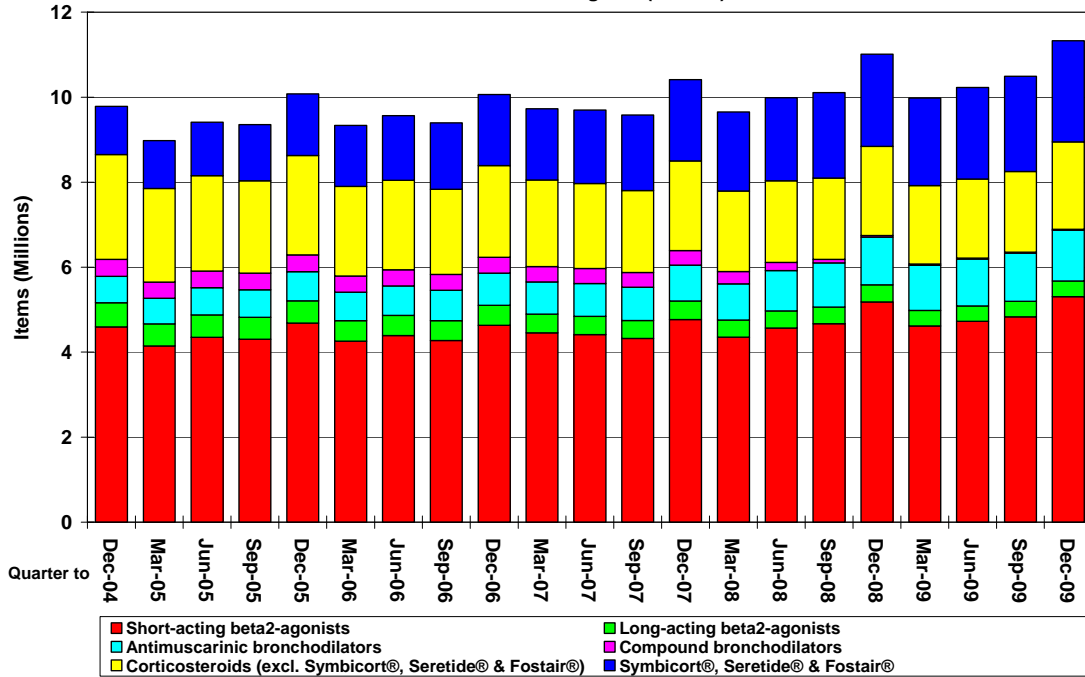


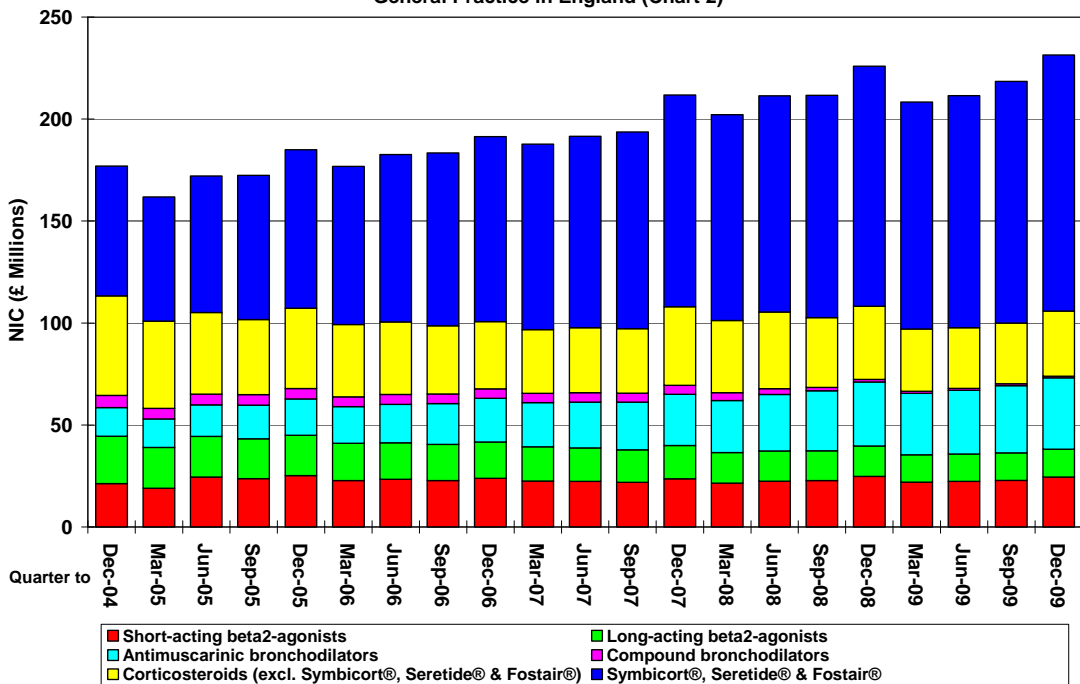
## Asthma and COPD

This review will focus on the most recent evidence regarding the safety of currently recommended options for treating chronic asthma and exacerbations in chronic obstructive pulmonary disease (COPD). Charts 1 and 2 show trends in prescribing and cost of the most frequently prescribed inhaled drugs for these conditions.

**Trends in Prescribing of Drugs for Asthma and COPD in General Practice in England (Chart 1)**



**Trends in Spending on Drugs for Asthma and COPD in General Practice in England (Chart 2)**



## Asthma

Asthma affects approximately 5.2 million people in the UK, including 1.1 million children in whom it is the most common long-term childhood medical condition. There are over 4.1 million GP consultations for asthma per year, and trends in UK death rates have shown little improvement over the last 20 years.<sup>1</sup> National guidelines on asthma are produced jointly by the British Thoracic Society (BTS) and Scottish Intercollegiate Guidelines Network (SIGN), sections of which are updated annually.<sup>2</sup> Their emphasis is very much on early intervention when asthma is suspected, prevention through early use of inhaled corticosteroids (ICS) and regular review.

In the current BTS guidelines for adults long-acting beta<sub>2</sub>-agonists (LABA) should be introduced at step 3 and given in addition to a short-acting beta<sub>2</sub>-agonist and ICS. If there is no response to the LABA it should be discontinued and the dose of ICS increased to the equivalent of beclometasone 800 mcg/day.<sup>2,3</sup>

