Changes to time trends for inhaled corticosteroid use and costs in New Zealand since April 2002

Dr Scott Metcalfe MBChB FAFPHM
Public Health Physician, externally contracted to PHARMAC as Senior Advisor (epidemiology and public health)

Draft 5, 29 September 2003

Table of contents

Changes to time trends for inhaled corticosteroid use and costs in New Zealand since April 2002 1
Key points 4
Summary 5
Context 7
Methods 10
Design 10
Source data 10
Outcomes measures 10
Analysis methods 11
Source calculations 11
Acknowledgments 11
Results 12
ICS dispensing volumes 12
Patients using ICSs 16
Switching from BDP to fluticasone 16
New ICS-naïve patients and BDP-lapsers 16
Variation by age-group 17
Timing of new patients and switching during the Flixotide® DTCA campaign 18
ICS costs 20
Costs per patient 20
Total ICS costs during the Flixotide® DTCA campaign 20
Impact of Flixotide® DTCA campaign on pharmaceutical spending 21
ICS average daily doses 22
Overall average daily doses (ADDs) 22
Variation by age-group 23
LABA dispensings 25
ICS total kg volumes 26
Comments 28
Choice of regression modelling used 28
Implications of changes in ICS ADDs 28
Lower ADDs in new patients suggest those patients switching from BDP to fluticasone had less severe asthma 29
ADD changes suggest new ICS-naive patients/BDP-lapsers starting fluticasone also had less severe asthma 30
Consistency with seasonal changes in ICS dispensings and ADDs 31
Temporal relationship between changes in fluticasone/BDP prescribing and the Flixotide® DTCA campaign 33
Causality 35
Effects of the Flixotide® DTCA campaign on BDP prescribing, as part of possible GSK wider strategy for the LABA/ICS market in New Zealand 36
Possible overall goal of Flixotide® DTCA 36
Possible ultimate goal of Seretide® combination LABA/ICS dominating the ICS/LABA market 36
Promotion of Seretide® in New Zealand 41
Effects of Flixotide® DTCA on the overall BDP market 41
Appendix 1: Seasonal variation in dispensings and ADDs, by ICS chemicals and by age-group 43
Appendix 2. Bradford Hill criteria for causation 46
Appendix 3. Effectiveness of combined ICS/LABAs delivery devices versus concurrent ICS and LABA via separate inhalers 48
Compliance with combination LABA/ICS devices 49
International guidelines re efficacy of combination LABA/ICS devices 50

Recently published meta-analysis of Seretide® (Nelson et al 2003)....51
Limitations with the Seretide® meta-analysis....52
1. Selective reporting of key findings....52
2. Reporting overstates the magnitude of physiological effects....54
3. No difference in clinically relevant outcomes....55
4. No analysis of withdrawals and adverse events, where these show significantly higher rates of reported adverse events with Seretide®....56
5. Seretide®'s physiological and clinical improvements were comparatively low....57
6. Quality of individual RCTs and meta-analysis....59
Message of international guidelines remains unchanged....60
Appendix 4: Age group-specific results....62
Appendix 5: Overall results....65

Key points

- This analysis examines the impact of last year's direct-to-consumer advertising (DTCA) campaign for Flixotide® on volumes and costs of fluticasone and beclomethasone (BDP) in New Zealand.

- Numbers of patients using fluticasone from April 2002 (when DTCA started) were markedly higher than expected from previous trends. This was countered by a decline in BDP patients. These patterns reversed however late in 2002, coinciding with when DTCA ended.

- BDP's accelerated decline was likely due to greater numbers of patients than usual (particularly late adolescents/adults) switching to fluticasone. There were also new ICS-naive patients starting fluticasone (particularly older children/early adolescents) not accounted for by switching.

- Conversely, fluticasone average daily doses (ADDs) decreased and BDP ADDs increased. This is similar to seasonal patterns in general, where dispensing volumes and ADDs move in opposite directions.

- Both (1) new ICS-naïve patients starting fluticasone and (2) patients switching from BDP to fluticasone were on lower daily doses than expected (particularly older children/early adolescents), arguably with less severe asthma.

- Between April 2002 and January 2003, excess prescribing of fluticasone amounted to $2.65 million. Of this, at the very least $900,000 (139,800 person-months) is estimated to be due to patients switching from BDP to fluticasone in excess of previous trends. Further costs will have occurred with patients who had lapsed from having their prescribed BDP dispensed to them ("BDP-lapsers"), who eventually restarted their ICSs with fluticasone.

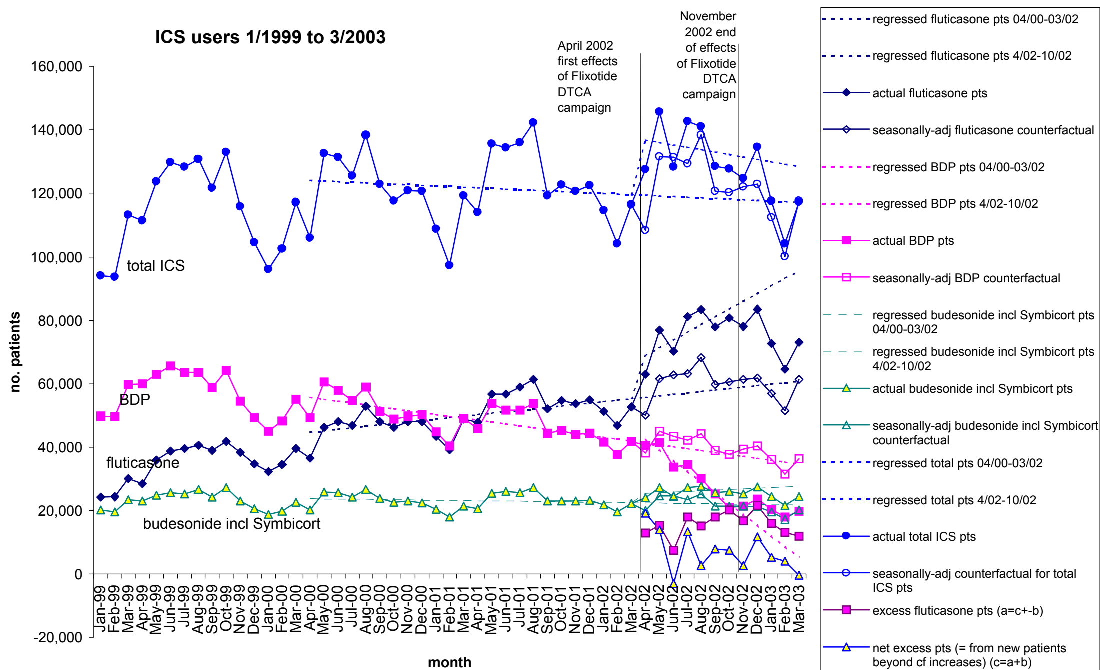
- The extent of association between DTCA for Flixotide® and switching from BDP strongly suggests causation (Flixotide DTCA® causing switching from BDP). The Flixotide® DTCA campaign may be the first part of a strategy by GSK to shift the whole New Zealand asthma preventive/modifier market to Seretide® (combined salmeterol/fluticasone).

Summary

Interrupted times series analysis indicates that since April 2002 the number of patients using fluticasone underwent an early surge and remained markedly higher than expected from previous trends. The trend of increased fluticasone/decreased BDP prescribing reversed however late in 2002. Prescribing of the fixed eformoterol/budesonide combination product (Symbicort®) also increased beyond expected.

Part of the early fluticasone surge was countered by a concomitant decrease for the competing inhaled corticosteroid (ICS) beclomethasone dipropionate (BDP). Over the same period there was an even greater decline in BDP patients, so that total patients using ICS declined at rates a little more than had been occurring historically. The trend of increased fluticasone/decreased BDP prescribing reversed however late in 2002 (figure 1).

Figure 1



BDP's accelerated decline might be explained in part by patients, particularly late adolescents/adults, switching to fluticasone way beyond the ongoing switching predicted from historical patterns. The additional fluticasone patients probably represent new patients, particularly older children/early adolescents (beyond growth that might have been expected historically, i.e. extra patients particularly in the initial months not accounted for by switching). There would also have been patients who had lapsed from having their prescribed BDP dispensed to them ("BDP-lapsers"), who eventually restarted their ICSs with fluticasone.

Conversely, fluticasone average daily doses (ADDs) quickly dropped and continued to decline, and BDP ADDs increased, in patterns opposite to the above usage patterns. Data suggest that both (1) new ICS-naïve patients/BDP-lapsers starting fluticasone and (2) patients switching from BDP to fluticasone were on lower daily doses than expected. These were arguably patients with less severe asthma. This particularly applied to older children/early adolescents.

Changes in ICS prescribing trends were closely associated with the March/April 2002 onset of a direct-to-consumer advertising (DTCA) campaign for Flixotide® (fluticasone), as part of overall increased marketing of fluticasone compared with before that time. Likewise, the reversal of this pattern correlated with the cessation of the DTCA campaign in September/October. The temporal trends in dispensings suggest a 1-2 month lag between exposure to any advertising episode and the last dispensing of medication.

For the ten months April 2002 to January 2003, before the 1 February 2003 implementation of fluticasone reference pricing, excess prescribing of fluticasone amounted to $2.65 million. Of this, $900,000 (139,800 person-months) at the very least is estimated to be due to patients switching from BDP to fluticasone in excess of previous trends, most likely due to the impact of Flixotide® DTCA March to October 2002.

The extent of association between DTCA for Flixotide® and switching from BDP strongly suggests causation (Flixotide DTCA® causing switching from BDP). The factors pointing to causation are strength of the association; consistency across populations (age-specific results for numbers of new patients and BPD switching versus ADDs enhance the overall patterns); specificity; temporality (close dose-response relationship between Flixotide® DTCA and dispensing/ADD changes); biological gradient (decreased switching as DTCA ceases); and plausibility.

The Flixotide® DTCA campaign may be the first part of a strategy by GSK to shift the whole New Zealand asthma preventive/modifier market to its combined salmeterol/fluticasone product (Seretide®). Switching patients using BDP to Flixotide® may be but an intermediate step towards intended Seretide® dominance of the asthma preventive/modifier market (as has happened in Australia, at great expense). If this is correct, this strategy goes beyond simply encouraging new ICS-naïve patients (and BDP-lapsers) to uptake necessary ICSs. Evidence shows that Seretide® is clinically no more effective than separate ICS and LABA inhalers. There is little evidence that compliance is improved. Despite this, Seretide® is much more expensive than the separate devices together.

Context

Between March and October 2002 Glaxo Smith Kline (GSK) undertook a direct-to-consumer advertising (DTCA) campaign promoting Flixotide® (fluticasone).[1] The campaign both raised awareness of symptoms of less-well controlled asthma in general terms, and specifically promoted Flixotide® as treatment (over other products such as beclomethasone dipropionate (BDP)).

The high profile campaign (public and professional) stated that the Becotide® and Becloforte® brands of BDP were being withdrawn later in the year because they contained CFCs. BDP users could well have inferred they had to change ('upgrade') to Flixotide® as their inhalers. The campaign did not mention that fully subsidised generic BDP inhalers (Beclazone®, Respocort®)) would still be available. Nor did the campaign say that one of the Flixotide® formulations contained CFC (except in the fine print). Nor was there any requirement at that particular time for GSK to withdraw CFC products.

Any excess switching of patients from BDP to fluticasone would not *prima facie* represent value for scarce health funds, given that until 1 February 2003 fluticasone cost nearly twice that of equivalent daily doses of BDP.[2] This is where there is insufficient evidence for fluticasone being superior to beclomethasone at equivalent doses for most patients.[3] On this basis, any switch to much more expensive drugs, resulting from DTCA, represents a monetary loss to the pharmaceutical budget with no material gain in population health status.

Dispensings and costs for fluticasone are known to have been increasing, at the expense of BDP, since 1999 and before (figures 2 and 3).

Figure 2

[1] Reference to DTCA in this paper specifically relates to television commercials screened, which were part of a comprehensive overall marketing campaign by GSK for Flixotide®. The marketing campaign comprised, amongst other things, press releases, newspaper articles, television commercials, leaflets included in the packaging of GSK's Becotide® and Becloforte® brands of BDP, and cards placed in doctors' surgeries.

[2] BDP $125 pa, fluticasone $239. #70304 sheet 'ICS + LABA nos. and costs' cells H77,H91 (BDP-equivalent annual cost/patient April 2002-Jan 2003, direct standardised to distribution of BDP patients by formulation) Note unadjusted fluticasone cost/patient of $276, reflecting higher daily doses and greater proportion of very high dose formulations used by fluticasone patients compared with BDP.

[3] Adams N, Bestall JM, Jones PW. Fluticasone versus beclomethasone or budesonide for chronic asthma (Cochrane Review). In: The Cochrane Library, Issue 1, 2002. Oxford: Update Software.

