Asthma affects over 5 million patients in the UK and has an annual treatment cost exceeding £1 billion per year. Poorly controlled asthma leads to significant morbidity, and results in 4.1 million GP consultations per year and 1.1 million work days lost. The recent confidential enquiry, National Review of Asthma Deaths (NRAD), highlighted a number of deficiencies in asthma care that might be contributing to the still significant mortality associated with asthma.

Despite good pharmacological treatments for asthma symptoms, many patients have symptoms that remain poorly controlled. There are several reasons that might contribute to this that include poor treatment adherence, under recognition of signs and symptoms of poor asthma control, and inappropriate prescribing practices.

The NRAD report highlighted both under prescribing of preventer medications and inappropriate long-acting beta, agonist (LABA) prescriptions as contributory factors in a number of the asthma deaths reviewed. A total of 80 per cent of cases reviewed had received fewer than 12 preventer medication prescriptions in the year preceding their death. A total of 14 per cent of patients who died had been prescribed a single agent LABA at the time of death and at least 3 per cent were on LABA monotherapy without inhaled corticosteroid (ICS) preventer therapy. The key recommendations associated with these findings were that adherence to medication should be routinely checked and that where LABA bronchodilators are prescribed for people with asthma, they should be prescribed in a single combination inhaler with an ICS.

One possible treatment strategy that might address both of these concerns is the use of combination ICS and LABA in a single inhaler as both maintenance and reliever therapy (SMART).

There is evidence that ICS use increases in patients who are prescribed SMART therapy implying that SMART may be a useful strategy to overcome poor adherence with ICS. Clinical trial data have also shown that the benefits of SMART go beyond improved adherence and the convenience of a single inhaler device: reduced frequency of severe exacerbations and reduced hospitalisation rates have been seen in SMART-treated populations on lower ICS doses than fixed-dose inhaler comparator groups.

The place for SMART
Guideline-based asthma management, such as described in the British Thoracic Society/Scottish Intercollegiate Guidelines Network (BTS/SIGN) asthma guideline (2014), advocates the use of SMART therapy in patients whose asthma remains poorly controlled despite the reg
ular use of an ICS (step 3). At this step, prescription of a combination inhaler containing both ICS and LABA is recommended in order to aid treatment compliance and ensure that the LABA is not being taken without the ICS. Most patients at Step 3 will be on at least two inhalers – a combination ICS/LABA inhaler and a short-acting beta\(_2\) agonist (SABA) inhaler – so using a single inhaler for maintenance and reliever therapy has the additional benefit of simplifying the treatment regimen for patients.

The pan-European INSPIRE study (\(n=3415\)), which looked at the attitudes and actions of asthma patients on regular maintenance therapy, found that most patients felt confident that they could self-manage their asthma (88 per cent). Most patients wanted treatment giving immediate relief of symptoms (90 per cent), but were concerned about taking too much medication when they felt well (54 per cent). The self-control offered by SMART therapy would be particularly suitable for this cohort of patients.

As with any symptom-directed therapy, there will be patients for whom SMART therapy is not suitable, such as habitual users of reliever medication and under perceivers of asthma symptoms. It is important that all patients being considered for SMART therapy have an understanding of the maximum daily allowance of additional reliever use and it is recognised that SMART therapy is not a treatment for all.

We would recommend that patients on SMART therapy use an appropriate self-management plan (see Figure 2).

### Licensed products

Budesonide/formoterol combination products Symbicort and more recently DuoResp are licensed for use as SMART therapy in adult patients (>18 years). The beclometasone/formoterol combination inhaler, Fostair, has also recently been licensed for use as SMART therapy in adult patients (>18 years).

Both combinations of ICS and LABA are suitable for use as maintenance and reliever therapy as they contain the LABA formoterol. Formoterol is a potent beta\(_2\) agonist that is well suited to maintenance and reliever therapy by virtue of its rapid onset of action (within one to three minutes of inhalation), required for quick symptom relief, and a lack of tolerability issues enabling repeated dosing.

### Dosing

The maximum daily dose of formoterol is 72\(\mu\)g, which limits the number of inhalations that can be used in a single day. Symbicort SMART regimens use the 6\(\mu\)g formulations (200/6 or 100/6). Symbicort inhalers containing 12\(\mu\)g are not licensed for use as SMART. Symbicort SMART can be prescribed as 100/6 or 200/6 two to four puffs in two divided doses for maintenance with up to eight additional puffs daily as required for relief of symptoms.

DuoResp 200/6 is also licensed at the same dose; two to four puffs in two divided doses for maintenance with up to eight additional puffs daily as required for relief of symptoms. The DuoResp inhaler containing 12\(\mu\)g is not licensed for use as SMART. Fostair 100/6 contains 6\(\mu\)g of formoterol and can be prescribed as 100/6 two puffs daily in two divided doses for maintenance with up to six additional puffs daily as required for relief of symptoms.

It should be noted that patients requiring ≥1 puff/day for the relief of symptoms should have their maintenance treatment reviewed and escalated if appropriate, as this would suggest that their asthma control is sub-optimal. It is also worth noting that Fostair, DuoResp and Symbicort inhalers all contain 120 actuations; a patient using the maximum daily dose for maintenance and reliever therapy will use a Symbicort or DuoResp inhaler in 10 days and a Fostair inhaler in 15 days.

### Product choice

The decision to prescribe Symbicort, DuoResp or Fostair should take account of the following.

