# Pharmacotherapy — add-on therapies

## Literature review

A literature search was carried out using MEDLINE and Google search engines and the NIH database and the key words "children" (and "pediatric"), "asthma," and 1 of "inhaled corticosteroids," "corticosteroids, add-on," "theophylline," "sodium cromoglycate," "nedocromil" and "omalizumab." Also included were the references from the Canadian Asthma Consensus Report, 1999,[1] the update in 2001,[2] the Third International Pediatric Consensus Statement on the Management of Childhood Asthma[3] and the guidelines of the Global Initiative on Asthma.[4] References were also obtained from the scientific departments of AstraZeneca, MerckFrosst and GlaxoWellcome. Publications through to December 2004 were also reviewed, but they contained insufficient data on the young child with asthma to modify our recommendations.

## Current evidence

ICSs are the agents of first choice for children with asthma. When control is inadequate despite the use of ICSs, the 1999 guidelines[1] recommend assessment to confirm the following:

- good delivery technique
- compliance with treatment
- the absence of a complicating illness (i.e., sinus disease, reflux)
- the absence of an alternative disease (cystic fibrosis, immunodeficiency, etc.)

Level V evidence (group opinion) suggests that most children with asthma will have adequate long-term control with ICSs alone and will not require additional therapy. For the minority of children with asthma who require additional therapy, there are several options.

### *ICSs and long-acting bronchodilators (LABAs)*

Studies of patients under 12 years of age can be divided into 2 types: studies in which the addition of LABA (salmeterol or formoterol) was compared with the existing dose of ICS and studies comparing LABA with placebo. In the latter, children continued to take their usual medications, 1 of which might be an inhaled steroid.

Of the 11 studies in this group,[5–15] 7 were published before the previous update. Nine of the studies involve salmeterol[5–13] and 2 formoterol.[14,15] A total of 2326 children took part in the salmeterol studies and 804 in the formoterol studies.

In 9 studies, the primary outcome measure was pulmonary function ($FEV_1$, PEF, methacholine challenge); in 1 study, the primary outcome measure was quality of life. In contrast to adult studies, none of these used frequency of asthma exacerbation as the primary end point.

In summary, this group of studies provides evidence that LABAs, when added to an ICS, improve pulmonary function, sometimes reduce symptoms and the use of rescue β-agonist and are safe. Concerns remain about tachyphlaxis to LABA with long-term use. There is no evidence that they reduce exacerbation frequency or can be used to reduce the dose of ICS.

No studies compare salmeterol and formoterol as add-on therapies.

One study[16] examined the effectiveness of adding a LABA compared with doubling the dose of inhaled steroid in 177 children on regular ICSs with symptoms of inadequate asthma control (several nocturnal awakenings per week). Study duration was 1 year and the primary outcome measure was $FEV_1$. There were 3 arms: beclomethasone dipropionate, 400 μg/day; beclomethasone dipropionate, 400 μg/day, plus salmeterol, 100 μg/day; and beclomethasone dipropionate, 800 μg/day. All 3 groups showed similar significant improvement in asthma control throughout the study and there were no differences in $FEV_1$ or in any of the secondary outcome measures (daytime and nighttime symptoms, morning PEF, methacholine challenge, exacerbation rates). There was no evidence of tolerance to salmeterol. In the beclomethasone plus salmeterol group, when salmeterol was discontinued, $FEV_1$ decreased significantly (5.6%). On the negative side, growth was significantly slower in the beclomethasone dipropionate (800 mg) group.[16] This investigation suggests that there is limited added benefit of LABA or even doubling the dose of ICS in children with mild-to-moderate persistent asthma. A limitation of this study is the fact that the doses used are now recognized as being near the top of the beclomethasone dipropionate dose–response curve.

### *LTRAs as add-on therapy*

Three studies[17–19] of LTRAs as add-on therapy involved 1304 patients; 2 of the studies were published since the last formal guidelines. No studies compare adding an LTRA with doubling of the ICS dose. The results are based on studies in which subgroups of patients happened to be using ICS. Montelukast is the only LTRA that has been studied in children. Compared with placebo, montelukast led to improvement in pulmonary function ($FEV_1$), better quality

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of life, a decrease in the use of rescue β-agonist (by approximately a third) and a decrease in the total number of days the patient experienced an asthma exacerbation. There was no evidence of tolerance to a bronchodilator response nor were there any concerns regarding adverse events.

The response to the use of an LTRA was independent of the use of ICSs. The response to the LTRA was the same regardless of ongoing use of an ICS. Thus, the study investigators concluded that the effect of LTRAs was additive to that of ICSs.

## Implications for research

1. In mild-to-moderate and moderate-to-severe pediatric asthma, comparison of a lower dose of ICS (e.g., beclomethasone 200 mg/day) with beclomethasone plus salmeterol and with a moderate dose of beclomethasone (e.g., 400 mg/d).
2. In children with mild-to-moderate asthma, comparison of ICS plus LABA with ICS plus LTRA.
3. In mild persistent asthma, comparison of low-dose and moderate-dose ICS with placebo and comparison of low-dose ICS with montelukast and with placebo.
4. Population studies to indicate the prevalence of mild intermittent, and mild, moderate and severe asthma.
5. Delivery and safety studies in children under 5 years of age.
6. Studies of montelukast as intermittent therapy for intermittent asthma.
7. Development of better methods to assess asthma severity, control and airway inflammation and repair in children.

## Implementation strategies

1. Introduce the asthma guidelines as previously recommended.
2. Consider a similar strategy to involve the public via an already established and credible organization.

## References


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