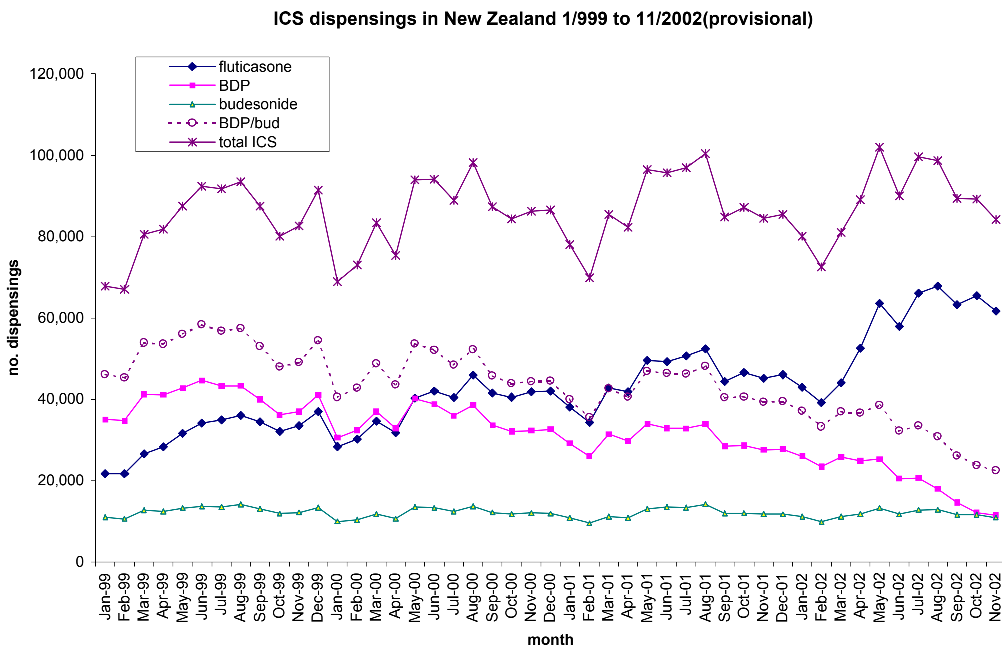
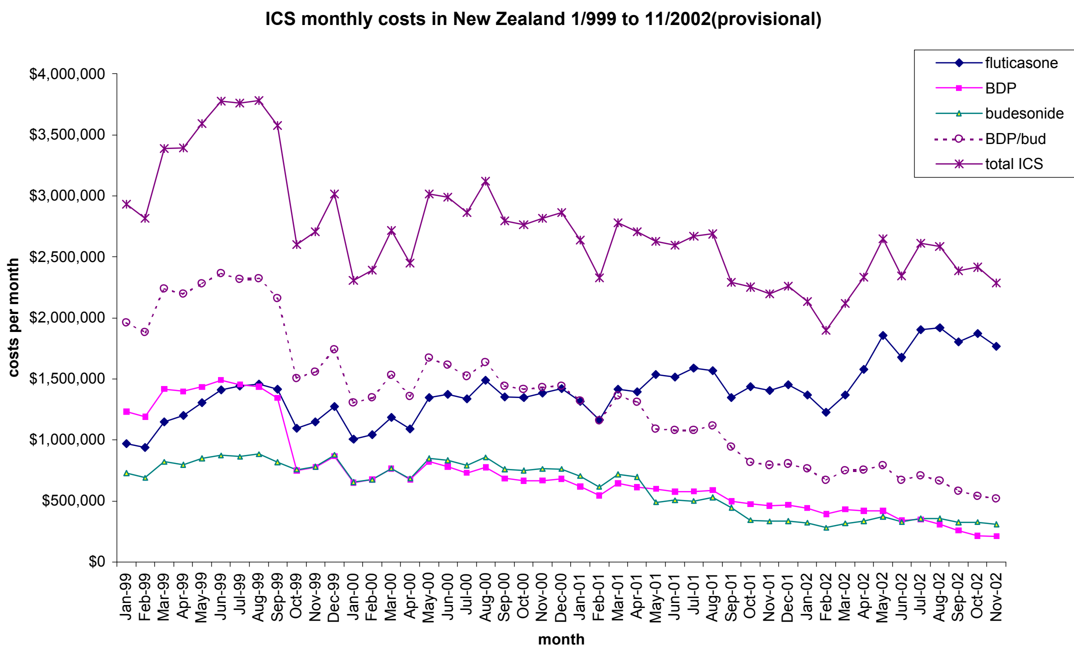


Figure 3



However, the relative magnitude and impact of the above increases in fluticasone dispensings, particularly any recent changes, are difficult to untangle when examining serial trends in volumes. This is because of the need to account for seasonal fluctuations in asthma prevalence and severity, with peaks occurring during winter.

One way to compare patterns before and after a particular point in time, countering confounding by seasonality, is to undertake interrupted time series analysis using logistically regressed proportions against serial time and that particular point in time. Changes in patterns of

proportions since that point of time (compared with the pattern before, being the counterfactual pattern) represent excesses or reductions. Similar analysis using linear regressions can be applied to total volumes and patient cost data to calculate give likely total and excess numbers and costs for each group. Group data can then be combined to give net excess numbers, indicating new patients beyond counterfactual growth.

Methods

Design
Interrupted time series analysis, based on logistic regression of percentage fluticasone/total ICS dispensings against time:

- before and since April 2002 (*prima facie* onset of effect of Flixotide® DTCA campaign on fluticasone market share), and then
- before and since November 2002 (*prima facie* end of effects of Flixotide® DTCA campaign on fluticasone market share).

Source data

- HealthPac dispensings claims summary data extracted through PHARMAC Forecast Database for the months January 1999 to March 2003 (downloads 3.02.03 and 18.05.03 TG1 group Respiratory System and Allergies, spreadsheet #68240).
- For ICS average daily doses (ADDs) and patient-month equivalents (pmes), formal extract of source HealthPac data for period 1/99-4/03 (spreadsheet #66486), which adjusts for missing and outlier daily dose information; age group-related data were derived from the HealthPac data patient category field (used to identify subsidy status).

Numerical and cost data before January 1999 are not readily available, due in part to coding inconsistencies relating to differing formulations and delivery systems for inhaled asthma medications (affecting treatment duration and dose strength data, hence daily dose and patient-month calculations).

Outcomes measures

- ICS dispensings, patient-month equivalents (pmes) and costs per month, comprising combinations of the following agents and patient age-groups:
  Agents:
  1. BDP (metered dose inhalers; breath activated devices; metered dose inhalers with spacers);
  2. budesonide (Pulmicort®) (metered dose inhalers; breath activated devices; nebuliser solution);
  3. fluticasone (metered dose inhalers; breath activated devices); and
  4. eformoterol/budesonide fixed LABA/ICS combination (Symbicort®) (breath activated devices);

  Age-groups:
  1. young children aged 0-5 years (patient category “Y” code);
  2. older children/early adolescents aged 6-16/18 years (patient category “J” code); and
  3. adolescents/adults aged 17 years and over (all other patient category codes, including nil coded).

- ICS average daily doses (ADDs), by agent (BDP, budesonide, fluticasone, and eformoterol/budesonide) combined with age-group (young children 0-5, older children/early adolescents 6-16/18, adolescents/adults 17/19+)

- long-acting beta agonist (LABA) dispensings per month (comprising: eformoterol; salmeterol; eformoterol/budesonide).

ADDs were also converted to beclomethasone-equivalent daily doses (BEDD), to account for fluticasone being twice as potent as BDP and budesonide (e.g. 500 ug fluticasone is equivalent to 1000 ug/day BDP).

Also there was conversion to beclomethasone adult-equivalent daily doses (BAEDD), to account for not only chemical potency but also age, where children aged under 12 years require half the nominal adult dose. Hence for instance, 800 ug/day BDP in adults = 400 ug fluticasone in adults or 400 ug BPD in children or 200 ug fluticasone in children, etc.

ICS total volumes were also calculated in BDP-equivalents (kgs), to adjust for different potencies and for varying mixes of daily doses, formulations and patient numbers over time. These comprised BDP (metered dose inhalers; breath activated devices; metered dose inhalers with spacers); budesonide (Pulmicort®) (metered dose inhalers; breath activated devices; nebuliser solution); fluticasone (metered dose inhalers; breath activated devices); eformoterol/budesonide fixed LABA/ICS combination (Symbicort®) (breath activated devices).

Analysis methods
Initially, proportions derived from logistic regression, to determine the extent of changes beyond counterfactual at which times. Then, applying linear regression[4] to total numbers (dispensings, patient-month equivalents, BDP-equivalent kgs) for each specific pharmaceutical agent, calculating projected counterfactual trends (based on previous 2 years' monthly volumes) and projected counterfactual volumes (trend x seasonal adjusters), then comparing with actuals to give likely total and excess numbers.

Fluticasone, BDP, budesonide and Symbicort® numerical changes (beyond counterfactual predictions) give net excess numbers, representing new ICS patients beyond counterfactual growth. BDP, budesonide and Symbicort® numbers combine to give other ICS changes excluding fluticasone.

Total costs calculated using actual monthly cost per item dispensed by pharmaceutical agent (calculated total cost per month divided by number of items per month by agent). Predicted counterfactual monthly costs per item by agent calculated from linearly regressed actual monthly costs per agent. Linear regression to calculate counterfactual monthly costs/item, to account for temporal changes in monthly costs due to mix effects by formulation and daily dose (changes independent of price changes to the Pharmaceutical Schedule). Regressed costs per item then applied to numbers of predicted counterfactual items dispensed by agent, giving total predicted counterfactual costs by agent. Total actual costs by agent then able to be compared with total predicted counterfactual costs.

Source calculations
spreadsheets #72455, #72935

Acknowledgments
Sean Dougherty for techniques for logistic regression, Jason Arnold for HealthPac ICS average daily dose (ADD) and patient-month equivalent (pme) extract. Sean Dougherty subsequently checked all spreadsheet calculations. Analysis reviewed by Natalie Ganley, Sean Dougherty, Dr Peter Moodie, Wayne McNee, Dr Derelie Richards, Professor Les Toop, PTAC's Respiratory Subcommittee. Subsequent comments on model structure provided by Matthew Brougham.

[4] Linear regression was used in this analysis. A more statistically robust form of regression would be to logistically regress the proportions of fluticasone and BDP dispensings (as proportions of total dispensings), then apply these to log-linear trends in total ICS volumes (actual and counterfactual), finally incorporating seasonal adjusters by month.

Results

ICS dispensing volumes

Since April 2002 there was a marked increase in fluticasone's market share (i.e. no. fluticasone dispensings/total ICS dispensings by month), with a concomitant decrease in share for BDP and budesonide. The accelerated changes since April 2002 were additional to the steady increase in fluticasone's market share at the expense of the other ICSs.

These changes in the mix of ICS were particularly marked during April/May 2002, but levelled off from November to reach a new steady state (figures 4 and 5).

Figure 4

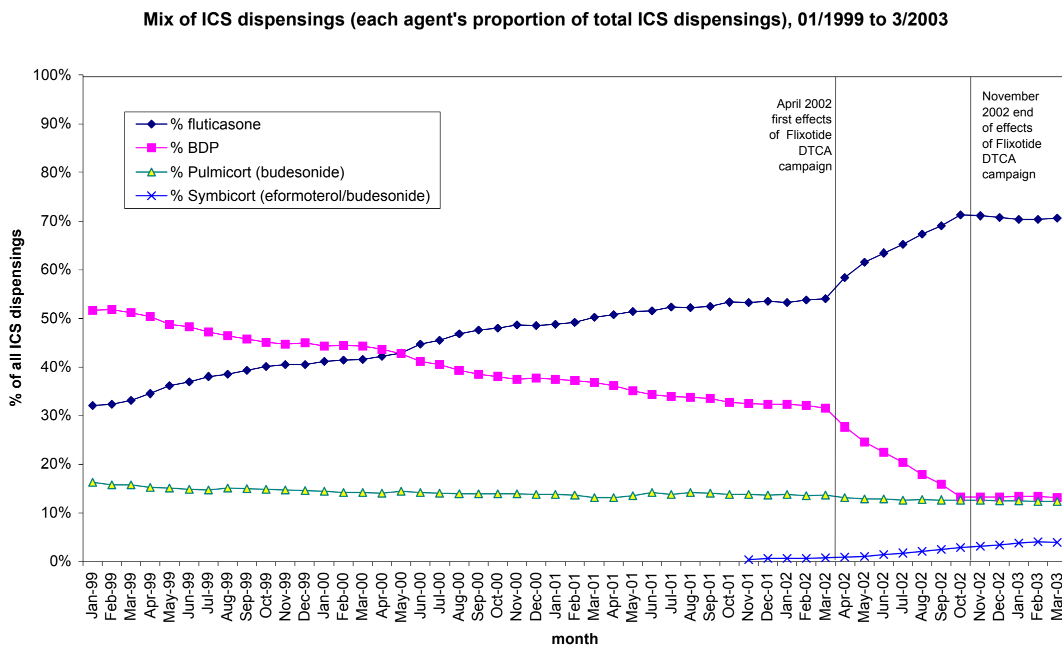
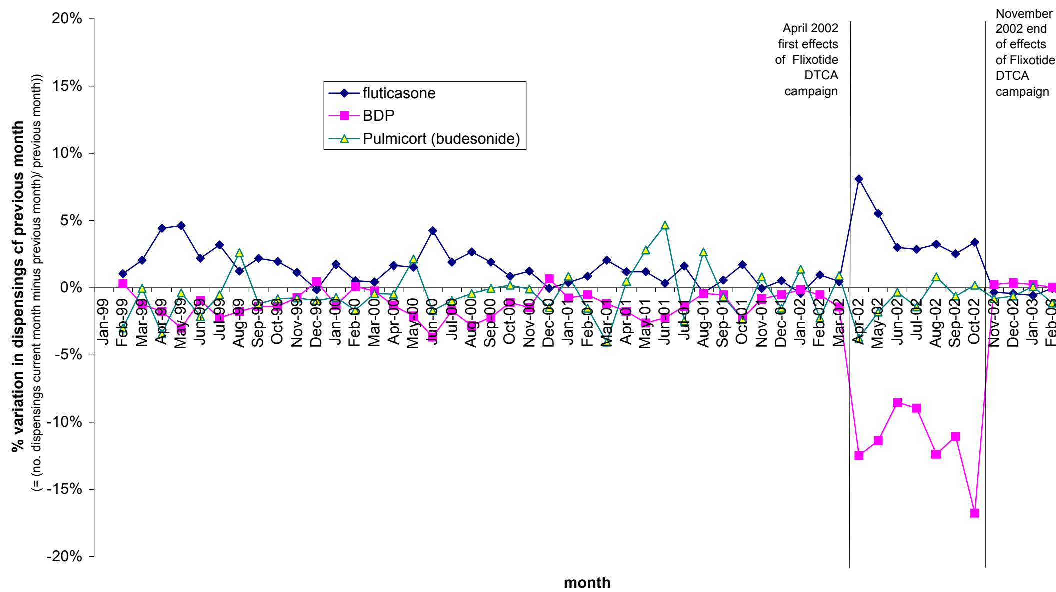


