

# Obtaining optimal control in mild asthma: theory and practice

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**Background.** Studies have shown that asthma severity is easily under-estimated and as a result, patients may be under-treated with reduced asthma control.

**Objective.** This study, performed in the General Practice Research Database (GPRD), investigates asthma control in patients treated as intermittent asthmatics (short-acting beta agonist (SABA) alone), or persistent asthmatics (additional inhaled cortico-steroid (ICS), no other medication).

**Methods.** Patients (0–45 years) diagnosed with asthma between 1 January 1995 and 31 December 2001 taking  $\geq 2$  scripts for SABA (SABA only group) or  $\geq 3$  scripts for ICS (ICS group) in the first six months following diagnosis were selected. Factors associated with drug prescriptions were assessed.

**Results.** SABA script rates were 3.6 and 5.1 per year in the SABA and ICS group respectively, i.e.  $>1$  dose/day. 10.5% of SABA group and 13.4% of ICS group used oral steroids. Within the SABA group, 37% were stepped up to ICS, the time to first ICS script being significantly associated with prior hospitalization (RR 2.26, CI 1.65–3.10) and atopy (RR 1.47, CI 1.33–1.63). A higher rate of oral steroid use was significantly associated with using ICS, being female, adult and smoking. Smokers and atopic individuals had increased risk of obtaining an earlier script for oral steroid (RR1.32, CI 1.10–1.59 and RR 1.28, CI 1.10–1.49, respectively).

**Conclusions.** Asthma control was sub-optimal in a substantial proportion of patients using relatively high doses of SABA, or SABA and ICS from the outset of asthma treatment in general practice. Being female, atopic, a smoker and prior hospitalization were all associated with lack of asthma control and could guide physicians in treatment prescribing.

**Keywords.** Asthma, control, severity, therapy.

## Introduction

Up to 80% of patients with asthma in the UK are diagnosed and treated within general practice.<sup>1</sup> To date there is little longitudinal epidemiological data available about the morbidity experienced by asthmatic patients who are treated using the standard therapies of either short-acting beta-agonist (SABA) monotherapy or additional inhaled corticosteroids (ICS). The Global Initiative for Asthma (GINA) and British Thoracic

Society (BTS) guidelines<sup>2–4</sup> advise that only patients with mild intermittent asthma should use SABA as monotherapy. All guidelines have always consistently stated that patients requiring oral steroids to treat exacerbations or who exhibit high reliever requirement should be stepped up in their therapy. The 2004 update of the BTS guidelines goes on to explain in more detail that ICS should be considered if patients use SABA or are symptomatic three times a week or more, or if they have night symptoms once per week or more.<sup>2</sup> This update also states that asthma control is generally assessed against the following standards: minimal symptoms during day or night; minimal need for reliever medication; no exacerbations; no limitation of physical activity; normal lung function ( $FEV_1$  or  $PEF >80\%$  predicted).

Nevertheless a large proportion of patients using medication consistent with mild intermittent or mild persistent asthma have been reported as having poor

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asthma control and high levels of morbidity in some studies, more akin to moderate or severe asthma.<sup>3,5,6</sup> Poor asthma control has previously been attributed to underestimation of severity by the physician and lack of prescription of ICS.<sup>7</sup> Lack of compliance and fear of steroids may also be reasons for some patients not to use the prescribed dose of steroids. This is unfortunate as timely use of ICS reduces morbidity and mortality and improves outcomes for all severity levels of asthma.<sup>8-10</sup> A better understanding of the outcome of standard treatments for asthmatic patients is required to improve clinical care and outcomes.

This study describes the level of asthma control over at least six months in paediatric and adult patients prescribed regular SABA monotherapy, or regular SABA and ICS without any add-on therapy, the traditional medication regimen found within general practice patients globally. Moreover, we analyse risk factors associated with drug utilization in both types of patients.

