

PRACTICE

THERAPEUTICS

Long acting β_2 agonists in adult asthma

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A 30 year old man with asthma, previously well controlled with inhaled beclometasone 100 μ g (two puffs twice daily) and salbutamol (as required), presented to his general practitioner with a three month history of increasing breathlessness and wheeze, primarily overnight and in the mornings. He was a non-smoker with no obvious trigger factors. He reported using his inhaler as prescribed, and his technique was satisfactory. He had no other medical history and no symptoms of allergic rhinitis. His general practitioner suggested a further inhaler containing a long acting β_2 agonist (LABA), but the patient expressed concerns as he had read that these inhalers were linked to an increased risk of fatal asthma.

What are long acting β_2 agonists?

LABAs have become an increasingly popular treatment over the past two decades as a supplement to inhaled corticosteroids in the management of persistent asthma.¹ They have a bronchodilator effect when bronchomotor tone (the state of airway smooth muscle contraction or relaxation regulating airway calibre) is low, and a protective (or “airway stabilising”) effect with increased bronchomotor tone.²

Salmeterol and formoterol (the two LABAs in widespread clinical use) are lipophilic, bind to airway smooth muscle β_2 adrenoceptors and exert effects for approximately 12 hours. Salmeterol has a slower onset of action (10-30 minutes) than formoterol (1-3 minutes). Both drugs can be prescribed in single inhaler devices, but they are commonly given with different inhaled corticosteroids with varying doses in combination inhaler devices (table 1⇓, fig 1⇓).

How well do they work?

Large randomised controlled studies and systematic reviews have shown that add-on LABAs for adults receiving inhaled corticosteroids reduce symptoms, relief inhaler use, and exacerbations and improve quality of life and lung function.^{3 4} For example, a systematic review of nine trials compared add-on salmeterol versus increasing the inhaled corticosteroid dose for 3685 adults with persistent asthma.³ After three months of

treatment, patients’ forced expiratory volume in one second (FEV_1) was significantly greater with add-on salmeterol (0.10 L (95% confidence interval 0.04 to 0.16)), and patients experienced significantly fewer exacerbations (329 v 359 respectively) amounting to a reduction of 2.73% (0.43% to 5.04%). A Cochrane review of randomised trials in patients with persistent asthma compared those receiving inhaled corticosteroids alone with those receiving add-on salmeterol or formoterol.⁴ The latter treatment significantly reduced the number of exacerbations requiring oral corticosteroids (480 v 385) across 30 studies (lasting between four and 54 weeks in duration) in which the vast majority of participants were adults; significant benefits were also found in terms of improvement in FEV_1 (in increase of 0.11 L (0.09 to 0.13)) and reduction in symptoms.

Because of the rapid onset of action of formoterol (similar to a short acting β_2 agonist), some formulations containing formoterol plus an inhaled corticosteroid in a single inhaler can be used both as a regular treatment and “as required” (so called maintenance and reliever therapy). Randomised placebo controlled trials showed that a combination of budesonide and formoterol used in this manner in patients with asthma significantly reduced the number of exacerbations requiring rescue oral corticosteroids with, on average, only one extra puff/day of the combination inhaler.⁵ A combination of formoterol and extra-fine beclometasone in a combination inhaler has also been given a licence in the UK to both prevent and relieve symptoms.⁶

How safe are they?

LABAs are usually well tolerated, but adverse effects include tachycardia, fine tremor, headache, muscle cramps, prolongation of the QT interval, hypokalaemia, occasional paradoxical bronchospasm, and feelings of nervousness. Over the past two decades, some studies have indicated that some patients using LABAs regularly may experience deteriorating asthma control.⁷⁻⁹ Proposed mechanisms for this effect include pharmacogenetic variations resulting in a diminishing response to LABAs, β_2

adrenoceptor down regulation, and patients less stringently adhering to inhaled corticosteroids, meaning that unchecked airway inflammation may be masked leading to delayed presentation of an exacerbation.¹⁰