Over the years, concerns have been expressed about the use of LABAs, in asthma, especially if not combined with an ICS. The Salmeterol Multicenter Asthma Research Trial (SMART) found that, in patients receiving salmeterol there were more respiratory- or asthma-related deaths, or life-threatening experiences compared with those receiving placebo.<sup>4</sup> A meta-analysis of 19 randomized controlled trials (RCTs) of LABAs in asthma also found that LABA use increased the risk of hospitalization for asthma (1.72% vs 0.6%; OR 2.6; 95%CI 1.6 to 4.3).<sup>5</sup> In a Cochrane systematic review of 34 RCTs comprising 62,630 patients with chronic asthma, the risk of mortality and non-fatal serious adverse events with salmeterol was compared with placebo or a regular short-acting beta<sub>2</sub>-agonist. The review reported the following:

- All cause mortality was higher with regular salmeterol than placebo but the increase was not significant (Peto OR 1.33; 95% CI 0.85 to 2.08).
- Non-fatal serious adverse events were significantly increased when regular salmeterol was compared with placebo (OR 1.15; 95% CI 1.02 to 1.29) but there was insufficient evidence to determine whether the risk in children was higher or lower than in adults. For every 188 people treated with regular salmeterol, one extra serious adverse event occurred over 28 weeks (95% CI 95 to 2606).
- There was no significant increase in fatal or non-fatal serious adverse events for regular salmeterol compared with regular salbutamol.