## Methods

The main objectives of the study were to assess asthma control defined as use of oral steroid and reliever medication in a selected population of asthmatic patients from the General Practice Research Database (GPRD), who had 6 months regular exposure to either SABA monotherapy or SABA with additional ICS therapy. Lack of asthma control was defined by the number of scripts for oral steroids, time to first oral steroid script and the number of scripts for SABA, adjusting for co-variables such as age, gender, atopy, obesity, and smoking, factors which may all influence control. Time to first ICS was also considered as a lack of control in those who started on SABA therapy alone.

Patients were selected from 133 000 patients with a diagnosis of asthma within the GPRD between 1 January 1995 and 31 December 2001. The flowchart explains the selection process (Fig. 1). Observation started after six months exposure to either drug regimen and continued for a minimum of one year for all patients. Patients had never before been treated with any other type of asthma drug. To be included patients had to have had 2 scripts for SABA (SABA group) and 3 scripts for ICS (ICS group) to show regular exposure (there are more doses in a SABA canister hence the lower number). The analyses followed the principles of intention to treat. The patient's initial treatment group remained their group until censorship, death, study end or migration. Censorship occurred when patients in either group had an additional drug prescribed during the observation period, i.e. long-acting beta agonists, theophyllines, cromolyns, leukotriene receptor antagonists, anticholinergics. For the SABA group this also included ICS.

Patients were excluded who had diagnostic codes for COPD, chronic bronchitis, emphysema, cystic fibrosis,

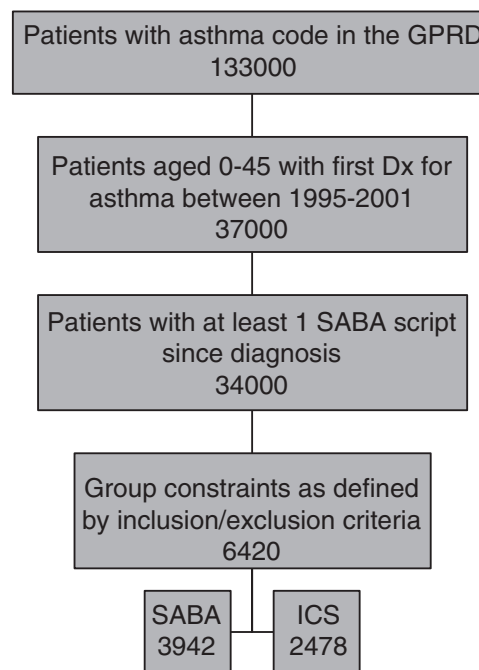


FIGURE 1 Flowchart of selection criteria

bronchiectasis, lung cancer or who used intra-nasal steroids at anytime prior to or during the observation period.

Factors associated with rate of oral steroid use and rate of SABA use in the first year were assessed using Poisson regression and are presented as percentage change, having converted the estimate using the formula  $(1 - RR)\%$  where  $RR = R1/R2$  ( $R1 =$  rate among treated and  $R2 =$  rate among those not treated). To prevent differential drop-out bias occurring, analyses were restricted to the fixed one year period post exposure so as to include all patients. Co-variables were defined as: age <18 years or 18 years and over; gender; obesity—a medical diagnosis of obesity in the patient notes at anytime during the defined study period; atopy—any label for allergic rhinitis, eczema or allergy during the defined inclusion period; smoker—any smoking status record from point of eligibility (in case patients carried more than one label e.g. transfer from being a smoker to a non-smoker, the last label was used); previous hospitalization—any asthma hospitalization label in the 180 day period *before* first drug date; asthma diagnosis 1997 or later versus those diagnosed from 1995–1996.

Factors associated with time to first ICS script (SABA group only) and first oral steroid script were calculated by means of a Cox's Proportional Hazards model. A  $P$ -value of  $\leq 0.05$  was considered significant.