A US Food and Drug Administration (FDA) meta-analysis of 110 randomised controlled trials (60 954 patients) reported that patients receiving a LABA (versus those not receiving one) experienced significantly more “events” (381 v 304 respectively) characterised by death, intubation, and hospital admission.¹¹ However, in many of the studies, inhaled corticosteroid use was not a prerequisite, and no deaths or intubations occurred in patients using inhaled corticosteroids and LABA in a combination device. The Salmeterol Multi-centre Asthma Research Trial (SMART) compared add-on salmeterol twice daily versus placebo over 28 weeks in a randomised, double blind study.⁸ An interim analysis revealed no significant differences for the primary outcomes of respiratory related death or life threatening experience, although there was a significantly increased risk of death or life threatening experiences in African Americans (of whom only 38% were using regular inhaled corticosteroids). In a review of three randomised placebo controlled studies evaluating effects of add-on formoterol, a dose higher than that currently recommended (24 µg twice daily) was associated with more frequent asthma exacerbations.¹² However, other reviews and meta-analyses have not demonstrated a significant association between LABAs and deteriorating asthma control.¹³⁻¹⁵

Although it is highly likely that worsening asthma control is related to under-treatment with inhaled corticosteroids rather than a direct effect of LABA use, the FDA has indicated that a “black box warning” on all inhalers containing a LABA should remain. Because of these concerns and ongoing controversy, the FDA has mandated a large trial of LABAs in asthma.¹⁶

What are the precautions?

There are few absolute contraindications to prescribing LABAs, and the Medicines and Healthcare Products Regulatory Agency (MHRA) indicates that the benefits of LABAs, when used with inhaled corticosteroids, outweigh any apparent risks.¹⁷ LABAs should be started only with patients who are already taking inhaled corticosteroids, and the inhaled steroid should be continued. In a UK primary care observational study of 73 486 patients with asthma during a single calendar year (2006), 5592 patients (7.6% (95% confidence interval 7.4% to 7.8%)) were prescribed a LABA in a separate inhaler. Of these, 17.7% (16.7% to 18.7%) used LABA as monotherapy.¹⁸ This supports the suggestion that manufacture of LABAs as a single inhaler should cease.¹⁹⁻²⁰

How cost effective are they?

Most economic assessments of LABAs are based on their use with inhaled corticosteroids in a combination inhaler, and cost effectiveness varies according to asthma severity and pre-existing levels of inhaled treatment. Although adding a LABA in patients with moderate to severe asthma (already receiving inhaled corticosteroids) falls within the currently accepted cost per quality adjusted life years (QALY) range (£4800-£18 000 per QALY), the initiation of combination inhalers in corticosteroid naïve patients has not been shown to be cost effective. In the UK, the estimated cost of add-on LABA to inhaled corticosteroid is £952/year.²¹⁻²³

How are they taken and monitored?

Before escalating asthma treatment, explore potential trigger factors such as cigarette smoking, occupational and aeroallergen exposures, and presence of allergic rhinitis plus adherence to treatment and inhaler technique. Instruct patients in the correct use of the device to help optimise drug delivery to the airways and minimise risks of local and systemic adverse effects. Advantages and disadvantages of different devices which deliver LABAs are shown in table 2.

The inhaled corticosteroid dose at which a LABA should be added is not clearly established. A meta-analysis of randomised controlled trials (8 studies, 2324 participants) evaluated effects of inhaled fluticasone in adolescents and adults with moderate to severe asthma. For all major clinical outcomes, the dose-response curve for beneficial effects began to reach a plateau at 100-200 µg/day, and little further benefit was observed beyond 500 µg/day (approximately 1000 µg of beclomethasone daily equivalent).²⁴ Moreover, studies have demonstrated benefit of add-on LABA in patients taking only 200 µg/day of inhaled beclomethasone.²⁵⁻²⁶ In a randomised placebo controlled trial of 852 patients (mean FEV₁ 76% predicted), adding formoterol to budesonide 200 µg/day reduced severe exacerbations by 26% compared with a reduction in severe exacerbations of 63% with the addition of formoterol to budesonide 800 µg/day.²⁶ This in turn emphasises the importance of giving adequate anti-inflammatory treatment prior to addition of a LABA in order to reduce exacerbation frequency.

The *British Guideline on the Management of Asthma* therefore advises that a LABA should usually be added at inhaled corticosteroid doses of 200-800 µg/day of beclomethasone or equivalent (fig 2) and that LABAs are the preferred add-on treatment for adults using such doses of inhaled corticosteroid who experience persistent symptoms and exacerbations.¹ Both the MHRA and National Institute for Health and Care Excellence (NICE) recommend the use of combination inhalers to guarantee that LABAs are not taken without regular inhaled corticosteroids. Advantages and disadvantages of this approach are shown in the box.

