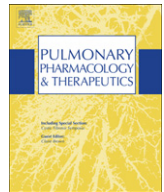


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## Review

## LABAs in asthmatic children: Highlights and new inside

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## ABSTRACT

International asthma guidelines recommend increasing the dose of ICS or adding leukotriene modifiers or the use of long-acting inhaled beta2-agonists (LABAs) in combination with inhaled corticosteroids (ICS) when uncontrolled asthma occurs in adult and children in treatment with low-dose inhaled corticosteroids. However, in children, the effects of this last treatment option are unclear because there are few studies on the efficacy and safety of these drugs in pediatric age. Furthermore, salmeterol is licensed for use in children over 4 years and formoterol in children of more than 6 years. Finally, recent data provides evidence that repeated bronchoconstriction induces epithelial cell stress that may lead to remodeling and these findings may have potential implications for asthma management, particularly for LABAs treatment in the future.

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## 1. Introduction

Asthma is the most common chronic childhood disease in nearly all industrialized countries. It is more prevalent in children with a family history of atopy, and symptoms and exacerbations are frequently provoked by a wide range of triggers including viral infections, indoor and outdoor allergens, exercise and tobacco smoke [1].

An effective management of asthma should include a comprehensive treatment plan that foresees the avoidance of airborne allergens [2,3] and irritant triggers wherever possible [4], as well as an appropriate pharmacotherapy and asthma education programs for patients and parents [1].

The goal of pharmacotherapy is the control of symptoms and the prevention of exacerbations with a minimum of drug related side effects. Treatment should be given in a stepwise approach according to the persistence, severity, and frequency of symptoms [1].

Medications to treat asthma can be classified as controllers or relievers. Controllers are medication taken daily on a long-term basis to keep asthma under control through their anti-inflammatory effect. They include inhaled corticosteroids (ICS), leukotriene modifiers (LTRA), long-acting inhaled beta2-agonists (LABAs) in combination with ICS, cromones, sustained release

theophylline, oral steroids and omalizumab. Relievers are used as needed to relieve asthma symptoms when they occur. They include short-acting inhaled beta2-agonists (SABAs), short-acting oral beta2-agonists, intravenous beta2-agonists, short-acting theophylline and inhaled anticholinergics [1,5].

SABAs are the treatments chosen for intermittent asthma and for preventing exercise-induced asthma [1,6]. The most commonly used drug is salbutamol for its safety and efficacy [1].

Children who suffer from mild persistent asthma generally have symptoms more than twice a week, but not more than once a day [6]. In these children ICS are the first-line treatment for persistent asthma and it should be introduced as initial maintenance treatment at low doses. If asthma control is inadequate an increase of ICS dose or additional therapy with LTRAs or LABAs should be considered [7,8]. Once control of asthma is achieved the dose of medication should carefully be titrated to the minimum required to maintain control, thus reducing the potential for adverse effects [6].

2. Inhaled  $\beta_2$ -agonists in asthma

In asthmatics, inhaled beta2-agonists are powerful agents used to relieve bronchoconstriction. They act by stimulating the beta2-receptors located in airway smooth muscle resulting in smooth muscle relaxation [9]. Inhaled beta2-agonists can be differentiated from one another by their onset and duration of action. SABAs, such as salbutamol and terbutaline, are hydrophilic and they interact directly with beta2-receptors, leading to a fast onset of action with

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effects lasting for 6 h or less [10]. LABAs provide longer symptom control, which is a particularly useful feature for preventing nighttime symptoms. There are two main LABAs, salmeterol and formoterol. Salmeterol is highly lipophilic and rather slowly diffuses through the lipid bilayer in muscle cell membranes to reach the beta2-receptors, explaining the slower onset and long duration of action [11]. Formoterol, less lipophilic, has a fast onset of action, similar to short-acting beta2-agonists, and it is believed to be incorporated into the lipid bilayer to serve as a reservoir, accounting for its prolonged action [12].

In children, however, salmeterol is licensed for use over 4 years and formoterol in children of more than 6 years, but there are few studies on the efficacy and safety of these drugs in pediatric age.