Individual patient data from the Serevent Nationwide Surveillance Trial were combined with the results of the SMART study, as all the asthma-related deaths in adults occurred in these studies. In patients who were not taking ICS, compared to those taking regular salbutamol or placebo, there was a significant increase in risk of asthma-related death with regular salmeterol, (OR 9.52; 95% CI 1.24 to 73.09). The confidence interval for patients taking ICS was too wide to rule in or out an increase in asthma mortality in this group.<sup>6</sup>

A further recent Cochrane review of 27 RCTs concluded that if LABAs were given to people who were not already using an ICS, there was no significant reduction in exacerbations compared with using an ICS alone. However, if a

LABA was added to existing ICS therapy, there were clinically small but statistically significant improvements in some measures of lung function (as well as a significantly increased risk of tremor compared with using ICS alone). This supports step 3 of the BTS guidelines.<sup>7</sup> To achieve an optimum risk-benefit ratio when using LABAs in asthma, the Commission on Human Medicines (CHM) advises:

- LABAs should only be prescribed with an ICS when regular use of an ICS has failed to control asthma adequately.
- LABAs should not be initiated in patients with rapidly deteriorating asthma.
- LABAs should be introduced at a low dose initially, monitored carefully and discontinued in the absence of benefit.
- LABAs should be stepped down when good long-term asthma control has been achieved.<sup>8</sup>

The BTS guidelines state that there is no difference in efficacy between giving a LABA/ICS combined in one device or separate inhalers. In the last five years, prescribing and spending of LABA/ICS preparations has doubled to 2.4 million items costing £125.6million. They account for 54% of all ICS prescribing and 80% of the cost. This may suggest that there is a tendency for people to be stepped up to step 3 and for treatment not to be reviewed and stepped back down again when control has been achieved. When a person is stabilised on combination inhalers, prescribers may perceive this as a reason not to change to separate inhalers. Alternatively, it could be the result of recent advice from the Medicines and Healthcare products Regulatory Agency (MHRA) with regard to their use in COPD (see below).

For the minority (fewer than 5% with asthma) who are poorly controlled at step 3, the combination inhaler budesonide/formoterol has been shown to improve control and is now licensed for use in people aged 18 years and over as a regular preventer and reliever treatment.<sup>4</sup> There are no systematic reviews evaluating this approach, however, and further evaluation is still needed.<sup>9</sup>

In light of the prescribing data over the last five years, it is worth mentioning oral leukotriene receptor antagonists (LTRAs, montelukast and zafirlukast). LTRAs have limited indications. For asthma, LTRAs should only be introduced at step 3 for children aged 5 years and over, and in adults who have not responded to increased doses of ICS following cessation of the LABA.<sup>2</sup> They can also be trialled at step 4 in adults and children aged 5 years and over who have persistent poor control despite taking high dose ICS and a LABA. Despite this their combined prescribing has doubled in the last five years to 328,000 items at a cost of £10.5million in the reporting quarter. Montelukast accounts for 97% of prescribing and 98% of cost.

## **Chronic Obstructive Pulmonary Disease**

In the UK 3.2 million people have COPD and it is the fifth most frequent cause of death, 86% of which is directly attributable to smoking.<sup>10</sup> The MHRA has recently reported on the safety of LABAs, anticholinergics and ICS in COPD. Their conclusions combined with evidence published more recently are summarized below.

**LABAs:** The MHRA has recently completed a review of LABAs in COPD, both as monotherapy and in combination with ICS.<sup>8</sup> The MHRA concluded that LABA/ICS combinations have greater efficacy than either used alone but the extent of the additional benefit provided by the LABA/ICS combination vs LABA alone is variable and not always clinically significant. There does appear to be a reduction in the rate of exacerbations with LABA/ICS but this has not been proven for milder disease and ICS should be used in line with NICE guidance. LABA/ICS combinations account for 87% of all LABA prescribing (single preparation LABAs and LABA/ICS combinations), and 90% of the cost.