Ask patients to monitor features indicative of asthma control (breathlessness, chest tightness, wheeze, cough, use of short acting β₂ agonists, time off work, and peak expiratory flow rate) to help determine effects of add-on treatment. Arrange a clinic review—for example, six weeks after starting new treatment—to facilitate this. Non-specific questions may underestimate symptoms, but overall control can be assessed by a questionnaire such as those in the Asthma Control Test, which has been validated in primary care in the UK.²⁷ Once clinical control of asthma has been stable for three to six months, consider back-titrating treatment. This may involve reducing the single combination inhaler to one puff twice daily (depending on the formulation) or stopping the LABA and reintroducing inhaled corticosteroids as monotherapy.

How do LABAs compare with other drugs?

LABAs are the preferred add-on treatment for adults receiving inhaled corticosteroids compared with leukotriene receptor antagonists (LTRA),¹ although the greater benefit is modest. For example, a Cochrane review of six randomised controlled trials (with duration 4-48 weeks) in adults (n=5571) with asthma inadequately controlled with low doses of inhaled corticosteroids alone, demonstrated that the addition of a LABA reduced exacerbations requiring oral steroids compared with add-on

Advantages and disadvantages of prescribing long acting β_2 agonists (LABAs) and inhaled corticosteroids in a single combination inhaler (versus drugs prescribed in separate inhalers)

Advantages

- Fewer puffs and devices
- Rapid onset of bronchodilatation in inhalers containing formoterol
- Ensures adherence with anti-inflammatory treatment due to inseparable nature of inhaler constituents
- Avoids risks of LABA monotherapy; no evidence of increased risk of asthma death

Disadvantages

- Altering the inhaled corticosteroid dose is less straightforward
- Temptation to start patients on combination inhalers when inhaled corticosteroids as monotherapy would adequately control symptoms
- Difficulty in back-titrating treatment dose without provision of a separate inhaler device containing inhaled corticosteroid alone
- Expense

LTRA: 251 versus 305 patients receiving a LABA and LTRA respectively had an exacerbation, amounting to a 2% ($P=0.02$) difference.²⁸ Add-on LABA was also significantly superior across secondary outcomes such as lung function and quality of life. However, LTRAs exhibit significantly superior effects in terms of attenuating airway hyper-responsiveness and reducing markers of underlying inflammation, although the long term relevance of this is uncertain.²⁹⁻³¹

Case outcome

The patient's general practitioner advises that current evidence suggests it is safe to take LABAs providing the patient continues taking inhaled corticosteroids regularly. To ensure adherence with inhaled corticosteroids, the general practitioner prescribes a combination inhaler containing both an inhaled corticosteroid and LABA, with complete symptom resolution on review six weeks later.

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Tips for patients

- Long acting β_2 agonists—usually called salmeterol and formoterol—are used when symptoms of asthma persist despite regular use of inhaled corticosteroids
- These drugs work by opening the airways (and keeping them open) for a prolonged (more than 12 hours) period.
- Long acting β_2 agonists are considered safe for long term use, although serious problems have been found in patients who have been using them without taking a regular inhaled corticosteroid (which are usually required to dampen airway inflammation)
- Never use inhalers containing salmeterol or formoterol alone without taking regular inhaled steroids: airway inflammation may become out of control when salmeterol and formoterol are used without inhaled steroids, leading to a flare-up of symptoms
- To help avoid hoarseness, alteration of voice quality, and oral thrush when using a single inhaler combining salmeterol or formoterol with an inhaled steroid, you should gargle and brush teeth afterwards
- Report symptoms of deteriorating asthma control (increased wheeze, breathlessness, chest tightness, cough, use of reliever inhaler, and fall in peak expiratory flow) after starting salmeterol or formoterol
- Make sure you are seen on a regular basis at an asthma clinic run by your GP or practice nurse
- If your asthma has been stable for 3-6 months, treatment can sometimes be reduced

Tables

Table 1| Combination inhaled corticosteroid and long acting β_2 agonist (LABA) preparations licensed for use in adults the UK

