Asthma: study finds many people have a substantial increase in dose of inhaled corticosteroid when started on combination inhaler therapy

The British guideline on the management of asthma recommends that inhaled corticosteroid (ICS) therapy should be maintained at the lowest possible dose at which effective control of asthma is maintained. A retrospective database analysis of 685 people with asthma in 46 general practice surgeries in Scotland found initiating combination ICS plus long-acting beta-2 agonist (LABA) therapy resulted in widespread increases in ICS dose. The average increase was about 50%, and was substantially greater among people previously on lower ICS doses. Many people received a high-dose combination inhaler regardless of their baseline ICS dose. This raises questions around the awareness of ICS doses in different preparations, and the authors of the study suggest that an evaluation of the appropriateness of high-dose combination inhaler therapy in primary care is needed.

Overview and current advice

The British guideline on the management of asthma advocates a stepwise approach for the treatment of asthma. If asthma is not adequately controlled with an inhaled corticosteroid (ICS) alone (at step 2), add-on therapy may be needed (step 3). For adults and children aged 5 years and over, an ICS and a long-acting beta-2 agonist (LABA) should be considered.

The guidance reminds us that before starting a new drug, practitioners should recheck adherence and inhaler technique, and support people in eliminating trigger factors. If there is no response to treatment the drug should be discontinued. No exact dose of ICS can be deemed the correct dose at which to add another drug. However, in adults and children aged 5 years and over, the British guideline states that a LABA should be considered before going above a dose of 400 micrograms beclometasone dipropionate (BDP) or equivalent per day and certainly before going above 800 micrograms BDP.
There are safety issues relating to the use of high doses of ICS in asthma. Unpleasant local side effects, including oral candidiasis and dysphonia, can occur with ICS at standard doses, but are more common with higher doses. Potentially serious systemic side effects, such as adrenal suppression, growth failure, decrease in bone mineral density, cataracts and glaucoma, may be associated with ICS particularly at high doses (above 800 micrograms BDP or equivalent per day in adults and above 400 micrograms BDP or equivalent per day in children)\(^1\).\(^2\).

**MHRA advice** for fluticasone propionate includes a warning that doses above 500 micrograms twice daily should be prescribed only for patients with severe asthma where additional clinical benefit is expected and demonstrated. Doses of this level should be initiated by a specialist in the management of asthma\(^3\).

The NICE technology appraisal on **ICS for the treatment of chronic asthma in adults and children aged 12 years and over** recommends a combination inhaler, within its marketing authorisation, as an option if treatment with an ICS and a LABA is considered appropriate. NICE recommends that the decision to use a combination inhaler or the 2 agents in separate inhalers should be made on an individual basis, taking into consideration therapeutic need and the likelihood of treatment adherence. If a combination inhaler is chosen, then the least costly device that is suitable for the individual is recommended.

See the **NICE Evidence topic page on asthma** or the **NICE Clinical Knowledge Summary on asthma** for a general overview of the condition.

**New evidence**

A retrospective database analysis (Covvey JR et al\(^4\)) looked at ICS dose changes when people with asthma were newly prescribed an ICS/LABA combination inhaler. The authors conducted their analysis in 46 general practice surgeries in Scotland, which serve nearly 300,000 people. The study included 685 people (403 female; median age 47 years, interquartile range 32–62 years) with asthma who had their first prescription for an ICS/LABA combination inhaler between January 2008 and December 2009. They had not received a LABA in the previous year.

Doses of ICS in both single-agent and combination inhalers were obtained from prescription records and standardised to BDP equivalents. In people over 12 years old, low-dose ICS therapy was defined as 400 micrograms BDP equivalent or less per day; medium-dose was defined as more than 400 micrograms but no more than 800 micrograms BDP equivalent per day; and high-dose as more than 800 micrograms BDP equivalent per day. For children aged 12 years or younger the dose cut-offs were halved.

The study found that a total of 541 (79%) people had been prescribed an ICS in the year before they were prescribed a combination inhaler; most commonly BDP (294 people [54%]). The most common combination inhaler prescribed was fluticasone propionate/salmeterol (497 people [73%]).

The initiation of combination inhaler therapy resulted in an overall mean increase in ICS dose of 354 micrograms BDP equivalent per day (95% confidence interval [CI] 302 to 407 micrograms; \(p<0.001\)). This represented an increase from a mean of 677 micrograms per day to 1043 micrograms per day, an increase of about 50% in relative terms. People who were originally on low-dose ICS therapy had an even higher mean dose increase of 550 micrograms BDP equivalent per day when a combination inhaler was prescribed, with 49% (122/250) of them being changed to a high-dose combination inhaler.