**ICS:** The MHRA have highlighted the increased risk of pneumonia with ICS as a key issue following the publication of recent studies. In the TORCH study the probability of pneumonia was 19.6% in a group of patients receiving salmeterol/fluticasone and 18.3% with fluticasone alone vs 12.3% with placebo.<sup>11</sup> A large systematic review of 12,446 patients showed a relative risk increase of 63% for pneumonia with LABA/ICS compared with LABA.<sup>12</sup>

**Short-acting (ipratropium) and long-acting (tiotropium) anticholinergics:** These have also come under recent scrutiny from the MHRA following the publication of two meta-analyses (ipratropium and tiotropium), an observational study (ipratropium only) and a large RCT (tiotropium vs placebo). At the time, the MHRA concluded that the conflicting findings made it difficult to draw any firm conclusions regarding the risk of all-cause mortality, cardiovascular death or stroke associated with inhaled anticholinergics and that further analyses were needed.<sup>11</sup> However, since these studies, a US cohort study in 82,717 veterans with COPD found that exposure to four or less 30-day equivalents of ipratropium within the last six months was associated with a 40% increase in cardiovascular events. In contrast, a report on the cardiovascular safety of tiotropium in COPD in 10,846 patients found that tiotropium does not increase the risk of cardiovascular events.<sup>13</sup> It should be remembered that none of these studies were designed to specifically look at cardiovascular endpoints and that these were reported based on adverse event reporting and not efficacy endpoints.

### **Prescribing Data**

**(Reporting quarter = October-December 2009, Index quarter = October-December 2004)**

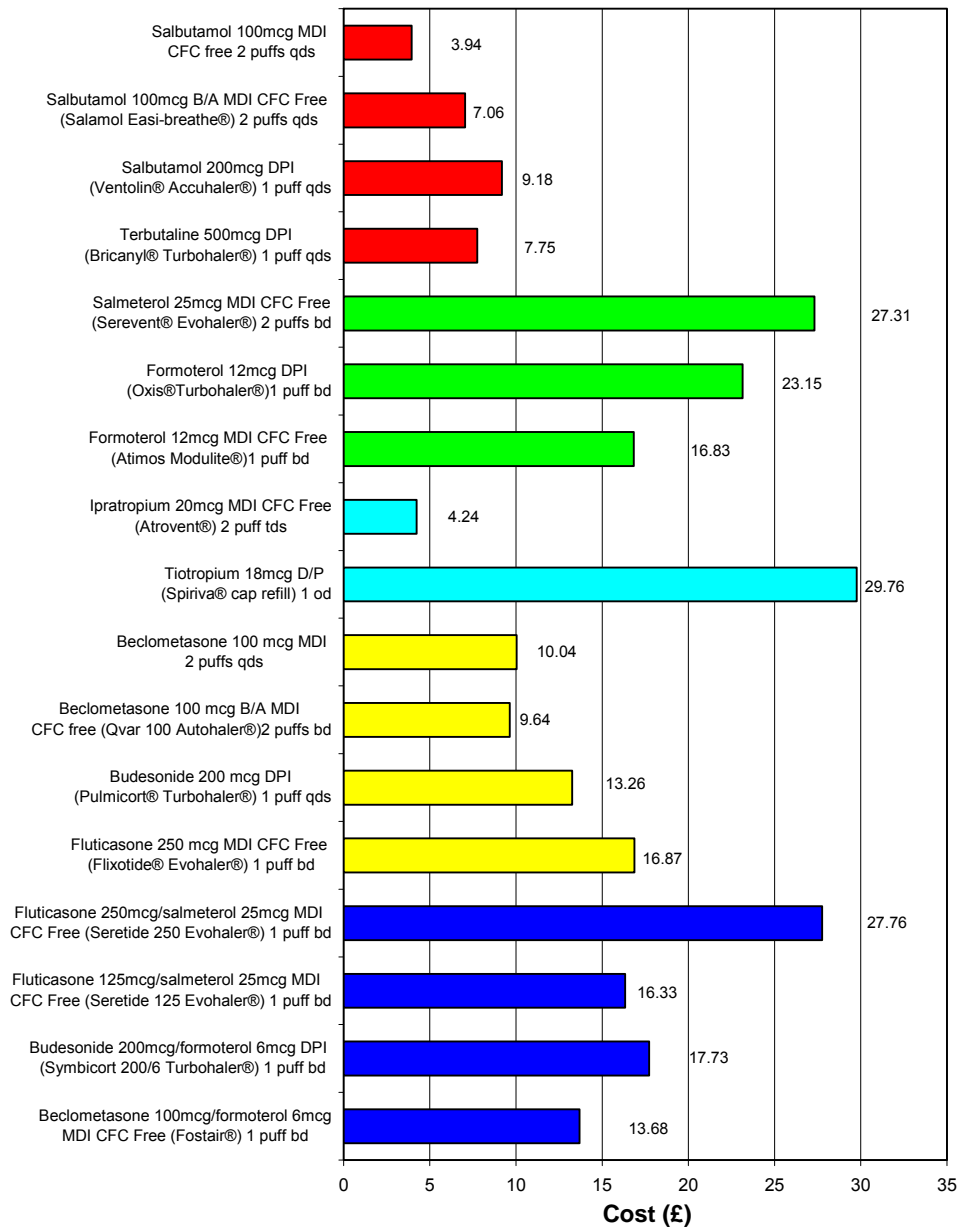
In the last five years, prescribing of antimuscarinic bronchodilators has almost doubled to 1.2 million items while costs have risen 148% to £34.9million. At 792,000 items, tiotropium now accounts for 66% of all antimuscarinic bronchodilator prescribing and 88% of the cost (£30.8million). Prescribing of ipratropium has barely increased (3% to 401,000 items) with costs decreasing