### 3. Efficacy of LABAs in children

In cases where ICS is not sufficient to control the disease in children, international guidelines recommend increasing the dose of ICS or adding leukotriene modifiers or long-acting beta2-agonists (LABAs) [5,13–15].

A previous systematic review [16] showed that in children, but not in adults, LABA added to ICS had not significantly reduced the risk of exacerbations requiring a short course of systemic corticosteroids compared with the use of higher doses of ICS. Moreover, children could be almost 3 times more likely than adults to require oral steroids when they were treated with a LABA than with ICS; however, some children included in the meta-analysis came from trials performed in mixed population (children and adults together).

Another important direct effect of asthma exacerbations is the use of rescue medication and lung function deterioration [17]. Castro Rodriguez et al. have found a significant modest reduction in the use of rescue medication among children on LABA + ICS than those on higher doses of ICS. There was also statistically significant but uncertain clinically significant improvement in lung function (morning and evening PEF) among children/adolescents using LABA + ICS compared with those using higher doses of ICS [18,19].

ICS treatment has a plateau, so that increasing the dose does not necessarily improve the clinical response, and systemic effects can occur [20]. In contrast, the synergistic effect of adding LABA to ICS has been reported [21,22] where LABA, along with its bronchodilator effect, increases the nuclear translocation of the glucocorticoid receptor. At the same time, ICS is delivered in the same device and along with its anti-inflammatory effect it increases the expression of beta2-receptors by increasing gene transcription. These findings could explain the higher performance of the combination of LABA + ICS versus higher doses of ICS.

Furthermore, short-term growth was significantly greater in children with combination therapy (370 mg/d of BDP or equivalent) compared with children with higher ICS doses (770 mg/d of BDP or equivalent) and this difference of 0.66 cm/y could be important, especially for children in their early years [18].

### 4. Safety of LABAs in children

Data assessing the safety of LABAs therapy in children are rather limited [23]. For over a decade, the FDA and the medical community have discussed how to safely use LABAs [24]. Even before U.S. approval of the first LABA, there was concern about a paradoxical increase in serious asthma exacerbations in some patients treated with these drugs [25–27]. The Serevent Nationwide Surveillance (SNS) study suggested an increased risk of asthma-related death in patients treated with salmeterol as compared with albuterol [28]. Shortly after approving salmeterol in 1994, the FDA began to receive reports of serious asthma exacerbations and deaths in

patients treated with the drug [29–31]. To further evaluate these reports, the manufacturer (Astra-Zeneca) conducted the Salmeterol Multicenter Asthma Research Trial, in which there were eight more asthma-related deaths per 10,000 patients among patients treated with salmeterol than among those given placebo [32]. The authors compared the safety of salmeterol or placebo added to usual asthma care. There was a small, significant increase in respiratory-related deaths and asthma-related deaths or life-threatening experiences in subjects receiving salmeterol vs. placebo. Smaller studies about safety of formoterol showed an excess of serious asthma exacerbations, some necessitating intubation [33]. Although the absolute risk observed was small, it was not inconsequential, given the number of patients with asthma currently receiving these drugs. The combination of budesonide and formoterol administered via pressurized metered-dose inhaler showed similar tolerability and greater efficacy compared with budesonide alone, in randomized, double-blind clinical trials in adults, adolescents and children 6–11 years with persistent asthma [34–37]. Berger et al. compared the safety of budesonide/formoterol versus budesonide alone in children with persistent asthma [38]. Safety parameters included adverse events, clinical laboratory data including 24-h urinary cortisol, 12-lead electrocardiograms, physical examination, and vital signs. Budesonide/formoterol and budesonide were well tolerated with a similar incidence of adverse events, most of mild or moderate intensity. No clinically important differences were observed for 12-lead electrocardiograms, hematology, serum glucose and potassium, and 24-h urinary cortisol. Sears et al. reported a comprehensive review of safety data obtained in completed Astra-Zeneca trials involving formoterol versus non-LABA treatment with respect to the risks of asthma-related and cardiac-related death and serious adverse events (SAEs), as well as all-cause mortality [39]. There were eight asthma-related deaths (0.34 per 1000 person-yrs) among 49,906 formoterol-randomized patients (92% using ICS), and two (0.22 per 1000 person-yrs) among 18,098 patients (83% using ICS) not randomized to formoterol, which was nonsignificant. Asthma-related SAEs were significantly fewer among formoterol-randomized patients. There was no significant difference in cardiac mortality or noncardiac nonasthma-related mortality in formoterol-randomized compared to non-LABA treated patients. All-cause mortality was similar [40]. Cates et al. in a recent Cochrane review evaluated 22 studies comparing regular formoterol to placebo and salbutamol [41]. Three deaths occurred on regular formoterol and none on placebo; this difference was not statistically significant. No significant increase in fatal or non-fatal serious adverse events was found when regular formoterol was compared with regular salbutamol or terbutaline. They found an increased risk of serious adverse events with regular formoterol, and this did not appear to be abolished in patients taking inhaled corticosteroids.