Figure 5



The above patterns in market share can be used to estimate the impact of changes in terms of excess patient numbers and costs beyond what might be expected if dispensing patterns had not changed over recent times. Specifically, logistic regression of fluticasone market share (no. fluticasone dispensings/total ICS dispensings by month) against serial time (October 2000 to March 2003) allows calculations of estimated excess fluticasone dispensings, by applying the % excess fluticasone market share since April 2002 (figure 6) to total numbers of ICS dispensings for the same time period. This then gives both:

- likely numbers of excess fluticasone dispensings since April 2002 (beyond historical patterns including ongoing switching from other ICSs to fluticasone); and
- changes to numbers of other ICS dispensings since April 2002 (beyond historical patterns including switching).

Combined fluticasone and other ICS dispensings changes (beyond counterfactual predictions) give net excess dispensings, suggesting new ICS patients beyond counterfactual growth.

Figure 6

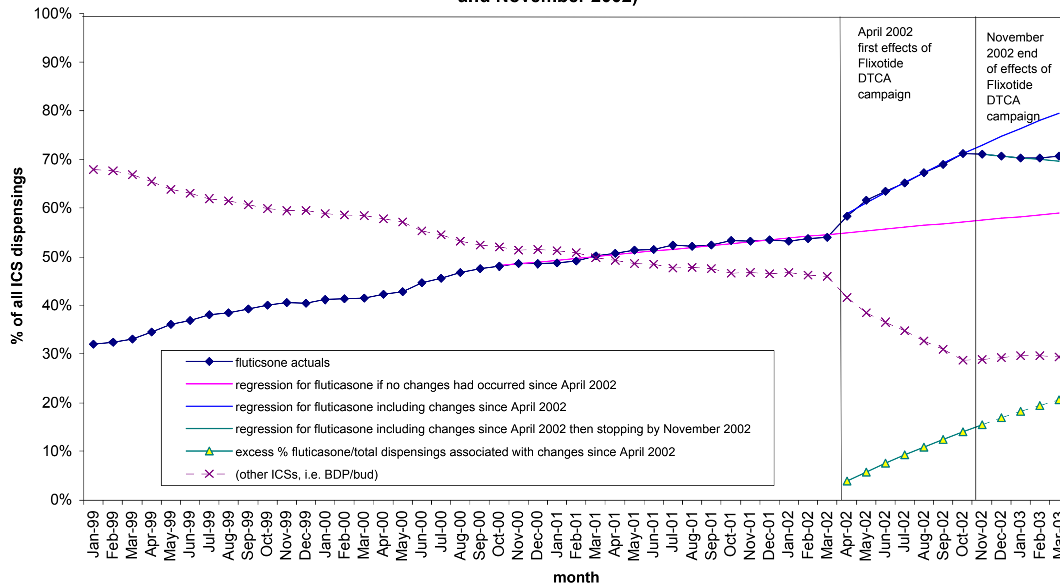


Table 1 below describes the estimated changes in dispensings, patient usage and costs of fluticasone and other ICSs since April 2002 (key features described below).

Table 1

ICS use and costs April 2002 to January 2003

	No. dispensings			No. patients		Costs	
	total 4/02 to 10/02	increase/month 4/02-10/02 (non-seasonal regressions)	total 4/02 to 1/03	average 4/02 to 10/02	average 4/02 to 1/03	total 4/02 to 10/02	total 4/02 to 1/03
fluticasone							
- actual (changes since April 2002)	436,841	1,720	625,188	76,660	77,327	$12,619,678	$18,100,548
- predicted counterfactual (if no change since March 2002)	349,261	310	493,815	61,276	61,056	$10,551,177	$14,823,479
- difference	87,580	1,410	131,373	15,385	16,271	$2,068,501	$3,277,068
- excess/predicted	1.25	4.55	1.27	1.25	1.27	1.20	1.22
BDP							
- actual (changes since April 2002)	136,095	-2,167	171,502	33,727	30,240	$2,313,590	$2,963,520
- predicted counterfactual (if no change since March 2002)	173,447	-478	236,015	43,099	41,886	$2,810,458	$3,791,144
- difference	-37,352	-1,690	-64,513	-9,372	-11,646	-$496,868	-$827,624
- excess/predicted	0.78	3.54	0.73	0.78	0.72	0.82	0.78
budesonide incl Symbicort							
- actual (changes since April 2002)	97,461	213	140,020	26,216	26,144		
- predicted counterfactual (if no change since March 2002)	85,705	-19	119,997	23,059	22,422		
- difference	11,756	232	20,023	3,157	3,722		
- excess/predicted	1.14	-12.05	1.17	1.14	1.17		
other ICS (BDP/budesonide/Symbicort combined)							
- actual (changes since April 2002)	233,556	-1,954	311,522	59,943	56,384	$5,826,124	$8,289,046
- predicted counterfactual (if no change since March 2002)	259,153	-497	356,011	66,564	64,515	$6,003,585	$8,562,322
- difference	-25,597	-1,457	-44,489	-6,621	-8,131	-$177,461	-$273,276
- excess/predicted	0.90	2.93	0.88	0.90	0.87	0.97	0.97
total ICS							
- actual (changes since April 2002)	670,397	-234.4	936,710	136,603	133,711	$18,445,802	$26,389,593
- predicted counterfactual (if no change since March 2002)	608,413	-186.8	849,826	127,840	125,571	$16,554,762	$23,385,801
- difference	61,984	-48	86,884	8,763	8,140	$1,891,040	$3,003,792
- excess/predicted	1.10	0.25	1.10	1.07	1.06	1.11	1.13

Excess ICS use and costs

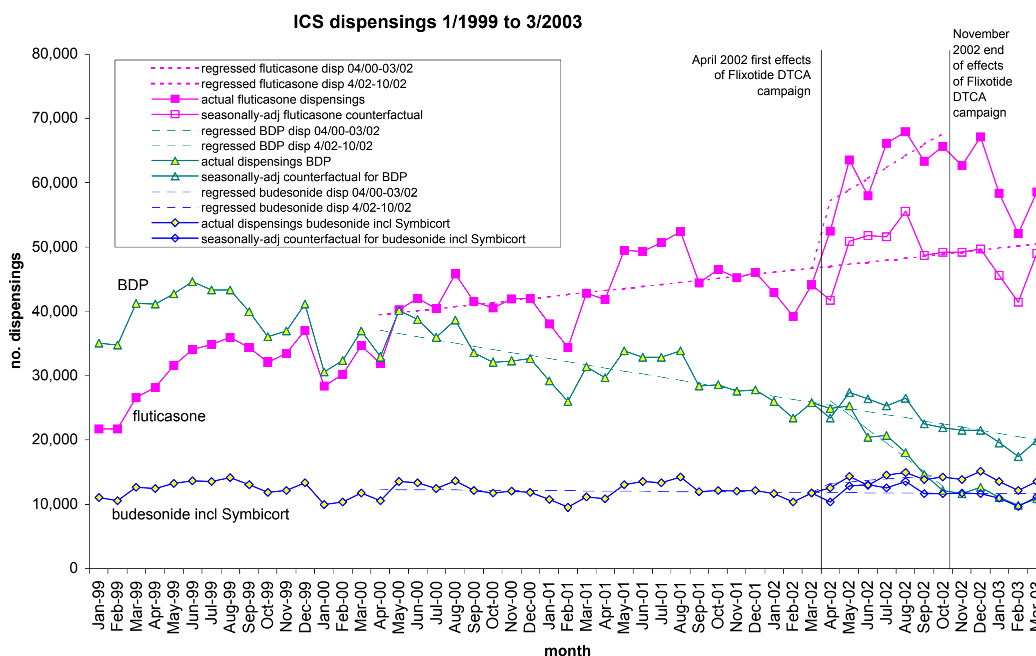
	No. dispensings total 4/02 to 10/02	total 4/02 to 1/03	No. patients average 4/02 to 10/02	average 4/02 to 1/03	Costs total 4/02 to 10/02	total 4/02 to 1/03
Excess fluticasone and BDP, April 2002 to January 2003:						
excess fluticsasone (a=d+e)	87,580	131,373	15,385	16,271	$2,068,501	$3,277,068
excess BDP (b)	-37,352	-64,513	-9,372	-11,646	-$599,921	-$1,025,683
net excess (= from new patients beyond cf increases) (c=a+b)	**50,228**	**66,861**	**6,012**	**4,625**	**$1,468,580**	**$2,251,385**
[net excess all ICS (including budesonides) (= from new naïve patients beyond counterfactual increases)]			8,763	8,140		
[net excess fluticasone (= from new naïve patients beyond counterfactual increases)] (d)			6,012	4,625	$946,135	$1,351,896
[excess from additional switching from BDP to fluticasone*] (e)			9,372	11,646	$522,445	$899,490
*(beyond switch occurring already						
% switching of excess fluticasone (e/a)			61%	72%	25%	27%
[predicted increase in fluticasone under counterfactual**]	8,859	17,397	1,690	2,324		
**i.e. if there had been no DTCA), i.e. switching from other ICS at ongoing rate						

Up until March 2002, counterfactual growth (slope) in fluticasone, at the expense of other ICS, had been moderate, increasing at around 300 extra dispensings each month - alongside 500 fewer dispensings each month for other ICSs, particularly BDP.

However, between April and October 2002 fluticasone dispensings (slope) increased to around 1700 more each month, around 1400 extra than previously (4½ times excess of counterfactual growth). By contrast, total ICS volumes decreased by 230 fewer /month (these had been decreasing by 190/month), reflecting an acceleration in the decline in BDP dispensings (had been 480 fewer each month, but 2200 fewer each month from April 2002).

Hence, for the seven months April to October 2002 there were 87,600 (actual) dispensings for fluticasone beyond predicted from previous trends, 37,400 fewer BDP dispensings, and 62,000 net excess ICS dispensings overall (including budesonide/Symbicort) (Table 1, figure 7).

