Original Article

Long-Acting β-Agonist in Combination or Separate Inhaler as Step-Up Therapy for Children with Uncontrolled Asthma Receiving Inhaled Corticosteroids

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What is already known about this topic? Current asthma guidelines recommend that children prescribed a long-acting β_2-agonist (LABA) should receive treatment as a fixed-dose combination (FDC) inhaler, rather than as an additional, separate inhaler alongside inhaled corticosteroids (ICS). The current literature, however, does not provide evidence to support this.

What does this article add to our knowledge? In a matched cohort study, LABA treatment as a separate inhaler was associated with poorer asthma control compared with an FDC inhaler.

How does this study impact current management guidelines? These findings support recommendations from British Thoracic Society, National Institute for Health and Care Excellence asthma guideline, and US Food and Drug Administration, to prescribe an add-on LABA as an FDC inhaler with ICS in children.

BACKGROUND: Adding a long-acting β_2-agonist (LABA) to inhaled corticosteroids (ICS) using a fixed-dose combination (FDC) inhaler is the UK guideline recommendation for children aged more than 4 years with uncontrolled asthma. The evidence of benefit of adding an FDC inhaler over a separate LABA inhaler is limited.

OBJECTIVE: The objective of this study was to compare the effectiveness of a LABA added as an FDC inhaler, and as a separate inhaler, in children with uncontrolled asthma.

METHODS: Two UK primary care databases were used to create a matched cohort study with a 2-year follow-up period. We included children prescribed their first step-up from ICS monotherapy. Two cohorts were formed for children receiving an add-on LABA as an FDC inhaler, or a separate LABA inhaler. Matching variables and confounders were identified by comparing characteristics during a baseline year of follow-up. Outcomes were examined during the subsequent year. The primary outcome was an adjusted odds ratio for overall asthma

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Abbreviations used
aOR- Adjusted odds ratio
aRR- Adjusted rate ratio
BDP- Beclomethasone dipropionate
BTS/SIGN- The British Thoracic Society and Scottish Intercollegiate Guidelines Network
CI- Confidence interval
CPRD- Clinical Practice Research Datalink
FDA- Food and Drug Administration
FDC- Fixed-dose combination
ICS- Inhaled corticosteroids
LABA- Long-acting β-agonist
LTRA- Leukotriene receptor antagonist
MPR- Medication possession ratio
OCS- Oral corticosteroids
OPCRD- Optimum Patient Care Research Database
NICE- National Institute for Health and Care Excellence
SABA- Short-acting β-agonist
SMART- Single maintenance and reliever therapy

control (defined as follows: no asthma-related hospital admission or emergency room visit, prescription for oral corticosteroids or antibiotic with evidence of respiratory consultation, and ≤2 puffs of short-acting β-agonist daily).
RESULTS: The final study consisted of 1330 children in each cohort (mean age 9 years; 59% male). In the separate ICS + LABA cohort, the odds of achieving overall asthma control were lower (adjusted odds ratio, 0.77 [95% confidence interval, 0.66-0.91]; *P* = .001) compared with the FDC cohort.
CONCLUSION: The study demonstrates a small but significant benefit in achieving asthma control from an add-on LABA as an FDC, compared with a separate inhaler and this supports current guideline recommendations. **(J Allergy Clin Immunol Pract 2016;■:■-■)**

Key words: *Asthma; Child; Inhaled corticosteroid; Long-acting β-agonist; Step-up therapy*

Asthma is common amongst children in the UK, with an estimated 7%, or 1.1 million, children prescribed current asthma therapy.[1,2] The British Thoracic Society and Scottish Intercollegiate Guidelines Network (BTS/SIGN) guideline for the management of asthma recommends a stepwise approach to therapy, to maintain symptom control and minimize future risk of exacerbations.[3] Inhaled corticosteroids (ICS), prescribed at step 2 of the current BTS/SIGN guideline, are effective controller medications for most children with persistent asthma. For 10%-25% of children with asthma, additional therapy is required.[4-6] For children aged 5-12 years on ICS monotherapy, adding a long-acting β_2-agonist (LABA) is the preferred step-up option (step 3) recommended by the BTS/SIGN when asthma is uncontrolled.[3]

Guidance from the UK National Institute for Health and Care Excellence (NICE) identifies a fixed-dose combination (FDC) inhaler containing ICS and LABA as the optimal means of adding a LABA.[1] However, some children continue to be prescribed separate inhalers. One risk of prescribing a LABA as a separate inhaler is its use without concomitant ICS therapy. This is a major concern discussed in the National Review of Asthma Deaths.[7]

The benefit of FDC over the addition of a separate LABA inhaler to ICS treatment for children with uncontrolled asthma is unclear. Two clinical trials, where adherence was closely monitored, found no difference in symptoms after 3 months[8] and 6 months,[9] when comparing groups randomized with a LABA as a separate inhaler or FDC. However, patient behavior and clinical outcomes are often different in the context of a clinical trial as opposed to "real-life" usual clinical care. One database study using real-life data observed a reduced need for short-acting β_2-agonist (SABA) and oral corticosteroid (OCS) treatment in children treated with a LABA as an FDC compared with a separate inhaler.[4] These results are limited, however, as there was no matching at baseline for factors known to be different between groups, including age and obesity.[10] We have recently reported that children stepped up to a LABA as a separate inhaler are younger and on a lower dose of ICS compared with those stepped up to FDC.[10] These baseline differences might explain the apparent superiority of FDC over a LABA as a separate inhaler.

Rigorously conducted observational research can provide information about outcomes of asthma therapy under conditions of usual clinical practice, to complement information from controlled trials.[11] Results of prior retrospective observational studies suggest that adherence and refill persistence may be better with a combination inhaler, at least among adults and adolescents.[12-14] In turn, better adherence and persistence could lead to better outcomes. The aim of this large population-based observational study was to compare outcomes between children stepped up to an add-on LABA as separate inhalers, versus those receiving FDC inhalers. Our hypothesis was that children stepped up to separate inhalers would have reduced odds for achieving asthma control compared with matched children stepped up to FDC.

METHODS

Data source and permissions

In a matched cohort study, we sourced medical records and prescribing data from 2 large primary care databases including approximately 15% of children in the UK, as previously described.[10] Duplicate records from individual children were identified and removed. The Clinical Practice Research Datalink (CPRD; formerly General Practice Research Database) is well validated and used frequently for observational research. It is the world's largest repository of anonymized longitudinal data from primary care, drawing from more than 600 subscribing practices throughout the UK.[15,16] The Optimum Patient Care Research Database (OPCRD) is a quality-controlled primary care research database, containing information from more than 400 UK practices caring for approximately half a million patients with asthma.[17] As well as anonymous medical records, the database contains patient-completed questionnaire data. Data were available from January 1990 through April 2012 for the CPRD and through December 2012 for the OPCRD.

The study was conducted to standards recommended for observational research[18] and is registered with the European Network of Centres for Pharmacoepidemiology and Pharmacovigilance.[19] (study reference ENCEPP/SDPP/10483) Use of the data was approved in 2010 by the Independent Scientific Advisory Committee of the (then) General Practice Research Database. The OPCRD has been approved by the Trent Multi Centre Research Ethics Committee for