Brand name	Inhaled corticosteroid dose	LABA dose	Device	Dosing regime
Symbicort 100/6*	Budesonide 100 μ g	Formoterol 6 μ g	Turbohaler	1-2 puffs once or twice daily
Symbicort 200/6*	Budesonide 200 μ g			
Seretide 50	Fluticasone 50 μ g	Salmeterol 25 μ g	Evohaler†	2 puffs once or twice daily
Seretide 125	Fluticasone 125 μ g			2 puffs twice daily
Seretide 250	Fluticasone 250 μ g			2 puffs twice daily
Seretide 100	Fluticasone 100 μ g	Salmeterol 50 μ g	Accuhaler	1 puff twice daily
Seretide 250	Fluticasone 250 μ g			
Seretide 500	Fluticasone 500 μ g			
Fostair*	Beclometasone 100 μ g	Formoterol 6 μ g	Metered dose inhaler†	1-2 puffs twice daily
Flutiform	Fluticasone 50 μ g	Formoterol 5 μ g	Metered dose inhaler†	2 puffs twice daily
	Fluticasone 125 μ g	Formoterol 5 μ g		
	Fluticasone 250 μ g	Formoterol 10 μ g		

*Drug and device is licensed for regular use in addition to "as required" ("maintenance and reliever therapy (MART)").

†Device can be used with a spacer.

Table 2| Advantages and disadvantages of different types of inhaler device used to deliver long acting β_2 agonists (LABAs) to the airways

Type of inhaler	Advantages	Disadvantages
Metered dose inhaler	• Portable • Inexpensive • Easy to use • Short treatment time • Contains many doses	• Actuation and inhalation requires good technique • Unpleasant chilling sensation of the throat ("cold freon effect") • Usually no dose counter • Priming (shaking) required for mixing of drug with propellant
Metered dose inhaler with spacer	• More effective drug delivery • Reduced local drug deposition • No cold freon effect	• Bulky • Maintenance and cleaning required • Priming • More education required for correct use • Additional cost of spacer • Usually no dose counter
Dry powder inhaler	• No actuation-inhalation coordination required • Portable • Short treatment time • Dose counter present	• Adequate inspiratory flow required

Figures



Fig 1 Examples of different types of inhaler device used to deliver long acting β_2 agonists (LABAs) to the airways: (a) Symbicort Turbohaler, (b) Seretide Accuhaler, (c) Seretide metered dose inhaler, (d) Fostair metered dose inhaler, (e) Flutiform metered dose inhaler

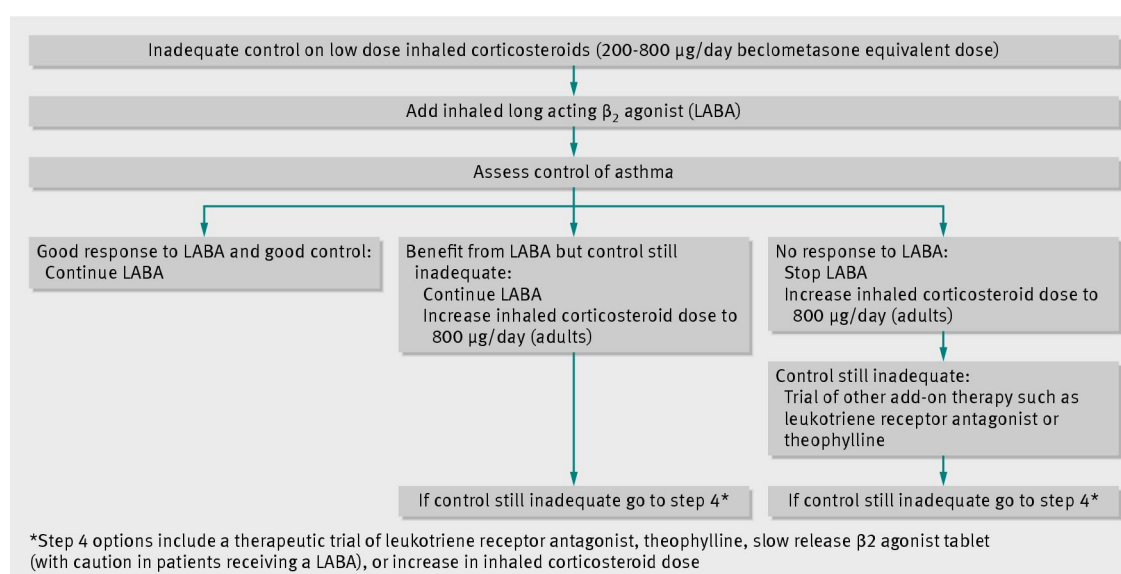


Fig 2 Summary of step 3 of treatment algorithm from *British Guideline on the Management of Asthma*. Adapted and reproduced with permission of British Thoracic Society/Scottish Intercollegiate Guidelines Network (BTS/SIGN)¹