Figure 7



Patients using ICSs

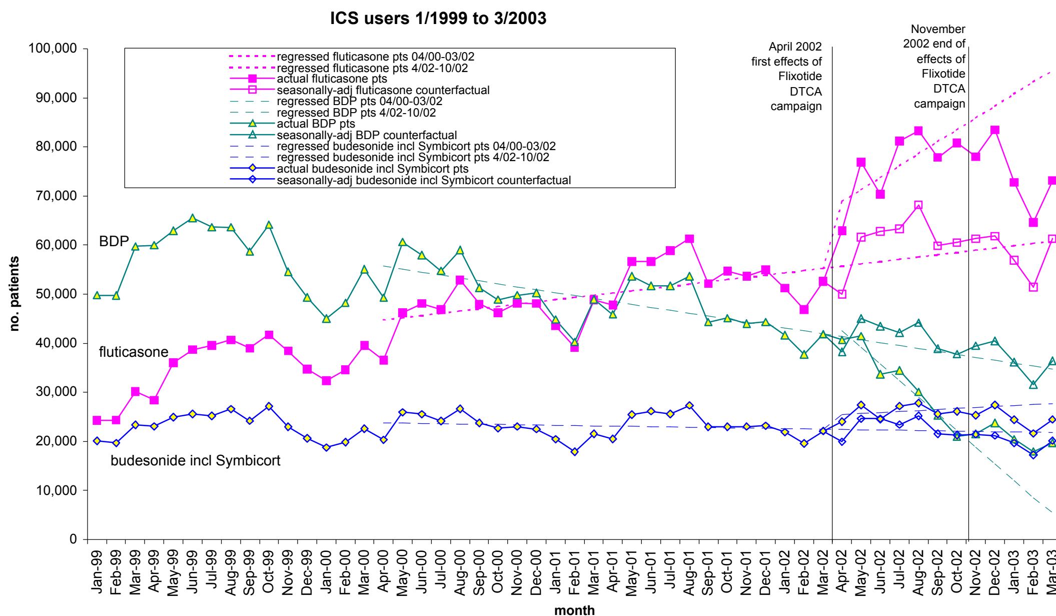
The above changes in dispensing patterns over the seven months April to October 2002 translated to on average 15,400 (25% increase) extra patients using fluticasone (76700 actual vs. 61300 predicted counterfactual, actual/predicted relative risk (RR) 1.25), with 9,400 (-22%) fewer using BDP (32800 vs. 43100, RR 0.78). Combined with changes to budesonide (including Symbicort®), there were on average 8,800 net extra patients (7% increase).

Switching from BDP to fluticasone
Of the above 15,400 extra patients using fluticasone during April to October 2002, 61% (9400) might have been due to patients switching from BDP MDI to fluticasone MDI (beyond the apparent switching that had been occurring historically). This number is reflected in the above 9,400 decrease in BDP numbers from counterfactual.

Such switching assumes a concomitant decrease in BDP volumes and increase in fluticasone volumes, due to marketing. This is rather than some BDP patients stopping all ICSs and a similar number of new ICS-naïve patients (or BDP lapsers, see below) starting fluticasone *de novo*.

New ICS-naïve patients and BDP-lapsers
The remaining 6,000 on average fluticasone patients (equal to the net extra patients) appear to have been either truly new ICS-naïve patients accessing fluticasone *de novo*, beyond what might be expected historically (and associated with fluticasone DTCA), or "BDP-lapsers" (Table 1, figure 8).

Figure 8



"BDP-lapsers" would have been patients who should have been using BDP (and had certainly been prescribed BDP) but whom had not recently had their BDP dispensed. On seeing TV advertising, they would have decided to reinstigate their inhaled corticosteroids, visited their prescriber asking for the "better" Flixotide as advertised, and been eventually prescribed and dispensed Flixotide. This BDP-lapser group is distinct from true new ICS-naive patients (people with moderate to severe asthma who had never used an inhaled corticosteroid (ICS) before, who's

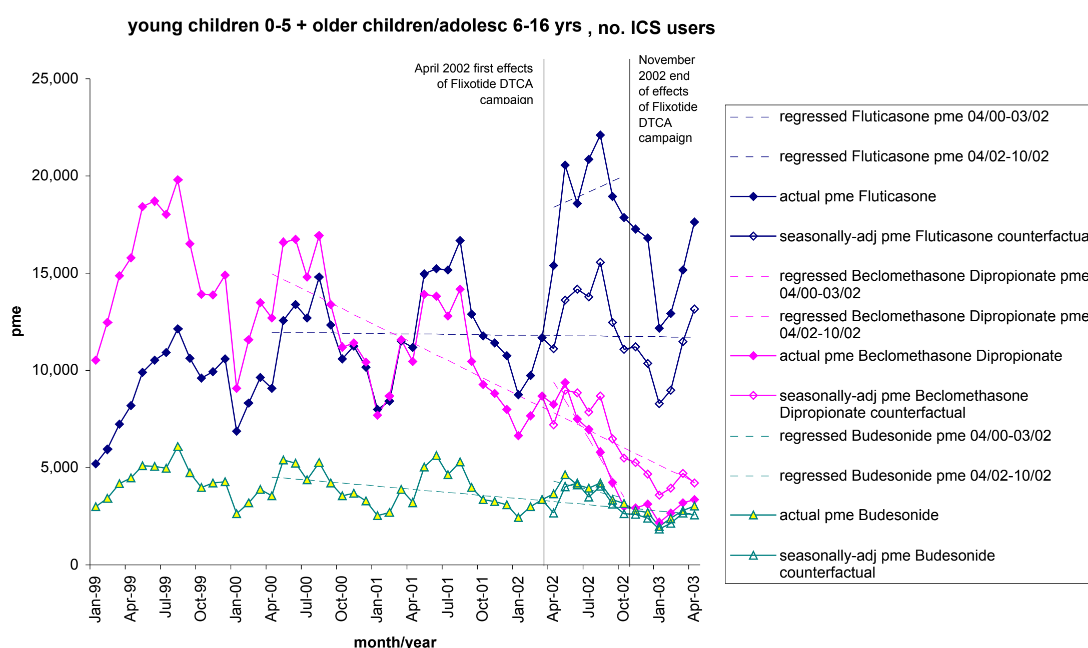
awareness was raised by DTCA and who presented for treatment and were then prescribed Flixotide). Current HealthPac dispensing data do not discriminate between BDP-lapsers and true new ICS-naïve patients.

Variation by age-group

Important variations occurred during April to October 2002 according to the age of the patients. There were proportionately higher increases in new ICS-naïve/BDP-lapsed children/early adolescents using fluticasone. However, there was proportionately higher switching from BDP to fluticasone in late adolescents/adults:

- Increases in fluticasone usage were particularly marked (46%) for children/early adolescents aged 0-16 years, with 6100 extra patients (19200 actual vs. 13100 predicted counterfactual) (figure 8A). This accounted for 37% of all extra fluticasone patients.

Figure 8A



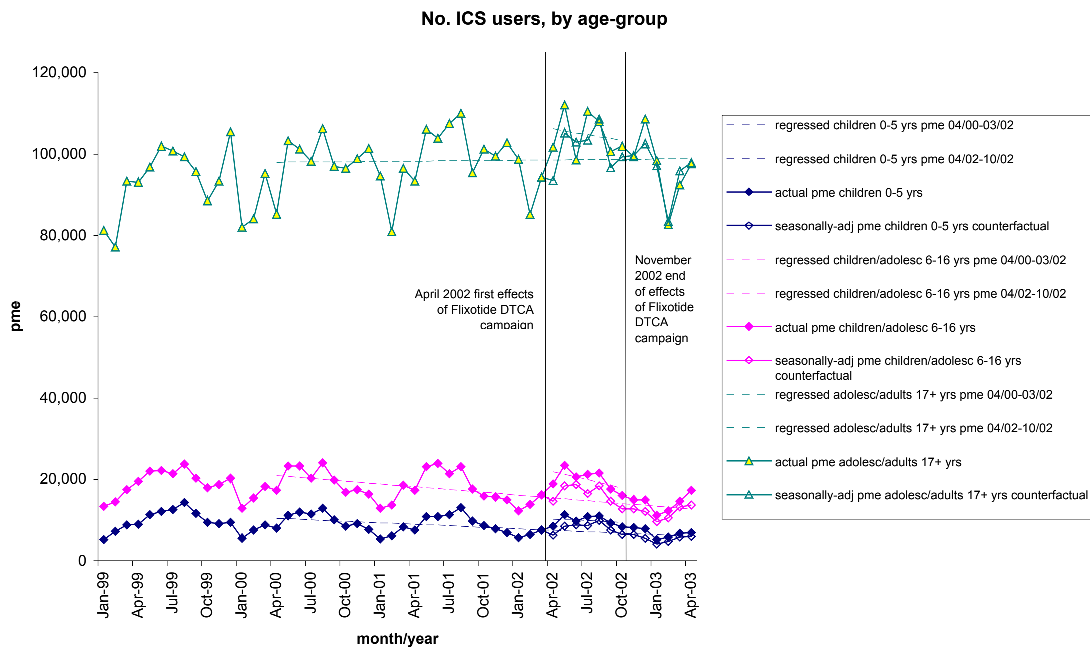
- By contrast, late adolescents/adults aged 17 years and over had a less marked increase in fluticasone use (22%).

- Budesonide increases were likewise proportionately larger for children/early adolescents than adults.

- Conversely, decreases in BDP were less marked in older children/early adolescents aged 6-16/18 years (-12% decrease) than in young children aged 0-5 years and late adolescents/adults (-22% to –23%).

- Hence overall, the number of child/early adolescent patients increased by 22%, but the number of late adolescent/adult patients increased by just 3% (figure 8B).

Figure 8B



- Most (87%) BDP patients switching to fluticasone occurred in the late adolescent/adult age group (7750 patients), whereas most (66%) new ICS-naïve patients were children/early adolescents (4900 patients).

Further detailed results are in the tables of Appendix 4.

Timing of new patients and switching during the Flixotide® DTCA campaign
The above new ICS-naïve patients/BDP-lapsers starting fluticasone appear to have started early on, during April-May 2002. In addition, the subsequent slower increase in fluticasone patients correlated with the decline in BDP patients. Decreases in BDP dispensing volumes and patient-month equivalents accelerated from June 2002 onwards, with the April/May decrease less marked (although still greater than had been historically). The decline in BDP patients was marked and greater than the subsequent continuing increase in fluticasone patients after the initial fluticasone surge in April-May 2002 (figures 9 and 10).

From November 2002 onwards, patterns reversed, with a decrease in both fluticasone growth and BDP decline (figure 10).

Figure 9

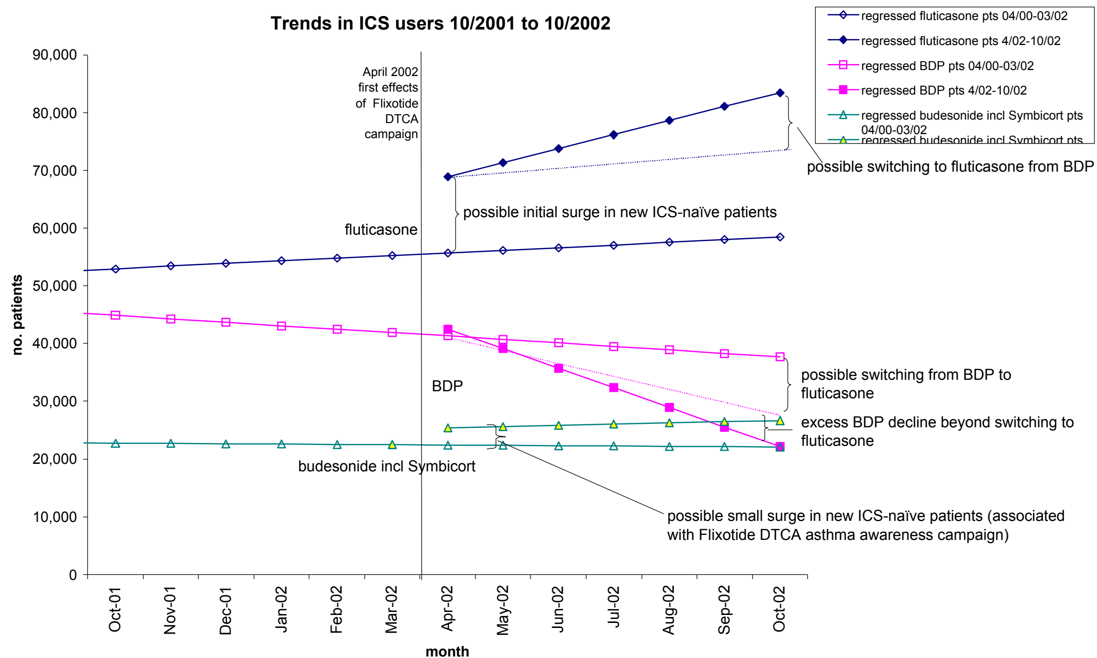
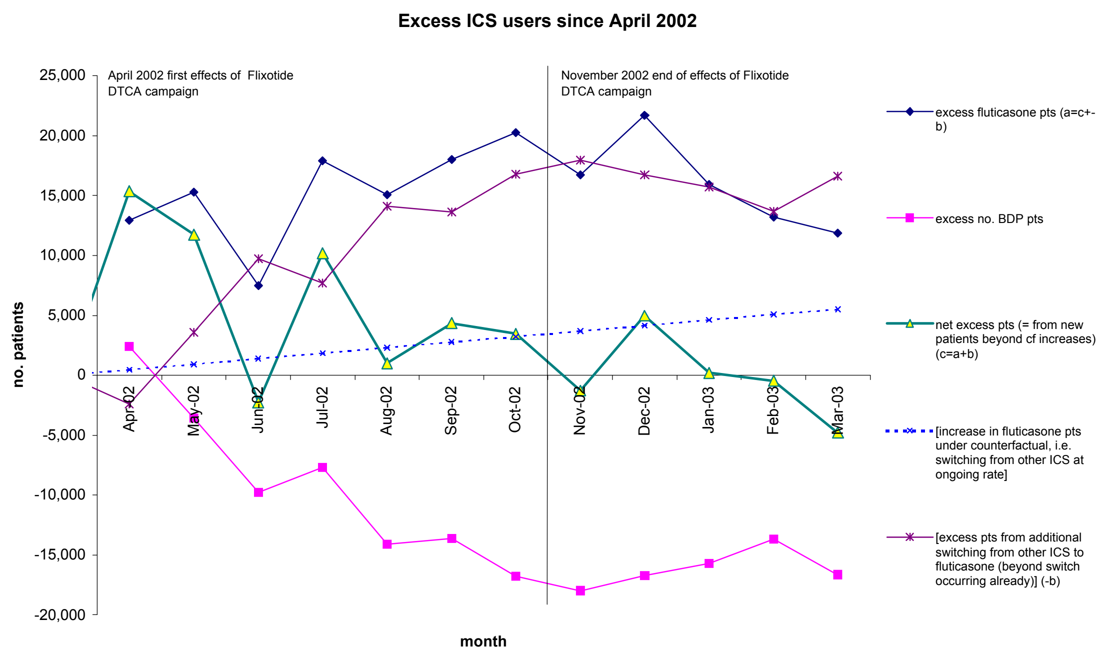