## Results

The flow chart (Fig. 1) indicates that this selected population of regular therapy users represented 17.4% of the total asthmatics diagnosed with asthma between

1 January 1995 and 31 December 2001 in the GPRD, 19% of whom had at least one script for SABA therapy (with or without any other type of medication). Patients excluded from this study were of the wrong age group, less regular users of either SABA (<2 scripts during the 6 months post diagnosis) or ICS therapy (<3 scripts during the 6 months post diagnosis), had medication that was not allowed, or had co-morbid conditions which might have confounded the outcomes under assessment.

The population at time of first drug index date is described in Table 1. There were 6420 patients in total, 3942 in the SABA group and 2478 in the ICS group. In both groups males were slightly under-represented compared to females (46% and 43%, respectively) and a greater number of patients were children (64% in SABA group and 63% in ICS group). 14% of patients were smokers in both groups and 26% of SABA users had atopy untreated with nasal steroids as opposed to 35% of ICS users.

The total number of scripts of oral steroid and SABA plus the rate in year one are reported in Table 2. A total of 28 835 SABA scripts were issued to the SABA group during the entire study period and 32 775 scripts were issued to patients in the ICS group. The rate of use of SABA in the first year was 3.7 scripts per patient in the SABA group and 5.1 per patient in the ICS group. Oral

steroid scripts numbered 798 in the SABA and 640 in the ICS group over the entire observation period. In the first year post drug exposure the oral steroid script rate per patient was 0.03 and 0.04 for the SABA and ICS group, respectively. Numbers of hospitalizations (total events) associated with asthma during the observation period were 57 in the SABA group and 25 in the ICS group (from 47 and 21 patients, respectively). Six patients in the SABA group and 4 in the ICS group died from asthma during the observation period.

Each new drug class that patients were stepped up to (point of censorship) during the observation period was assessed and results are shown in Figure 2. This Figure shows that 37% of SABA group patients were additionally given ICS at some point during the observation period. A very limited percentage of patients were stepped up to any other type of asthma drugs in either group (1% in the SABA group and 6.7% in the ICS group).

Factors associated with the time to obtaining an ICS script in the SABA group are shown in Table 3. Only

TABLE 1 Description of the population at point of first drug prescription

	SABA Group n = 3,942 n (%)	ICS Group n = 2,478 n (%)
Male	1802 (45.7)	1045 (42.5)
Age: 0–18	2525 (64.0)	1552 (62.6)
≥18	1417 (36.0)	926 (37.4)
Smokers	553 (14.0)	345 (13.9)
Atopic	1040 (26.4)	855 (34.5)
Obese	56 (1.4)	42 (1.7)
Previously hospitalized <sup>a</sup>	29 (0.7)	40 (1.6)
Diagnosed 1997 or after	2621 (40.8)	1721 (26.8)

<sup>a</sup> Number of people with ≥1 event.

TABLE 2 Number and rate of prescriptions for SABA and oral steroid by treatment group

	SABA Group n = 3942	ICS Group n = 2478
Total SABA scripts	28 835	32 775
Rate of SABA scripts per patient in first year	3.7	5.1
Total oral steroid scripts	798	640
Rate of oral steroid script per patient in first year	0.03	0.04

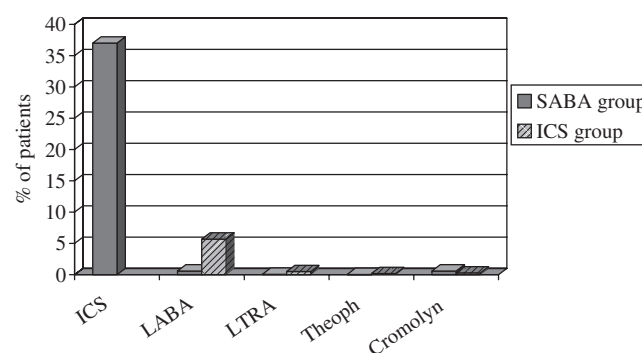


FIGURE 2 First new drug (point of censorship) given to patients in either group since initial therapy. ICS = Inhaled Corticosteroids; LABA = Long Acting Beta-2-Agonists; LTRA = Leukotriene Receptor Antagonists; Theoph = Theophyllines; Cromolyns = Sodium Cromoglycates