People with co-morbid COPD were included in the study, but excluding these 89 people did not affect the results. There was still an overall mean increase in ICS dose of 463 micrograms BDP equivalent per day, and high-dose combination inhalers were given to 54% of people (321/596).
There was no pattern to short-acting beta agonist or oral corticosteroid prescribing between the ICS dose categories, suggesting that presence of symptoms or having exacerbations were not affecting the dose of combination inhaler chosen.

The analysis included 44 children (aged 12 years or younger), 27 (61%) of whom were changed from low-dose ICS to low-dose combination therapy; 9 received high-dose combination therapy.

**Commentary**

The authors of this study suggest their analysis shows significant use of high-dose combination inhalers in people with asthma in primary care. Nearly 80% of people had been prescribed an ICS in the year before they were prescribed a combination inhaler, suggesting that, in most people, treatment was being stepped up in line with the British guideline on the management of asthma. However, add-on therapy with a LABA in a combination inhaler resulted in widespread ICS dose increases. Many people were changed to a high-dose combination inhaler regardless of their baseline ICS dose or, it would seem, their symptom or exacerbation history.

In this analysis, the most commonly used high-dose combination inhaler was fluticasone propionate/salmeterol. In a post-hoc analysis, 149 of the 394 people prescribed a high-dose combination inhaler were prescribed doses of 1600 micrograms BDP equivalent per day or more, and all but 5 of these people received fluticasone propionate/salmeterol. It may be that this was inadvertent prescribing because of a lack of awareness about potency differences between ICS. The British guideline on the management of asthma acknowledges that dosage equivalents will depend on other factors such as different delivery devices and inhaler technique, but states that BDP and budesonide are approximately equivalent in clinical practice, whereas fluticasone propionate provides equal clinical activity to BDP and budesonide at half the dosage (see below).

Five ICS/LABA combination inhalers are now licensed in the UK for the treatment of asthma:

- fluticasone propionate/salmeterol (Seretide) metered-dose inhaler and dry-powder inhaler
- fluticasone propionate/formoterol (Flutiform) metered-dose inhaler
- budesonide/formoterol (Symbicort) dry-powder inhaler
- beclometasone/formoterol (Fostair) metered-dose inhaler
- fluticasone furoate/vilanterol (Relvar Ellipta) dry-powder inhaler.

The British guideline on the management of asthma provides a table (table 8b) with dosage equivalences for inhaled steroids (please note this does not contain information for some of the inhalers launched since the guideline was last updated). The potencies of the ICS in these combination inhalers vary, with 400 micrograms of budesonide per day in Symbicort being approximately equivalent to 200 micrograms of fluticasone propionate per day in Seretide or Flutiform. Fostair contains extrafine particle size BDP, and 200 micrograms of BDP per day in Fostair is approximately equivalent to 400 micrograms of BDP per day in a non-extrafine formulation. Relvar Ellipta contains fluticasone furoate, which at 92 micrograms once a day is approximately equivalent to fluticasone propionate 250 micrograms twice a day, and at 184 micrograms once a day is approximately equivalent to fluticasone propionate 500 micrograms twice a day.

These combination inhalers also differ in their cost, licensing status and recommended dosing (see summaries of product characteristics for details).
NICE has published evidence summaries: new medicine publications on the use of fluticasone propionate/formoterol (Flutiform) and fluticasone furoate/vilanterol (Relvar Ellipta) in asthma.

The British guideline on the management of asthma recommends starting therapy at the step most appropriate to control asthma, but also stepping down therapy once asthma is controlled. In particular, ICS therapy should be maintained at the lowest possible dose at which effective control of asthma is maintained. The widespread use of high-dose combination inhalers in this study raises a concern that people with asthma may be receiving a higher dose of ICS than is needed when these combination inhalers are initiated. There is also a concern that people could remain on these high doses long-term if they are not reviewed regularly and their treatment stepped down where possible. The authors of the study comment that the dose-response relationship of ICS could result in people who receive high doses having an increased risk of local and systemic adverse effects with little gain in asthma control. They suggest that an evaluation of the appropriateness of high-dose combination inhaler therapy in primary care is needed.

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References


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