Figure 10

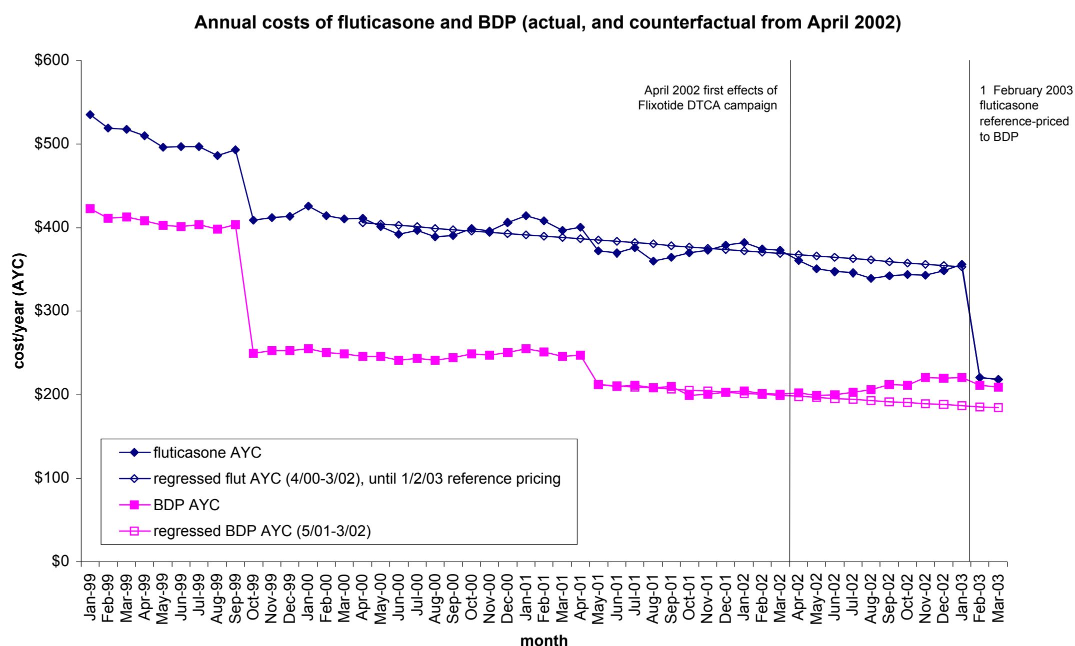


These patterns suggest ICS-naïve patients and BDP-lapsers started fluticasone during early DTCA, whereas switching from BDP to fluticasone occurred more gradually. The later switching perhaps reflects fluticasone prescribing at the time of routine consultations for BDP script renewal.

ICS costs

Costs per patient
Compared with predicted counterfactual costs (derived as above from linear regression of cost/item data prior to April 2002), actual costs per dispensing, and actual average annualised costs per patient[5], were lower for fluticasone and higher for BDP. For fluticasone, actual costs/patient for April 2002 to January 2003 were on average 3% lower than regressed counterfactuals ($347 vs. $360), while for BDP actuals were on average 9% higher ($207 vs. $190) (figure 11). Patterns were similar for budesonide and Symbicort® (budesonide: $338 actual vs. $343 cf. (- 2%); Symbicort®: $1,128 vs. $1,020 (9%).

Figure 11



These differences between actual and predicted counterfactual monthly patient costs are consistent with:

- patients on lower doses of BDP being more likely to switch to fluticasone from April 2002, and
- both new ICS-naïve patients/BDP-lapsers and BDP-switchers starting fluticasone on lower daily doses than before April 2002.

Total ICS costs during the Flixotide® DTCA campaign
The above changes in dispensing volumes and patient numbers, combined with the regressed counterfactual costs per dispensing/annual patient costs per month, translated to $2.1 million extra expenditure on fluticasone over the seven months April to October 2002. This amount was partly balanced by -$600,000 less spending on BDP, hence $1.5 million net increased expenditure. Twenty five percent ($520,000) of the fluticasone extra spending could be attributed

[5] calculated 12 * [total costs] / [total items dispensed], assuming monthly dispensing

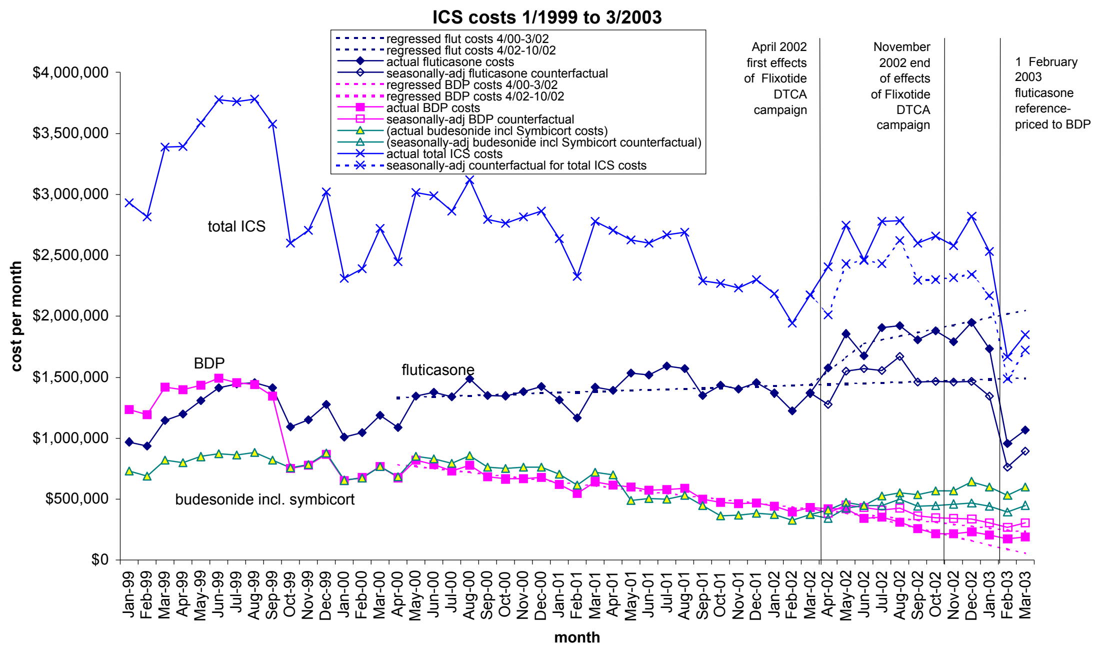
to switching from BDP, the remainder being new/lapsed patients (see Table 1, and figure 12 below).

Impact of Flixotide® DTCA campaign on pharmaceutical spending
Although patterns reversed in the 1-2 months following cessation of the Flixotide® DTCA campaign, the patients who did switch from BDP would have carried on with Flixotide® after October 2002. For the intervening months November 2002 to January 2003, until the implementation of reference pricing, these patients using fluticasone rather than BDP represented a monetary loss to the pharmaceutical budget with no material gain in population health status.

Over the ten-month period April 2002 to January 2003 (which incorporates both the April-October 2002 changes due to DTCA and the November 2002-January 2003 aftermath), there were on average 16,300 extra patients using fluticasone and 11,650 fewer using BDP (139,800 person-months). These translated to $3.28 million extra expenditure on fluticasone, -$1.03 million less spending on BDP, hence $2.25 million net increased expenditure before reference pricing.

$900,000 (27%) of the fluticasone extra spending April 2002-January 2003 could be attributed to switching from BDP, the remainder being due to new/lapsed patients (Table 1, figure 12). There is insufficient data to calculate additional monetary loss to the pharmaceutical budget from BDP-lapsed patients restarting their ICSs with fluticasone (when BDP would be no less effective).

Figure 12



ICS average daily doses

Overall average daily doses (ADDs)
Although there was the increase in fluticasone and decrease in BDP dispensing/patient volumes, fluticasone average daily doses (ADDs) conversely decreased markedly during April to August 2002. However, BDP ADDs increased and budesonide ADDs decreased slightly:

- Before April 2002, fluticasone ADDs had been tracking at 593 μg/day (1187 μg/day BDP-equivalents), but during the seven months April to October 2002 averaged 527 μg/day, an 11% decrease.

- BDP ADDs rose to 626 μg/day (had been tracking at 615 μg/day), while budesonide (including Symbicort®) reduced to 901 μg/day (was 953).

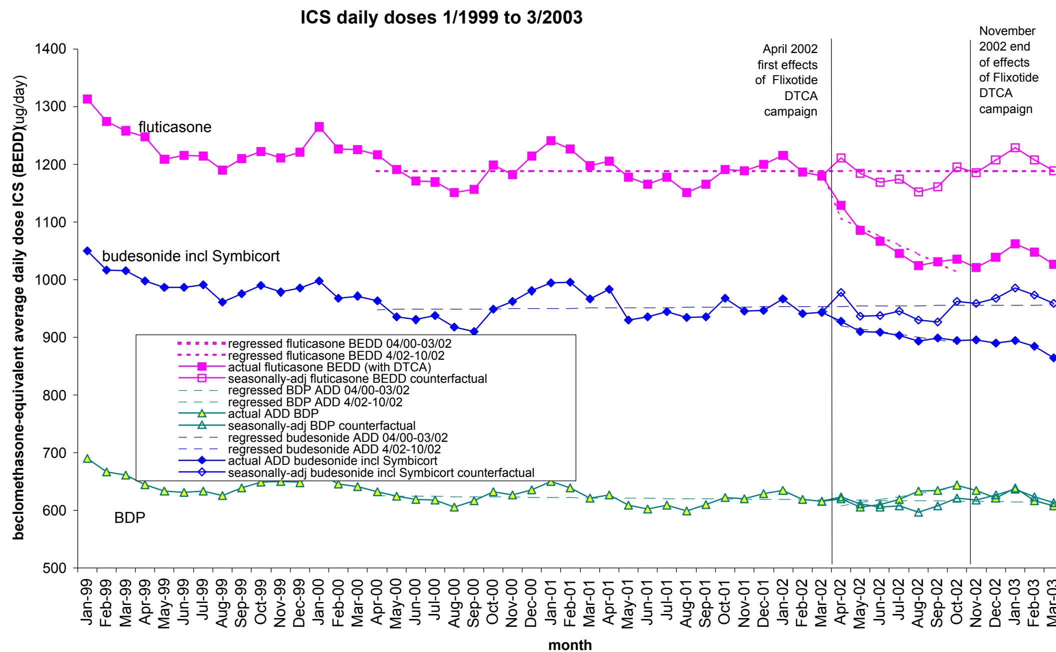
- By October 2002, ADDs had stabilised at 517 ug/day for fluticasone and 644 μg/day for BDP (Table 2, figure 13).

However, following the November cessation of DTCA effects, ADDs remained stable (figure 13).