The FDA conducted a comprehensive review of the benefits and risks of using LABAs to treat asthma [24]. The agency concluded that the benefits of LABAs continue to outweigh the risks when the drugs are used appropriately and that the agents should remain available for the treatment of asthma. However, because of their serious risks, the FDA recommended that LABAs should be reserved for patients whose asthma could not be adequately managed with asthma controller medication such as an inhaled corticosteroid. Furthermore, until additional data were available from large, randomized, controlled trials evaluating the safety of LABAs when administered with an inhaled corticosteroid, the FDA believed that long-term use of LABAs should be limited to patients who required prolonged use of these drugs (see Table 1) [24]. There were several reasons for these label changes. First, although it was already common practice that a LABA should not be used without concurrent use of an asthma-controller medication, the new contraindication emphasized the

**Table 1**  
Specific label changes for long-acting beta2-agonists (LABAs) [24].

1. Contraindicate the use of LABAs for asthma in patients of all ages without concomitant use of an asthma-controller medication such as an inhaled corticosteroid.
2. Stop use of the LABA, if possible, once asthma control is achieved and maintain the use of an asthma-controller medication, such as an inhaled corticosteroid.
3. Recommend against LABA use in patients whose asthma is adequately controlled with a low- or medium-dose inhaled corticosteroid.
4. Recommend that a fixed-dose combination product containing a LABA and an inhaled corticosteroid be used to ensure compliance with concomitant therapy in pediatric and adolescent patients who require the addition of a LABA to an inhaled corticosteroid.

seriousness of the risk associated with LABA monotherapy. Second, the FDA believed that the risks of LABAs could be minimized if the agents were used judiciously and that patients who did not require long-term LABA therapy should not be exposed to the risk. Data indicated that many patients were administered the combination products containing an inhaled corticosteroid and a LABA without first undergoing stepwise increase in treatment with an inhaled corticosteroid alone. Third, long-term use of LABAs in patients with asthma should be limited to those whose asthma could not be controlled with asthma-controller medications. Finally, the FDA recommended the use of combination products containing an inhaled corticosteroid and a LABA in children and adolescents because of the difficulty of ensuring compliance with both medications when they were administered separately in these groups [24].

## 5. New insight

In patients with asthma the persistence of inflammatory condition is associated with airway remodeling, characterized by structural changes in airway tissues such as epithelial goblet-cell hyperplasia, sub-epithelial collagen deposition, and smooth-muscle hypertrophy. These changes are associated with bad long-term clinical outcomes and have been attributed to eosinophilic inflammation [42]. However, *in vitro* studies indicate that the compressive mechanical forces that arise during bronchoconstriction may induce remodeling independently from inflammation [43–45]. More recently, and with the aim of testing this hypothesis in humans, Grainge et al. performed repeated inhalation challenges with exposure to either allergen (so as to induce bronchoconstriction with airway eosinophil recruitment) or methacholine (so as to induce bronchoconstriction alone) in volunteers who had mild atopic asthma and then they analyzed bronchial biopsy specimens obtained before and 4 days after completion of the challenges [46]. The results showed that both challenges induced significant airway remodeling. The changes appeared to be independent of eosinophils recruitment into the airways and they were independent of the stimulus causing the bronchoconstriction. These data show the potential contribution of airway narrowing to airway remodeling and these findings may have implications for the management of asthma. At present, the primary aim of asthma management is to control the disease by reducing airway inflammation. The results of this study suggest that an additional target should be to stabilize airway caliber, in order to prevent bronchoconstriction. These findings may have potential implications for asthma management, in particular about LABAs treatment [46].