#### Inhaler device

Symbicort and DuoResp are delivered by dry-powder inhaler (DPI) devices. Symbicort uses a Turbohaler device, while DuoResp uses the breath-activated inhaler device, Spiromax. Fostair is delivered via a metered-dose inhaler (MDI). The MDI is compatible with spacer devices. Patient preference for different inhaler devices and competence at using the device will influence choice.

#### Particle size

Fostair delivers beclometasone/formoterol as an extra fine hydrofluoroalkane particle formulation, targeting

<table>
<thead>
<tr>
<th>Product</th>
<th>ICS</th>
<th>LABA</th>
<th>Inhaler device</th>
<th>SMART dosing</th>
<th>Max daily dose</th>
<th>30 day cost equivalent (1 puff bd)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Symbicort 200/6</td>
<td>Budesonide 200(\mu)g Formoterol 6(\mu)g</td>
<td>DPI Turbohaler</td>
<td>1–2 puffs bd + up to additional 8 puffs/24hrs</td>
<td>12 puffs</td>
<td>£19.00</td>
<td></td>
</tr>
<tr>
<td>Symbicort 100/6</td>
<td>Budesonide 100(\mu)g Formoterol 6(\mu)g</td>
<td>DPI Turbohaler</td>
<td>1–2 puffs bd + up to additional 8 puffs/24hrs</td>
<td>12 puffs</td>
<td>£16.50</td>
<td></td>
</tr>
<tr>
<td>DuoResp 200/6</td>
<td>Budesonide 200(\mu)g Formoterol 6(\mu)g</td>
<td>DPI Spiromax</td>
<td>1–2 puffs bd + up to additional 8 puffs/24hrs</td>
<td>12 puffs</td>
<td>£14.98</td>
<td></td>
</tr>
<tr>
<td>Fostair 100/6</td>
<td>Beclometasone 100(\mu)g Formoterol 6(\mu)g</td>
<td>MDI</td>
<td>2 puffs bd + up to additional 6 puffs/24hrs</td>
<td>10 puffs</td>
<td>£14.66</td>
<td></td>
</tr>
</tbody>
</table>

Table 1. Combination inhaler preparations licensed for use as SMART therapy.
both large and small airways with improved deposition in the smaller airways compared with the other combination inhalers. Patients with small airways dysfunction (reduced forced expiratory flow$_{25-75}$) might benefit from Fostair targeting the smaller airways.\(^7\)

**Clinical evidence**

In 2005, evidence was published to support the use of budesonide/formoterol as both maintenance and reliever medication in asthma.\(^8\) This double-blind, randomised controlled trial of 2760 patients using low maintenance dose budesonide/formoterol showed that in those patients where SABA was replaced with budesonide/formoterol as reliever medication there was an increased time to first severe exacerbation ($p<0.001$) resulting in a 45–47 per cent lower exacerbation risk compared to budesonide/formoterol with SABA reliever.

A Cochrane Review published in 2013 assessed the efficacy and safety of SMART (budesonide/formoterol) in comparison with maintenance treatment provided by combination inhalers with higher ICS dose and SABA for relief of symptoms.\(^9\) Four studies with a total of 9130 patients were included. All of the studies were funded by the pharmaceutical company AstraZeneca. The review concluded that SMART therapy reduces the number of patients having an asthma exacerbation requiring oral steroids and the number requiring hospitalisation or emergency department visit compared with those treated with fixed-dose combination inhalers.

The mean daily dose of ICS required in the SMART therapy group was lower than in the fixed-dose combination inhaler group, suggesting that increasing the ICS in response to symptoms, but keeping the dose lower when stable, is more effective and leads to lower overall ICS requirements. The review was unable to comment on several secondary outcomes such as lung function measures, quality of life and asthma symptom control.

In order to address the issue of whether SMART therapy improves asthma control, a large post hoc analysis was carried out on five clinical trials (>12,000 patients) of budesonide/formoterol SMART treatment.\(^10\) This concluded that the proportion of patients achieving target levels of current clinical control were similar or higher with SMART compared with the same or a higher fixed-dose combination inhaler plus SABA as reliever.

A recent study that evaluated the use of beclometasone/formoterol as SMART therapy supporting its licence for this treat-
ment regimen extended the results seen with budesonide/formoterol SMART. A total of 1714 patients were randomised to receive either beclometasone/formoterol plus SABA as required or beclometasone/formoterol plus beclometasone/formoterol as required (up to eight inhalations per day). Beclometasone/formoterol SMART significantly prolonged the time to first exacerbation (by 75 days; \( p=0.0003 \)) and significantly reduced the risk of experiencing a severe exacerbation by 36 per cent (95% CI 18 to 51 per cent; \( p=0.0005 \)).

Beclometasone/formoterol SMART also reduced the yearly rate of severe exacerbations by 34 per cent, hospitalisations and emergency department visits by 33 per cent and oral corticosteroid courses by 35 per cent (all \( p<0.001 \)) when compared to beclometasone/formoterol and SABA.

**Conclusion**
The use of a single combination ICS and rapid-onset LABA for maintenance and reliever therapy in patients with moderate-to-severe asthma has a number of attractions. It may not be suitable for all patients, but for selected patients there are clear advantages.

Owing to its simplicity, the treatment regimen may help to improve adherence while reducing the overall ICS dose required to achieve asthma control. This may have an impact on long-term treatment side-effects and their associated morbidity.

Several studies have now shown that SMART treatment can increase the time to first exacerbation, and reduce the frequency of severe exacerbations and asthma hospitalisations. Asthma exacerbations place a significant burden on healthcare resources and means of controlling symptoms to improve patient’s quality of life while reducing healthcare expenditure should be embraced.

**References**

**Declaration of interests**
None to declare.

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