TABLE 3 Time to first ICS (SABA group only)

	Adjusted risk ratio	Lower 95% CI	Upper 95% CI
Female	1.08	0.98	1.20
Age ≥18	1.06	0.95	1.18
Smoker	0.95	0.82	1.11
Atopy	1.47*	1.33	1.63
Obese	1.02	0.68	1.51
Previous hospitalization	2.25*	1.64	3.08
1 Oral Steroid prior to ICS	0.98	0.81	1.19
2+ Oral Steroid prior to ICS	0.98	0.76	1.27
Diagnosed 1997 or later	0.92	0.83	1.02

\*  $P < 0.05$ . The model was adjusted for the co-variables shown.

atopy and previous hospitalization (before the drug index) were significantly associated with a shorter period to the first ICS prescription.

Factors associated with the number of prescriptions of SABA used by both groups in the year following the first script for SABA, were calculated using a Poisson regression (Table 4). The adjusted model indicates that over the first year the rate of SABA scripts in the ICS group was 36% higher than that in the SABA group. Females had 7% less SABA scripts than males. Being an adult and a smoker increased the rate of SABA scripts by 16% and 17% respectively. Being diagnosed after 1997 was not associated with rate of SABA scripts.

Factors associated with the number of oral steroid scripts prescribed to both groups in the year following the first script for asthma drug, a marker of severity and lack of disease control, are shown in Table 5. The ICS group had a 31% higher rate of oral steroid use than the SABA group. Being female, a smoker and over 17 years old all significantly and independently increased the number of oral steroid scripts. Figure 3 illustrates the percentage of patients from each group that were prescribed one or more oral steroid scripts over the entire observation period. In total oral steroids were used by 416 (10.5%) patients in the SABA group and 333 patients (13.4%) of the ICS group. 148 patients (3.8%) in the SABA group and 127 patients (5.1%) in the ICS group had multiple scripts of oral steroids.

Factors associated with time to first oral steroid script are shown in Table 6. Being a smoker and being atopic significantly increased the risk of obtaining a script earlier than those who were non-smokers or who were non-atopic (RR 1.32, CI 1.10–1.60 and RR 1.28, CI 1.10–1.49, respectively). Adults were significantly more likely to be given a script at an earlier time than children (RR 1.65, CI 1.41–1.92). Being female showed a trend

TABLE 4 Factors associated with percentage change in rate of SABA prescriptions in the first year of observation

	% change	Lower 95% CI	Upper 95% CI
ICS Group	36*	33	40
Sex (female)	-7*	-10	-5
Age (≥18)	16*	13	19
Smoker (yes)	17*	13	21
Atopy (yes)	0	-3	2
Obese (yes)	8	-1	19
Diagnosed 1997 or later	1	-2	3

Adjusted estimates for use within the first year's observation including 180 days (only patients with 1 year's data contribute). SABA group n = 3708, ICS group n = 2277 (model is adjusted for the co-variables shown).

\* P ≥ 0.05.

towards increased risk of earlier script than males (RR 1.15, CI 0.99–1.33). Being diagnosed in 1997 or later significantly increased the risk of obtaining a script more quickly than those diagnosed prior to 1997.

TABLE 5 Factors associated with percentage change in the rate of oral steroid prescriptions in the first year of observation

	% change	Lower 95% CI	Upper 95% CI
ICS group	31*		267
Sex (female)	59*	22	108
Age (≥18)	67*	28	118
Smoker (yes)	54*	14	109
Atopy (yes)	24	-5	62
Obese (yes)	-44	-82	76
Diagnosed 1997 or later	13	-13	47

Adjusted estimates for use within the first year of observation (only patients with 1 years complete data without censorship contribute). SABA group n = 3708, ICS group n = 2277. The model is adjusted for co-variables shown.