## 6. Discussion

Asthma guidelines recommend LABAs (formoterol or salmeterol) plus low-dose CSI as the preferred controller treatment on step 3 of the asthma management plan [6]. Probably the inclusion

of LABA therapy in pediatric guidelines is derived from studies in adults and adolescents with asthma which suggested that the addition of salmeterol and formoterol to ICS therapy was more effective to control asthmatic symptoms compared to double dose of ICS. Recommending the use of LABA in pediatric patients was therefore an extrapolation from adult data.

However, asthma in children is different from asthma in adults in many aspects. Pediatric asthma is often an episodic disease with a particular strong seasonality, associated with few symptoms and near-normal lung function for long periods alternate by periods of increases in symptoms and exacerbations [47]. Children therefore, go up and down quickly from the scale of asthma severity often [47]. Traditional dosing strategy emphasizes fixed dosage for long time but many parents and patients use controller and bronchodilator therapy intermittently for short periods, and once the children are asymptomatic and parents and patients think that their asthma is again well controlled, they stop therapy and restart therapy only when symptoms recur. Written management plans are recommended [6] but rarely applied [48] and adherence is generally poor [49] and of limited effectiveness [50]. Therefore pediatric patients need further study. LABAs have mainly been studied in children older than 5 years as add-on therapy for patients whose asthma is not controlled on low to high doses of inhaled glucocorticosteroids. Significant improvements in peak flow and other lung function measurements have been found in most studies. However, their effects on other outcomes such as symptoms and need for reliever medication have been consistent and have only been observed in about half of the trials conducted.

As for LABAs effectiveness to reduce asthmatic exacerbations in children, most studies suggest that treatment with formoterol or salmeterol does not offer protection against asthma exacerbations in children with asthma, compared to corticosteroids, to SABA or placebo. The risk of exacerbation and asthma-related hospitalizations is generally increased by regular treatment with LABA [51].

The number of asthmatic exacerbation is, however, an essential measure of asthma control and it can be considered as a marker of airways subclinical inflammation. So the analysis of exacerbation and hospitalization rate due to asthma constitutes a central point in the evaluation of the effectiveness of therapy in pediatric patients.

However, there are limitations to the conclusions that can be drawn from these studies. Clinical trials are analyzed for different design, population, type of drug and duration. There were different definitions of asthmatic exacerbation. Studies in adults have shown a moderate protective effect of LABA added to CSI, but there are also clinical trials that indicate a worsening of conditions.

The lack of protective effect of LABA is evident even when there was an improvement in lung function values.

The lack of improvement in the asthma control (as underlined by the exacerbation and hospitalization rate) can be explained by the inability to evaluate the subclinical inflammation. However, this account does not explain the increase of the exacerbations rate in patients treated with LABA + ICS. It is possible that chronic exposure to LABAs could be directly related to adverse effects in the airways, regardless of treatment with CSI or it is possible that, as in adults than in children, a kind of tolerance to LABAs develops. Children treated with salmeterol showed over time a reduced protection against exercise-induced asthma, despite the concomitant use of ICS [52].

Certainly there is no evidence in the pediatric literature to suggest a protective effect of LABA against asthma exacerbation. Future studies are urgently needed to point out this aspect.

These results suggest that it is better, as FDA recommends, to stop using the LABA, if possible, once asthma control is achieved and to maintain the use of an asthma-control medication, such as an inhaled corticosteroid, because whereas some subgroups of

children with asthma can benefit from this therapy (there is still no strong evidence that direct in this regard), further studies are needed to obtain a stronger evidence of its objective efficacy and safety.

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