Use of budesonide/formoterol in people at risk of severe asthma exacerbations

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This randomised controlled trial found that budesonide/formoterol maintenance and reliever treatment did not reduce the likelihood of episodes of high use of reliever treatment over 24 weeks, compared with standard maintenance treatment with budesonide/formoterol and as needed salbutamol. Maintenance and reliever treatment did not appear to increase the risk of people overusing relievers without medical review, or increase long-term systemic corticosteroid exposure. Although the study provides some reassurance around the risks and benefits of budesonide/formoterol maintenance and reliever treatment, it does not provide any strong evidence for using this treatment regimen ahead of standard maintenance treatment with an inhaled corticosteroid and long-acting beta-2 agonist plus as needed reliever. Clinicians should continue to follow the British guideline on the management of asthma and consider which treatment regimen to use on an individual patient basis.

Overview and current advice

The British guideline on the management of asthma\(^1\) 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 children aged 5 years and over and adults, an ICS and a long-acting beta-2 agonist (LABA) should be considered.

As well as being licensed for regular maintenance treatment, 2 ICS/LABA combination inhalers (beclometasone/formoterol [Fostair\(^2\)] and budesonide/formoterol [Symbicort\(^3\)]) are licensed for maintenance and reliever therapy in adults, meaning they are taken as regular maintenance treatment and as needed in response to asthma symptoms. ICS/LABA maintenance and reliever treatment has been shown to reduce the risk of severe asthma exacerbations in people with moderate to severe asthma compared with ICS/LABA maintenance treatment plus as-needed salbutamol\(^4\).

When the British guideline on the management of asthma\(^1\) was updated in 2011, budesonide/formoterol (Symbicort\(^3\)) was the only product available that was licensed for maintenance and reliever treatment. The guideline advises that budesonide/formoterol maintenance and reliever treatment is an alternative to the stepped approach to asthma treatment for some people at steps 2 and 3.

Beclometasone/formoterol (Fostair\(^2\)) was licensed for maintenance and reliever therapy in asthma in December 2012. See the NICE evidence summary: new medicine on Fostair\(^2\) for more information.
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

This study\(^4\) assessed whether budesonide/formoterol maintenance and reliever treatment reduced the likelihood of people with asthma needing episodes of high use of beta-2 agonist to control symptoms, and when such episodes did occur, if people would be less likely to seek medical review. It also assessed whether any subsequent reduction in severe asthma exacerbations was at a higher burden of systemic corticosteroid.

The study\(^4\) was a 24-week, open-label, randomised controlled trial in 4 primary care practices and 1 hospital in New Zealand. It included 303 people aged 16 to 65 years (mean age 42 years) with asthma, a current prescription for an inhaled corticosteroid, and at least 1 asthma exacerbation in the previous year. All patients received budesonide 200 micrograms/formoterol 6 micrograms (2 inhalations twice a day) and were randomised to as-needed treatment with either 1 inhalation of budesonide 200 micrograms/formoterol 6 micrograms (n=151) or 1 or 2 inhalations of salbutamol 100 micrograms (n=152). Allocation was concealed.

The primary outcome was the proportion of patients with at least 1 episode of high use of beta-2 agonist during the study. This was defined as more than 8 inhalations in addition to the 4 maintenance doses per 24 hours in the as needed budesonide/formoterol group, and more than 16 inhalations of salbutamol per 24 hours in the as needed salbutamol group. (Note that these doses are higher than recommended in the summaries of product characteristics.) Patients were advised to seek medical advice at these high-use thresholds. Electronic monitors were incorporated into the inhalers to measure the date and time of inhalations. Secondary outcomes included inhaled medication use, corticosteroid use, severe exacerbations and adverse events.

The results of the study are outlined in the table below.\(^4\) It found that budesonide/formoterol maintenance and reliever treatment did not statistically significantly reduce the risk of episodes of high use of reliever treatment, compared with standard maintenance treatment with budesonide/formoterol and as needed salbutamol. However, there were statistically significantly fewer days of high use in the as needed budesonide/formoterol group. When high-use days occurred, people in the as needed budesonide/formoterol group had statistically significantly fewer days of high-use without medical review compared with those in the as needed salbutamol group; however, the proportion of high-use days without medical review was similar in the groups.

Although the ICS dose per day was statistically significantly higher in the as needed budesonide/formoterol group, the oral corticosteroid dose over the course of the study was higher in the as needed salbutamol group. This was possibly due to the higher number of exacerbations in the as needed salbutamol group. Annual systemic corticosteroid exposure was estimated to be similar in the 2 groups. (See table for details.) The incidence and type of adverse events seen were similar in the 2 groups.

Table: Primary and secondary outcomes and comparisons for as needed budesonide/formoterol and as needed salbutamol

<table>
<thead>
<tr>
<th>Analysis</th>
<th>p value</th>
</tr>
</thead>
<tbody>
<tr>
<td>As needed budesonide/formoterol (n=151)</td>
<td>As needed salbutamol (n=152)</td>
</tr>
<tr>
<td>Proportion of people with at least 1 episode of high use of reliever</td>
<td>56% (n=84)</td>
</tr>
<tr>
<td>Number of days of high use</td>
<td>5.1 days</td>
</tr>
<tr>
<td>Number of high-use days without</td>
<td>8.5 days</td>
</tr>
<tr>
<td>medical review in people with at least 1 high-use episode</td>
<td></td>
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</tr>
<tr>
<td>Proportion of high-use days without medical review in people with at least 1 high-use episode</td>
<td>93%</td>
</tr>
<tr>
<td>Budesonide dose per day</td>
<td>943.5 micrograms</td>
</tr>
<tr>
<td>Prednisone dose over 24 weeks</td>
<td>77.5 mg</td>
</tr>
<tr>
<td>Estimated yearly systemic corticosteroid dose (prednisone equivalent)</td>
<td>793.7 mg</td>
</tr>
<tr>
<td>Number of severe exacerbations (weighted mean rate per year)</td>
<td>35</td>
</tr>
</tbody>
</table>

**Abbreviations:** CI, confidence interval; RR, relative risk

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### Commentary

**Commentary provided by the NICE Medicines and Prescribing Centre**

The open-label design of the study means it is subject to bias. However, the authors note that if a double-blind trial had been used, patients assigned to budesonide/formoterol maintenance and reliever treatment would have had to take 2 inhalers negating any possible advantages of single inhaler therapy and reducing the generalisability of the findings.

Budesonide/formoterol metered dose inhalers (MDIs) were used, rather than Turbohalers, because validated electronic dose monitors were not available for the Turbohaler. This may affect the applicability of the results to UK clinical practice. However, the authors note that studies have shown that the MDI and Turbohaler are clinically comparable.

Although the study provides some reassurance around the risks and benefits of budesonide/formoterol maintenance and reliever treatment, it does not provide any strong evidence for using this treatment regimen ahead of the traditional stepped model of asthma care. Both treatment regimens are options in the British guideline on the management of asthma and clinicians will need to consider the most appropriate treatment on an individual basis, taking the views of the person with asthma into account when making a shared decision.

### Study sponsorship

Health Research Council of New Zealand

### References


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