\* P ≥ 0.05.

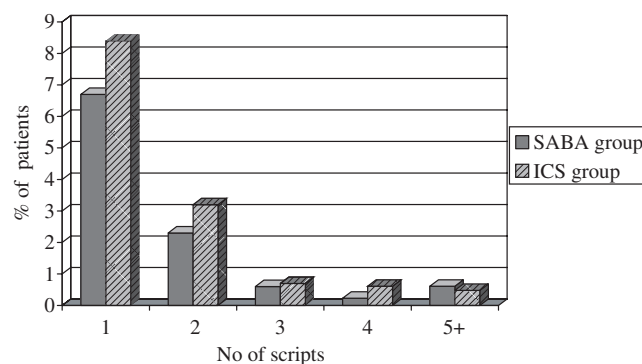


FIGURE 3 Percentage of patients prescribed one or more oral steroid scripts

TABLE 6 Factors associated with time to first oral steroid script

% of patients	Adjusted risk ratio	Lower 95% CI	Upper 95% CI
ICS Group	1.06	0.92	1.22
Female	1.15	0.99	1.33
Age ≥18	1.65*	1.41	1.92
Smoker	1.32*	1.10	1.60
Atopy	1.28*	1.10	1.49
Obese	1.43	0.92	2.21
Diagnosed 1997 or later	1.70*	1.45	2.00

\* P < 0.05. The model is adjusted for the co-variables shown.

## Discussion

Optimal control is described in the guidelines as no exacerbations requiring emergency care or oral steroids, and a minimal need for rescue beta-2 agonist.<sup>2,4,11</sup> However, in our study a considerable number of patients from both treatment groups exhibited daily requirement for SABA, one or more oral steroid scripts, and were occasionally hospitalized. From our data, we cannot discern whether more compliant use of inhaled steroids, use of higher dose of inhaled steroids, or addition of other asthma medication such as long acting beta-2-agonists would have improved asthma control but, based on the guidelines and many studies, this would be the likely outcome.

A recent study from a Dutch general practice population of 399 asthmatic patients reported that only 40% had good disease control.<sup>6</sup> A previous phone survey by Rabe *et al.* reported that large proportions of supposedly mild patients exhibit high morbidity, with less than half of the interviewed patients using inhaled steroids despite their symptoms fitting the description of severe asthma.<sup>5</sup> The authors concluded that patients and their physicians appeared to accept poor asthma control as the norm. A recent paper by Haughney *et al.* reported that when 40 mild to moderate asthmatic patients were given in-depth interviews for a qualitative assessment of asthma, many admitted to ignoring symptoms or tolerating them, thus not reporting them to the physician.<sup>12</sup> Five hundred and seventeen patients were also selected for quantitative structured interviewing and completed questionnaires. A percentage admitted to increasing the dose of medication at time of an exacerbation, but this was mainly SABA with 38% of patients increasing the dose without consultation. ICS was not taken regularly by 68% of respondents and only 18% increased ICS dose at times of illness. This toleration of symptoms, lack of communication to the doctor, and poor understanding of the role of ICS by the patient indicates need for improved patient education.

Previous studies have indicated that early treatment with ICS in supposedly mild patients, such as the patients in this study, is more beneficial than allowing patients to remain on SABA and then stepping-up treatment to include an ICS only if they exacerbate. Selroos *et al.* also reported that early use of ICS in mild to moderate asthmatics was associated with greater symptom improvement than in those who had delayed ICS treatment.<sup>13</sup> Delaying ICS treatment for up to two years has also been shown to result in the reduction of the effect of the anti-inflammatory potential of the steroid. It resulted in less improvement in airway hyperresponsiveness<sup>14</sup> and significantly reduced PEF values and increased symptoms compared to those who received ICS at start of therapy.<sup>15</sup> In the current study, 37% of the SABA only group had to be, at some point, stepped up to ICS. The previous studies suggest that these patients would have obtained greater

benefit from ICS if it had been given around the time of therapy initiation.