10% to £4.1million. Compound bronchodilator prescribing and spending have fallen by around 90% to 23,000 items and £844,000. The majority of the prescribing and cost (over 99%) are for ipratropium with salbutamol (Combivent®)

Prescribing of short-acting beta<sub>2</sub>-agonists has increased by 16% over the last five years to 5.3 million items and their cost increased 15% to £24.5million. Salbutamol represents 96% of all prescribing of short-acting beta<sub>2</sub>-agonists and 91% of cost. Prescribing and spending for single preparation LABAs have decreased by 36% and 41% respectively to 370,000 items and £13.7million per quarter. Salmeterol is the most commonly prescribed LABA accounting for 90% of all items and cost.

Over the last five years prescribing of ICS as single preparations has decreased by 17% to 2.1 million items and cost has fallen by 35% to £31.9million. Beclometasone is still most commonly prescribed (1.7 million items, £21.5million). Prescribing of fluticasone has fallen by 39% to 187,000 items while costs have fallen by 51% to £5.3 million. Prescribing and cost of budesonide have decreased by around 40% to 155,000 items and £4.7million. Over the last five years prescribing of fluticasone with salmeterol (Seretide®) has increased by 90% and now stands at 1.7 million items and £91.3million, accounting for over 70% of prescribing of and spending on LABA/ICS preparations. Prescribing of budesonide with formoterol (Symbicort®) is 666,000 items at a cost of £33.2million. Prescribing of beclometasone with formoterol (Fostair®) is 30,000 items costing £1million.

### Cost for 28 Days Treatment



Prices based on Drug Tariff May 2010 and the NHS dictionary of medicines and devices. Dose based on WHO DDDs where possible, otherwise BNF stated dose. The WHO DDD is a unit of measurement based on the assumed average maintenance dose in adults. It may not necessarily reflect the actual dose used.