Table 2
ICS ADDs since April 2002

	ADD ug/day 4/02-1/03			ADD ug/day at 10/02		
	actual (changes since April 2002)	predicted cf	new/"lost" pts	actual (changes since April 2002)	predicted cf	new/"lost" pts
fluticasone	527	593	275	517	598	278
(BDP-equivalent DD)	1054	1187	549	1035	1195	557
- difference	-66			-80		
- actual/predicted	0.89			0.87		
BDP	626	615	592	644	621	594
- difference	11			22		
- actual/predicted	1.02			1.04		
budesonide	901	953	599	895	962	592
- difference	-51			-68		
- actual/predicted	0.95			0.93		
other ICS (BDP/budesonide)	755	733	591	781	742	596
- difference	22			39		
- actual/predicted	1.03			1.05		
total ICS (BDP-equivalents)	926	951	951	941	966	966
- difference	-25			-25		
- actual/predicted	0.97			0.97		

Figure 13



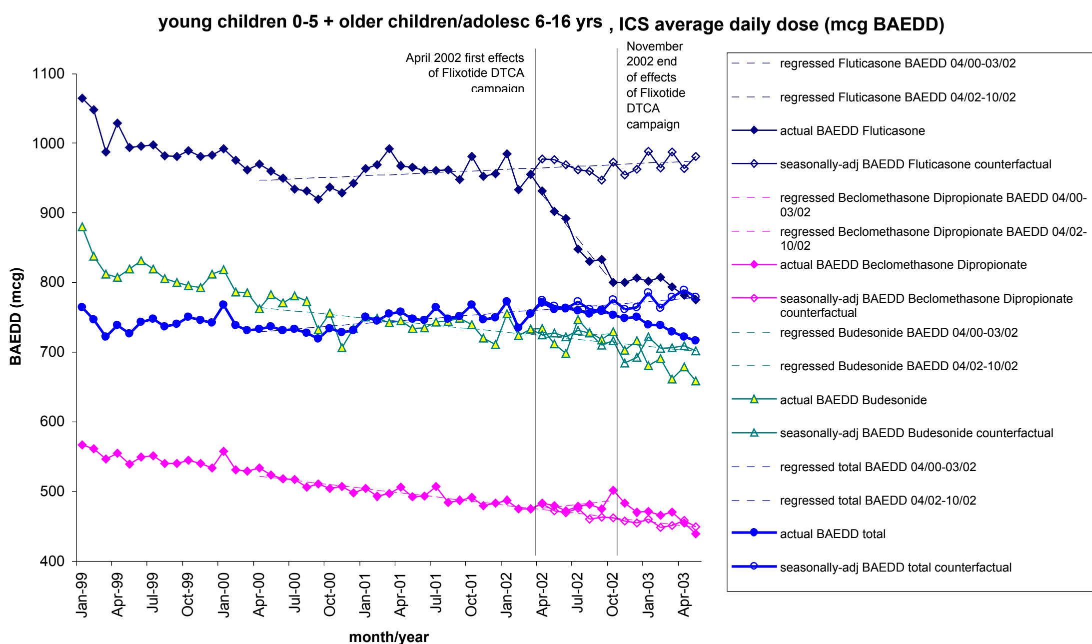
Variation by age-group

Important variation in ICS ADDs again occurred by age group during April to October 2002, with fluticasone ADD decreases particularly occurring in older children/early adolescents:

- Fluticasone ADD decreases were particularly marked (-11%) for older children/early adolescents aged 6-16/18 years (312 µg/day actual vs. 350 µg predicted counterfactual). For these children, this equates (adjusting for age and ICS potency) to an equivalent dose of an adult using BDP (BDP adult-equivalent daily dose, i.e. BAEDD)[6] of 862 µg/day actual vs. 966 µg predicted counterfactual (figure 13A);

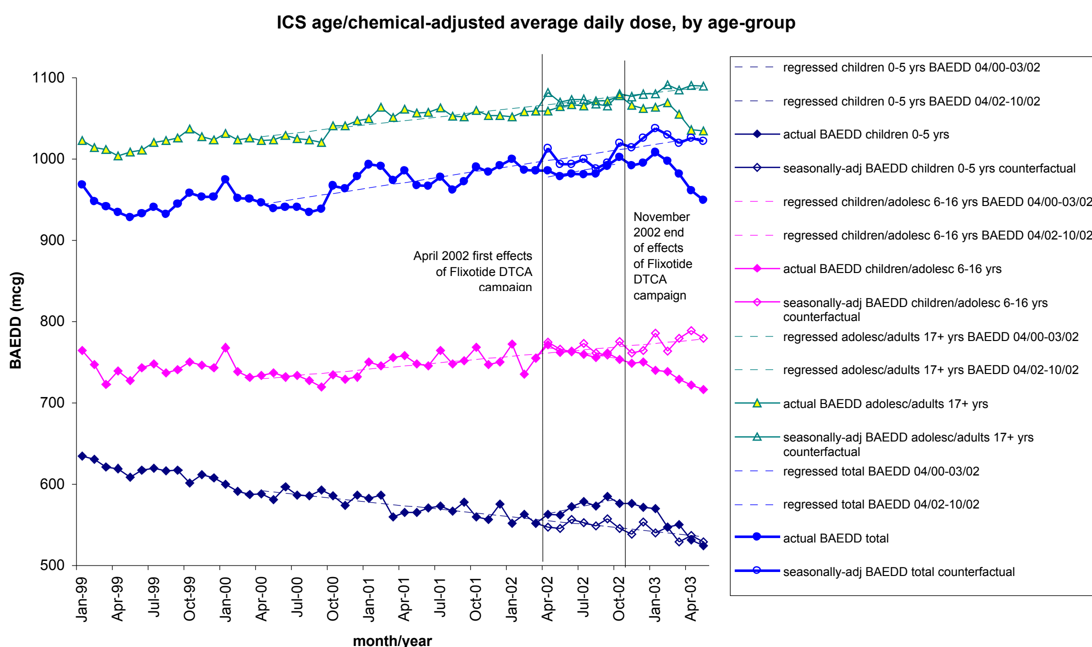
  Figure 13A

[6] BAEDD = BDP adult-equivalent daily dose (e.g. 800 ug/day BDP in adults = 400 ug fluticasone in adults or 400 ug BPD in children or 200 ug fluticasone in children, etc.). This measure adjusts (standardises) for both the different potencies of ICS chemicals (fluticasone is twice as potent as BDP or budesonide at the same nominal µg dose) and the different dosing requirements of children compared with adults (children aged under 12 years require half the nominal adult dose).



- By contrast, the small increase in BDP ADDs (2% overall) was consistent across all age groups; and
- Overall BAEDD levels across all chemicals were slightly higher for young children and slightly lower for older adults/adolescents/adults (figure 13B).

Figure 13B



Note that a large (12%) increase in budesonide ADD for young children may have been a chance variation due to small numbers (n=135-163).

Further detailed results are in the tables of Appendix 4.

LABA dispensings

Eformoterol 6 µg (Oxis Turbohaler® 6µg) dispensings LABA similarly increased 25% more than expected (7470 patient-months averaged over April-October 2002, versus 5960 predicted)[7] (Table 3, figure 14).

Coincidentally, the increase for Oxis 6 declined following cessation of the Flixotide® DTCA campaign (see figure 14).

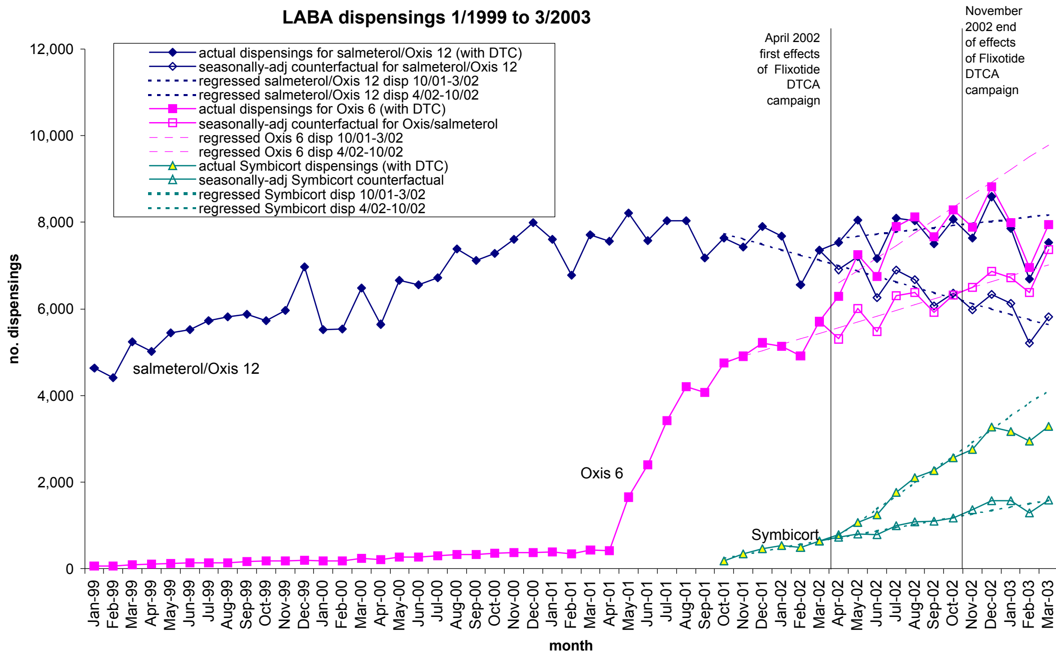
Table 3

Excess LABA patient numbers since April 2002

	No. dispensings total 4/02 to 10/02		No. patients av pme 4/02 to 10/02		pts at 3/03	
	actual (changes since April 2002)	predicted cf	actual (changes since April 2002)	predicted cf	actual (changes since April 2002)	predicted cf
eformoterol+budesonide combination LABA (Symbicort)	11,806	6,676	1,687	954	3,285	1,582
- difference	5,130		733		1,703	
- actual/predicted	1.77				2.08	
Oxis 6	52,274	41,744	7,468	5,963	7,940	7,372
- difference	10,530		1,504		568	
- actual/predicted	1.25				1.08	
salmeterol/Oxis 12	54,442	46,369	7,777	6,624	7,533	5,817
- difference	8,073		1,153		1,716	
- actual/predicted	1.17				1.30	
(total salmeterol/eformoterol)	106,716	88,113	15,245	12,588	15,473	13,189
- difference	18,603		2,658		2,284	
- actual/predicted	1.21				1.17	
total LABAs	118,522	94,789	16,932	13,541	18,758	14,771
- difference	23,733		3,390		3,987	
- actual/predicted	1.25		1.25		1.27	
Excess associated with fluticasone DTCA						
excess eformoterol+budesonide combination LABA	5,130		733		1,703	
excess salmeterol/eformoterol LABA	18,603		2,658		2,284	
total LABAs	**23,733**		**3,390**		**3,987**	

Figure 14

[7] This is where access to Oxis 6 (via endorsement) is less restrictive than for other LABAs; Symbicort® also had a greater-than-predicted increase in volumes, but its restriction under Special Authority to 1500 µg BDP adult-equivalent ICS daily dose makes it irrelevant in this context

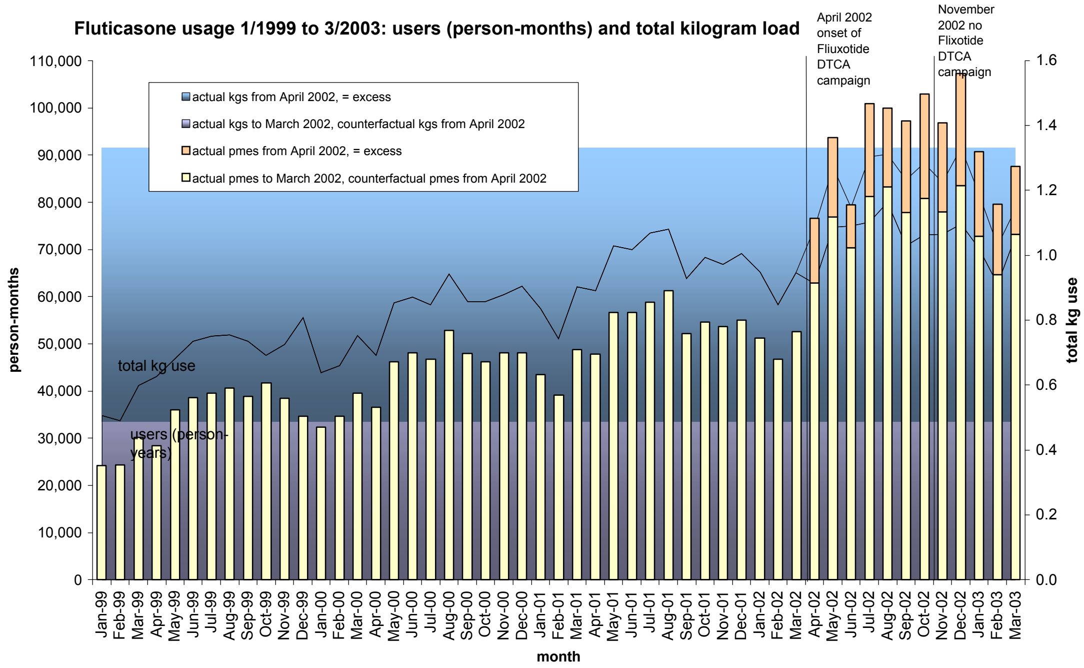


The increases in Oxis 6 dispensings above expected is consistent with possible increased awareness of poor asthma control resulting from the Flixotide® DTCA campaign. Hence this is further indirect evidence of more-than-expected new ICS-naïve patients accessing fluticasone since April 2002 (and perhaps budesonide to a lesser extent), alongside decreases in fluticasone ADDs.

ICS total kg volumes

Combining both changes in patient numbers and ADDs is best summarised by total kilogram volumes of ICS chemicals. Figure 15 below shows the increase in fluticasone use during April to October 2002 beyond predicted, similar to that for patient numbers but less marked:

Figure 15



The less marked increase in total kg volumes reflects confounding from the effects of lowered ADDs due to new ICS-naïve patients

Comments

Choice of regression modelling used

This analysis used simple linear regression to model changes in proportions and then total volumes.

