alone, both treatments induced a significant improvement over baseline at each time point investigated, however, mean increases in FEV1 were always higher after budesonide/formoterol than formoterol alone (for example, 50 ml higher 15 min after inhalation). The area under the FEV1 curve (AUC) after budesonide/formoterol was significantly larger than that after formoterol alone both during the first 15 min and the whole 60 min period explored. Both treatments induced a significant reduction in a dyspnea visual analogue scale (VAS) score but did not modify heart rate in a statistically significant manner. This study indicates that the addition of budesonide enhances the fast bronchodilatory action of formoterol without inducing systemic effects. [72].

Many COPD studies have evaluated the long-term effects of LABA and their combinations with ICS. Considering that bronchodilators are pivotal in the management of COPD symptoms, long-acting preparations being preferred when symptoms are persistent [4]. A recent meta-analysis by Cope et al compared the efficacy of long-acting bronchodilators in patients with moderate to severe COPD, in terms of lung function, health status, and dyspnoea [73]. Fifteen studies with salmeterol were included (10 vs placebo, 3 vs tiotropium and 2 vs indacaterol), whereas 5 were included with formoterol (4 vs placebo and 1 vs indacaterol). Thresholds for clinically important differences were established for active treatments versus placebo in terms of FEV1, total St. George's Respiratory Questionnaire (SGRQ) score, and total Transitional Dyspnea Index (TDI) score. At 6 months, formoterol treatment resulted in 80–90% higher probability of increasing the proportion of patients showing improvements in the TDI and SGRQ scores as compared to salmeterol. Moreover, with 88% probability formoterol treatment was more efficacious than salmeterol in improving the total SGRQ score at 6 months [73].

In more severe patients the use of a triple combination with inhaled corticosteroid, LABA and long-acting muscarinic antagonist (LAMA) is often adopted. Welte et al [74] evaluated the efficacy and tolerability of budesonide/formoterol added to tiotropium during a 12-week period in 660 COPD patients with a mean FEV1 of 38% of predicted value and eligible for inhaled ICS/LABA combination therapy. This study demonstrated that budesonide/formoterol added to tiotropium versus tiotropium alone provided more rapid and sustained improvements in lung function, health status, morning symptoms and activities, and reduced severe exacerbations [74]. Similarly, Aaron et al. investigated whether combining tiotropium with fluticasone/salmeterol or with salmeterol only, improves clinical outcomes in adults with moderate to severe COPD compared with tiotropium alone. Tiotropium plus fluticasone/salmeterol improved lung function and disease-specific quality of life and reduced the number of hospitalisations for COPD exacerbation and all-cause hospitalisations compared with tiotropium plus placebo. In contrast, tiotropium plus salmeterol did not statistically improve lung function or hospitalisation rates compared with tiotropium plus placebo [75].

Regarding asthma treatment, both formoterol and salmeterol when added to ICS treatment, reduce asthma exacerbations. However, the systematic review and meta analysis of parallel-group, blinded, randomised, controlled trials with at least 12 weeks of treatment in patients concomitantly using ICS, showed that only formoterol, but not salmeterol, reduced significantly asthma-related hospital admissions when compared with placebo at the similar dose of ICS used [76]. Similarly, in the largest double-blind study comparing fixed-dose combination therapy with budesonide/formoterol versus fluticasone/salmeterol at equivalent ICS doses, budesonide/formoterol treatment resulted in a statistically significant 32% lower rate of asthma-related hospitalisations/emergency room visits [77].

The fast onset of action of formoterol, as fast as for short-acting β2 adrenoceptor agonists [78], allowed introducing a new treatment concept in asthma where budesonide/formoterol combination in one

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inhaler (Symbicort®) is used as Symbicort Maintenance and Reliever Therapy (SMART®). In this therapy, patients inhale budesonide/formoterol from one inhaler once or twice daily and whenever they feel a need of using a rapid acting bronchodilator to relieve symptoms. The SMART® therapy has been extensively validated in randomised controlled clinical trials [79] as well as has been shown to be valid in daily clinical practice [80]. Efficacy and safety data on this strategy are consistent and is worldwide considered a relevant to in reducing the exacerbation and the overall dose of inhaled steroid needed [81,82].

5. Conclusions

The evidence published in the last decades support the fundamental role of long-acting β_2 adrenoceptor agonists both in asthma (always combined with inhaled steroid) and in COPD and highlighted many additional effects which are not related to bronchodilation. Although similar outcomes can be achieved by formoterol and salmeterol, at similar safety profile, the fast onset of action and the full agonism of formoterol need to be considered when selecting the best pharmacological treatment of asthma and COPD.

Conflict of interest

All authors disclose any actual or potential conflict of interest including any financial, personal or other relationships with other people or organisations within three years of beginning the submitted work that could inappropriately influence, or be perceived to influence, their work.

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