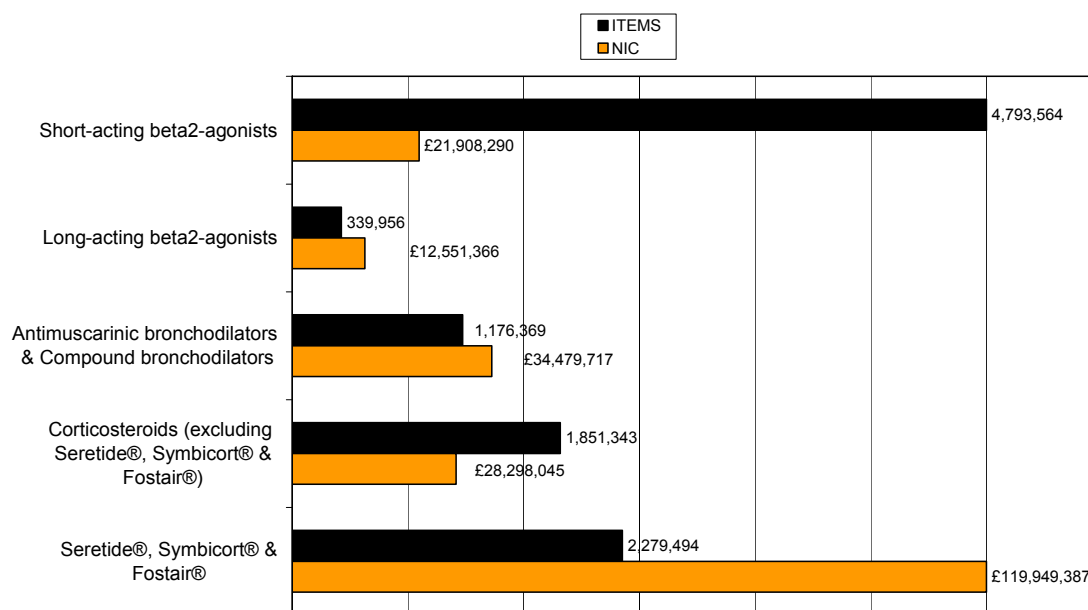
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2. British Guideline on the Management of Asthma. British Thoracic Society/ Scottish Intercollegiate Guidelines Network (2009).  
[www.sign.ac.uk/pdf/sign101.pdf](http://www.sign.ac.uk/pdf/sign101.pdf)
3. National Prescribing Centre. Asthma - Data-focused commentary. Available from  
[www.npci.org.uk/therapeutics/resp/asthma/data\\_commentary/data\\_focussed\\_commentary\\_asthma.php](http://www.npci.org.uk/therapeutics/resp/asthma/data_commentary/data_focussed_commentary_asthma.php)

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12. Rodrigo GJ et al. Safety and efficacy of combined long-acting beta-agonists and inhaled corticosteroids vs long-acting monotherapy for stable COPD. *Chest* 2009; 136; 1029-38
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#### SUMMARY

- There are over 4.1 million GP consultations for asthma per year.
- LABAs should only be prescribed for asthma when regular use of an ICS has failed to control the symptoms. They should be increased gradually and stopped in the absence of effect.
- COPD is the fifth most frequent cause of death in the UK.
- ICS should usually not be used alone in COPD but rather used with a LABA; combination products of ICS and LABA show no greater efficacy than separate inhalers.
- Evidence to date suggests that ipratropium is more likely to cause cardiovascular events than tiotropium.

**Prescribing and Spending on Drugs used in Asthma and COPD  
in England for Quarter to March 2010**



	Quarter to March 2010	
	National	
	ITEMS/1000 PUs	NIC/1000 PUs
Ipratropium Bromide	5.07	£52.03
Tiotropium	10.83	£411.91
Long-acting beta <sub>2</sub> -agonists	4.67	£172.70
Seretide®, Symbicort® & Fostair®	31.36	£1,650.45
Leukotriene Receptor Antagonists	4.39	£140.14