A more statistically robust form of regression would have been to logistically regress the proportions of fluticasone and BDP dispensings (as proportions of total dispensings), then apply these to log-linear trends in total ICS volumes (actual and counterfactual), finally incorporating seasonal adjusters by month:

- Logistic regression simply transforms proportions (or dichotomous yes/no data) to make sure that results are not less than 0.0 and not more than 1.0.

- Similarly, the use of log-linear regression of total volumes avoids anomalies caused by linearly regressed lines having the ability to cross zero (i.e. potentially giving negative volumes – a statistical impossibility).

However, given the relatively short time periods projected, this paper reports the results from modelling using simple linear regression. This is a conservative assumption; the use of log-linear regression of proportions applied to log-linear regression of total volumes gives $1.078 million fluticasone extra spending April 2002-January 2003 that could be attributed to switching from BDP. This compares with the lower estimate of $900,000 extra spend calculated using linear regression, as described in Table 1 and figure 12 above.

Implications of changes in ICS ADDs

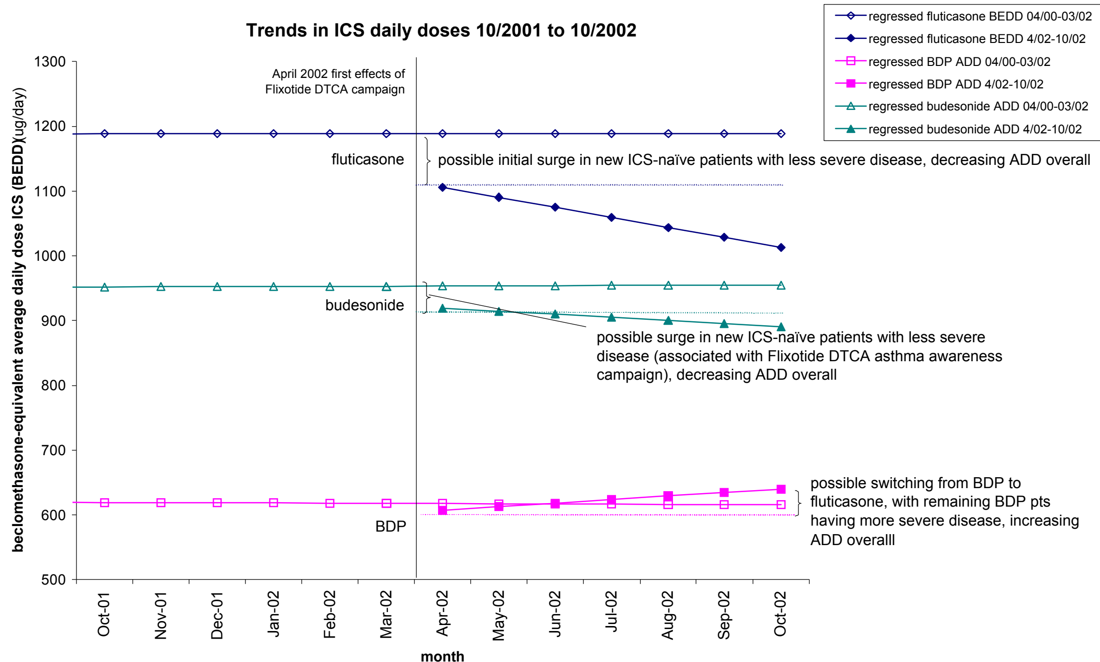
The above changes in fluticasone and BDP ADDs are indirect evidence supporting the above changes to patient numbers, with:

- a possible initial surge in fluticasone use by new ICS-naïve patients/BDP-lapsers with less severe disease, decreasing fluticasone ADD overall,

- a possible small surge in budesonide use from new patients with less severe disease (associated with Flixotide® DTCA asthma awareness campaign), decreasing ADD overall, and

- a possible switching from BDP to fluticasone, with remaining BDP patients having more severe disease, increasing ADD overall (figure 16).

Figure 16



In addition, by age, older children/early adolescents (aged 6-16/18 years) had both the biggest proportional increase in probable new ICS-naïve patients/BDP-lapsers using fluticasone (85% of all new patients) and the largest decrease in fluticasone ADD (-11%).

Lower ADDs in new patients suggest those patients switching from BDP to fluticasone had less severe asthma

Taking into account both the increases in patient numbers since April 2002 and the changes in ADDs since that time, then very simplistically we can estimate what the ADDs of "new" or "lost" patients since that time[8] (see Table 2 above):

- If people already taking fluticasone before April 2002 were to have maintained the same daily dose (593 µg/day), then the excess fluticasone patients since that time would have had to be using on average a putative daily dose of 275 µg/day (549 µg BEDD), in order to reduce the overall ADD from 593 to 527 µg/day.

- Likewise, the excess budesonide (including Symbicort®) patients would have had to use on average 599 µg/day (to cause ADD reduction from 953 to 901 µg/day).

- The "lost" BDP patients would have been using maybe 592 µg/day, and losing them caused the putative ADD to rise to 626 µg/day (from 615 µg).

This implies that those patients switching from BDP to fluticasone were on lower daily doses than average, i.e. these were patients with less severe asthma (if, suspending disbelief, magnitude of ICS daily dose relates solely to severity).

The implication that patients who switched had less severe asthma particularly applied for older children/early adolescents:

[8] algebraically solving for ADD for "new" or "lost" patients, where ([new overall no. patients] * [new overall ADD]) = (([no. old patients] * [old ADD]) + ([no. "new" or "lost" patients] * [ADD for "new" or "lost" patients]))

- For older children/early adolescents aged 6-16/18 years, the (relatively fewer) patients switching to fluticasone (15% of all excess fluticasone older children/early adolescents) had a 274 µg/day putative ADD for BDP. This was just 81% of the 340 µg/day putative predicted counterfactual ADD for existing BDP patients in this age group.

- By contrast, BDP ADDs for young children aged 0-5 years and late adolescents/adults aged 17/19+ years switching to fluticasone were within 5% of predicted age-specific BDP counterfactual ADDs (for young children, 203 µg/day for switchers vs. 215 µg counterfactual; for late adolescents/adults, 654 µg/day for switchers vs. 691 µg counterfactual).

Further detailed results are in the tables of Appendix 4.

ADD changes suggest new ICS-naive patients/BDP-lapsers starting fluticasone also had less severe asthma
The above BDP-equivalent ADD for all new fluticasone patients of 549 µg BEDD was similar to that of "lost" BDP patients' ADD of 592 µg/day (-7.2% variation).

It is possible to calculate putative average daily doses for the subgroup of new ICS-naïve patients/BDP-lapsers starting fluticasone. This involves using the above ADDs and patient numbers, and depends upon assumptions made about fluticasone ADDs for the subgroup of those patients switching from BDP[9] (table 4).

- Making an untested assumption that all of patients switching from BDP were placed on an appropriate equivalent dose of fluticasone (i.e. a straight 2:1 change in µg dose), then new ICS-naïve patients/BDP-lapsers starting fluticasone would have done so at an average daily dose of 242 µg/day.

- Conversely, if a notional 10% of patients switching from BDP were placed in an inappropriate 1:1 µg equal nominal dose of fluticasone (i.e. prescribers mistakenly assume equipotency and double the effective dose of ICS), then new ICS-naïve patients/BDP-lapsers starting fluticasone would have done so at an average daily dose of 196 µg/day. Such a scenario is plausible, given indirect evidence of such 1:1 dosing.[10]

Table 4
ADDs for new fluticasone patients, April-October 2002

	no. patients	if all pts switch at approriate dose equivalence		if 10% of pts switching have inappropriately 1:1 dosing	
		BEDD ug/day	ADD fluticasone ug/day	BEDD ug/day	ADD fluticasone ug/day
new ICS-naïve patients, beyond counterfactual increases	6,012	483.3	241.7	391.1	195.5
patients additional switching from BDP*	9,372	591.8	295.9	651.0	325.5
total new fluticasone patients	15,385	549.4	274.7	549.4	274.7

* assumes that patients switching from BDP are placed on an appropriate equivalent dose of fluticasone (i.e. a straight 2:1 change in µg dose)

[9] algebraically solving for new ICS-naïve patients' ADD,
where ([new overall no. patients] * [new overall ADD]) = (([no. new ICS-naïve patients/BDP-lapsers] * [new ICS-naïve/BDP-lapser ADD]) + ([no. patients switching from BDP] * [presumed ADD for patients switching from BDP])),
where [presumed ADD for patients switching from BDP] incorporates previous BDP ADD and assumes a proportion (0%, 10%) will have inappropriate 1:1 dosing.
[10] Black PN, Lawrence BJ, Goh KH, Barry MS. Differences in the potencies of inhaled steroids are not reflected in the doses prescribed in primary care in New Zealand. Eur J Clin Pharmacol. 2000 Aug;56(5):431-5.

Note that as such, any speculative inappropriate dosing of fluticasone in patients swapping from BDP represents waste, and would be a further monetary loss to the pharmaceutical budget with no material gain in population health status.

As with patients switching having less severe asthma, any low fluticasone ADDs for new ICS-naïve patients/BDP-lapsers would have particularly applied for older children/early adolescents. They also however applied to late adolescents/adults:

- For older children/early adolescents aged 6-16/18 years, the (relatively-high number of) new ICS-naïve patients/BDP-lapsers (85% of all excess fluticasone older children/early adolescents) had a 230 µg/day putative ADD for fluticasone. This was just 66% of the 350 µg/day predicted counterfactual ADD for existing older children/early adolescents.

- Likewise for late adolescents/adults aged 17/19+ years, new ICS-naïve fluticasone patients/BDP-lapsers had a 423 µg/day putative ADD, just 64% of the 662 µg/day predicted counterfactual ADD for existing fluticasone late adolescents/adults.

- By contrast, ADDs for fluticasone for new ICS-naïve/BDP-lapsed young children aged 0-5 were within 10% of predicted counterfactual ADDs for existing young children (142 µg/day for new ICS-naïve patients/BDP-lapsers vs. 159 µg counterfactual).

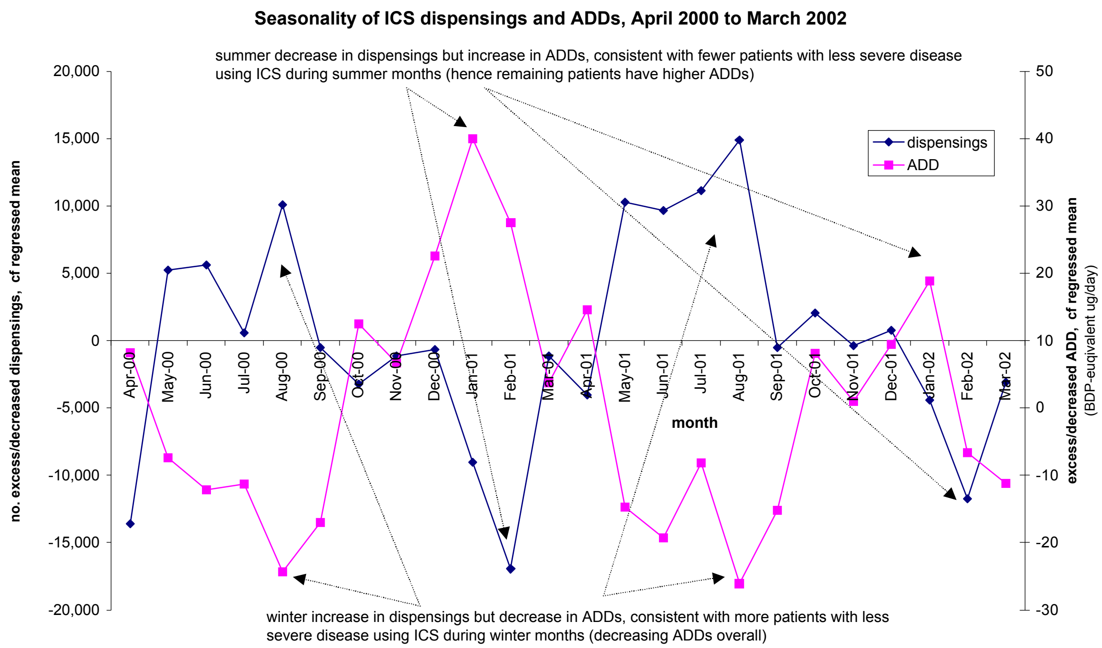
Further detailed results are in the tables of Appendix 4.

Consistency with seasonal changes in ICS dispensings and ADDs
Note the above linking of changes in patient usage with opposite changes in ADDs is supported by observational data for historical ICS dispensings and ADDs (BDP, budesonide and fluticasone April 2000 to March 2002). Here there is:

- a summer decrease in dispensings but increase in ADDs, which is consistent with fewer patients with less severe disease using ICS during summer months (hence remaining patients have higher ADDs); and

- a winter increase in dispensings but decrease in ADDs, which is consistent with more patients with less severe disease using ICS during winter months (decreasing ADDs overall) (figure 17).