The current investigation shows that not only a considerable proportion of patients who are prescribed SABA are under-treated, but also patients in the ICS group exhibited lack of asthma control, showing greater than once per day dosing of SABA, or oral steroid use, and a limited number of hospitalizations. Only a small number of patients were stepped up to long acting beta-agonist (LABA) therapy and in some cases reliance seems to have been placed on use of one or even repeated oral steroid to control exacerbations, rather than on introducing LABAs (see Fig. 2) as recommended in the current guidelines.<sup>2,3</sup> However, due to selection criteria and study design, it is hard to assess at the individual level how patients were treated over time within each group. Whether morbid patients had their ICS doses increased to try to gain control, which used to be standard practice prior to recommendation of LABAs, is impossible to say. It is likely that some patients would exhibit resistance to high doses of steroids or regular use of steroids despite their clinicians best efforts to control their disease.<sup>12</sup>

It would be of benefit to clinical decision making to know which factors contribute to lack of asthma control in milder asthmatic patients. The current study shows that smokers from both groups (SABA and SABA + ICS) were at risk of greater SABA and oral steroid use, and had shorter time to first oral steroid script. It has been shown that smokers who use either inhaled or oral steroid have a reduced response to the anti-inflammatory effects of the steroid compared to non-smokers.<sup>16,17</sup> We therefore suggest that GPs should continue to advise and encourage asthmatic patients to quit smoking, for many reasons but also to gain optimal efficacy from all types of steroid treatments.

A record of previous hospitalization was associated with greater likelihood of obtaining an ICS, which must influence the doctor's assessment of severity. A patient presenting with mild, possibly intermittent symptoms who fails to mention prior hospitalization would be treated quite differently to one who presents with the same symptoms but is known to be at risk of sudden, severe exacerbations requiring hospital treatment.

In this study, allergic rhinitis (untreated with nasal steroid) and other types of atopy, reduced the time to first prescription of oral steroid. Atopy has been shown to be a major determinant of airway hyperresponsiveness in the general and asthmatic population, and furry animals in particular have shown a strong association with increased airway hyperresponsiveness.<sup>18,19</sup> Treatment of allergic rhinitis with intra-nasal steroid has been shown to reduce asthma morbidity and these patients may have benefited from such treatment.<sup>20</sup> Females in this study had a rate of oral steroid use that was 58% greater in the first year than that seen in males, and being adult was associated with greater oral steroid use, plus greater SABA use and less time to first script of oral steroid. This indicates that in this

study population, adults, and females in particular, were not as well controlled as children, even after adjusting for factors such as smoking. Whether these factors are due to treatment bias by age, or gender, or differences in compliance is impossible to say from these data but would benefit further investigation.

This study in a large group of intermittent or persistent asthma patients, representing 19% of all incident patients who had ever received at least one script for SABA between 1995 and 2001, shows that asthma control is sub-optimal in a considerable number of them. Of those who took SABA as monotherapy (i.e.  $\geq 2$  scripts during the 6 months post diagnosis), 37% had to be stepped up to ICS and a number of patients were treated with one or more oral steroid courses and were using more SABA than appropriate for intermittent asthmatics. Patients in the ICS group also showed high use of oral steroids, reliance on SABA and very few were stepped up to additional medication such as a LABA. This indicates that disease severity is under estimated in some adult and paediatric asthma patients from general practice but this may partly be due to lack of compliance or communication by the patient. Factors that are easily determined by history taking, such as previous hospitalization for asthma, smoking and allergy, should alert the physician to the risk of reduced asthma control and act as a guide to appropriate prescribing.

## Declaration

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Ethical approval: ethical approval was obtained from SEAG of the GPRD (protocol 513 R).

Conflicts of interest: none.

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