Figure 17

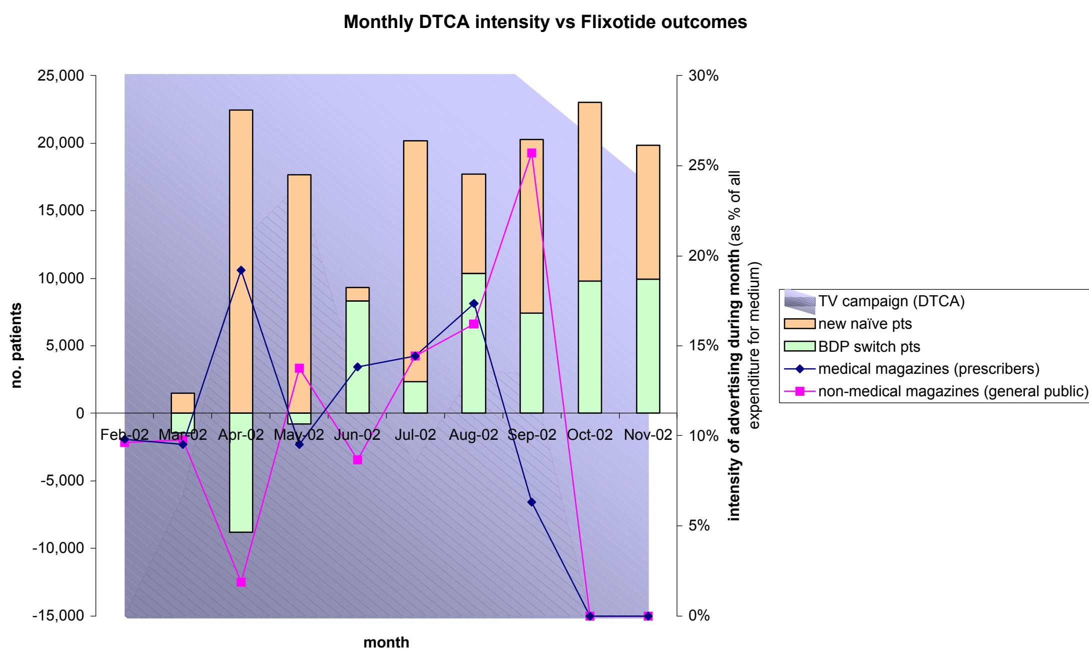


Note that seasonal mirroring of variation in dispensings relating inversely to variation in ADDs is consistent across all ICS chemicals. Contrastingly, when analysed by age the relationship is most marked in late adolescents/adults (for details, see figures 17A to 17E in Appendix 1).

Temporal relationship between changes in fluticasone/BDP prescribing and the Flixotide® DTCA campaign

Independent advertising monitoring data (AC Neilson ratecard expenditure) relating to GSK confirm the time course of the Flixotide® DTCA campaign, with it taking place between March and September 2002, peaking during April and May. The temporal trends in dispensings suggest a 1-2 month lag between exposure to any Flixotide® DTC advertising episode and the last dispensing of medication (figure 18):

Figure 18



This lag is consistent with inevitable delays caused by all potential patients needing to be exposed to DTCA; then contemplating whether their asthma is poorly controlled; then contemplating whether their asthma might be amenable to fluticasone (if a new patient) or whether they should switch from their existing medication to fluticasone (for those patients already using BDP); then deciding to seek medical advice; then booking a medical appointment; then getting to see their medical practitioner; then being prescribed fluticasone; and then getting the prescription dispensed. The speed of this process might be expected to vary across patients.

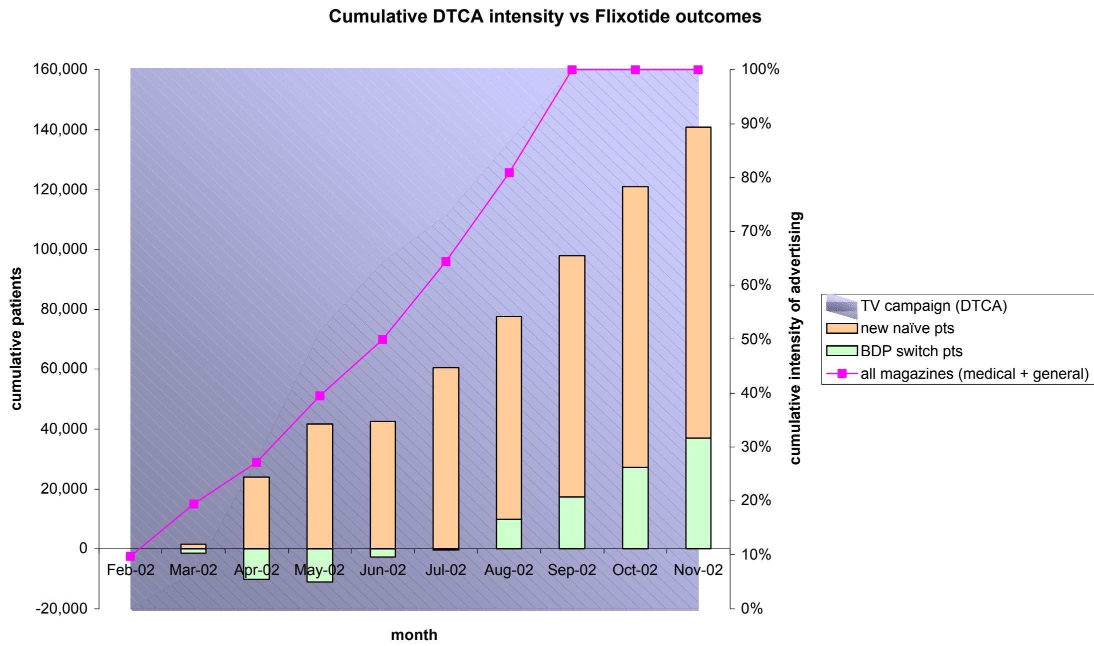
By contrast, advertising in the medical media (as indicated by medical magazine advertising placements) preceded the televised DTC advertising and remained constant over April to September 2002. In addition, there were mail-outs to prescribers sent in April. Advertising to the general public also occurred outside the televised DTCA during this period and finished during September.

Note a greater lag might be expected for some patients switching from BDP to fluticasone, as distinct from new ICS-naïve patients/BDP-lapsers. This is because switching patients might wait until their current BDP prescription was finished (typically 3-month scripts). However, this is countered by the DTCA also having offered the inducement of a free Flixotide® inhaler for a

limited time. This may have encouraged BDP patients to switch earlier rather than at the end of their current prescription.

The differential rates of switching over time (as distinct from patterns for new patients) reflects the mix of these two competing factors (figure 19):

Figure 19



Causality

The above analysis relates to dispensing volumes and costs, examining changes occurring after a certain date (1 April 2002) associated with onset of appreciable Flixotide® DTCA campaigning compared with before that time. As such it is a descriptive before-and-after analysis, using proxy controls for some semblance of context (viz. patterns of ICS average daily doses and LABA dispensing volumes). These correlations are simply associations, and do not of themselves demonstrate causation. Other factors not explorable in the present data may be important.

However, there are strong indications that the above associations between DTCA for Flixotide® and switching from BDP do demonstrate causation when considering the Bradford Hill criteria[11] (further detailed in Appendix 2). This is indicated particularly by:

- the strength of the association;
- consistency across populations (age-specific results for numbers of new patients and BPD switching versus ADDs enhance the overall patterns);
- specificity (no replication in patterns with Symbicort®, salmeterol and Oxis 12 use, for instance);
- temporality (close dose-response relationship between Flixotide® DTCA and dispensing/ADD changes);
- biological gradient (decreased switching as DTCA ceases); and
- plausibility.

[11] Bradford-Hill A. "The Environment and Disease: Association or Causation?" Proc Royal Soc Med 1965;58:295. in turn, adapted from: US Department of Health, Education and Welfare. Smoking and Health: Report of the Advisory Committee to the Surgeon General of the Public Health Service, Public Health Service Publication 1103. Washington, D.C.: Government Printing Office, 1964.

Effects of the Flixotide® DTCA campaign on BDP prescribing, as part of possible GSK wider strategy for the LABA/ICS market in New Zealand

Possible overall goal of Flixotide® DTCA
The Flixotide® DTCA campaign may be the first part of a strategy by GSK to shift the whole asthma preventive/modifier market to its combined salmeterol/fluticasone product (Seretide®) - away from the current mix which includes BDP and budesonide ICSs with some concurrent eformoterol LABA use.

For the reasons presented below, it seems that the Flixotide® DTCA campaign may have had at least three goals:

1. To improve the uptake of ICSs (specifically Flixotide®) in patients needing ICSs but not currently using them (i.e. new ICS-naive patients).

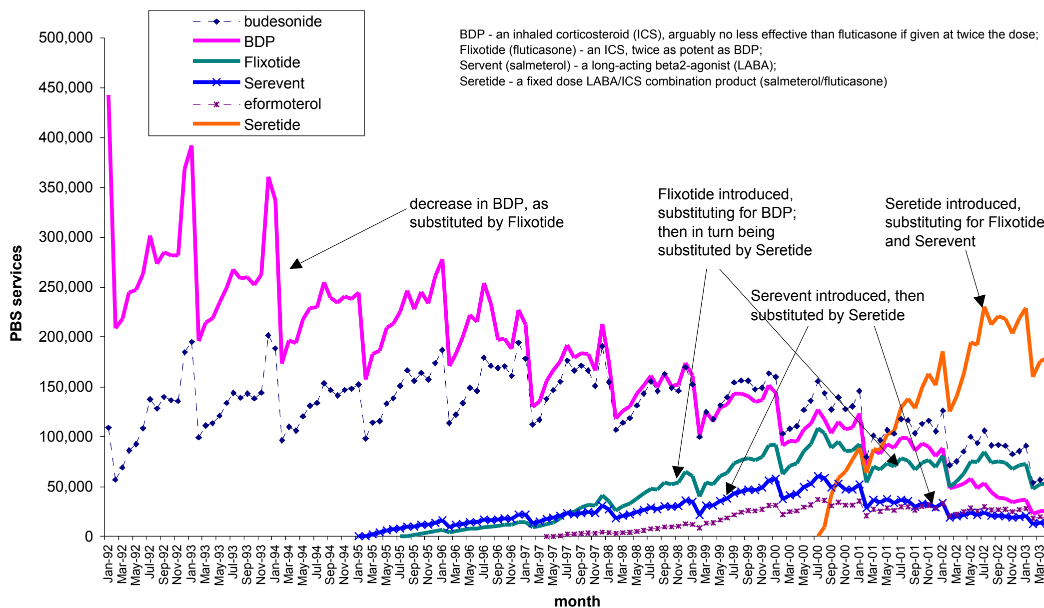
2. To switch patients using BDP to Flixotide® - possibly as but an intermediate step towards a goal of Seretide® fixed LABA/ICS combination product solely dominating both the ICS and LABA markets in New Zealand.

3. To materially affect the remaining BDP market, at the expense of potential competitors in that market.

Possible ultimate goal of Seretide® combination LABA/ICS dominating the ICS/LABA market
In terms of the second of GSK's apparent goals, GSK's strategy in New Zealand of promoting Flixotide® as allegedly more superior and as being CFC-free, over CFC-containing Becotide® and Beclomethasone®, appears consistent with what appears to have occurred in Australia. Following the introduction and marketing of Flixotide, the market there shifted from BDP to Flixotide® as the dominant ICS. The Serevent® LABA (salmeterol) was introduced at the same time but will soon to be phased out, ostensibly because it is CFC-containing (see below).

The inferred overall goal in Australia now appears to be to have the Seretide® combination LABA/ICS CFC-free product as the sole product in both the ICS and LABA markets. These changes can bee seen in figure 20, which shows the shifts from beclomethasone to fluticasone and salmeterol and then to Seretide:

Figure 20



source: PHARMAC analysis of PBS data at http://www.hic.gov.au/statistics/dyn_pbs/forms/pbs_tab1.shtml, using PBS codes (http://www1.health.gov.au/pbs/scripts/listtherlvl1.cfm?sched=GA) for BDP (1649T, 1650W, 1651X, 1652Y, 8142M, 8406K, 8408M, 8409N, 8143N, 8407L) budesonide (2067T, 2068W, 2069X, 2070Y, 2071B, 2072C), Flixotide® (2716Y, 2717B, 8091W, 8145Q, 8147T, 8148W, 8149X, 8345F), salmeterol (3027H, 8005H, 8141L), eformoterol (8136F, 8239P, 8240Q)

In line with the above possible goal of dominance of Seretide® fixed combination LABA/ICS inhalers,[12] at an international level GSK appears to be withdrawing its Serevent® inhaler formulations of salmeterol LABA (which contain CFCs). For instance, recent advice posted on the US FDA website (dated 10 June 2003, at http://www.fda.gov/cder/drug/shortages/default.htm#disc) states that GSK anticipates that Serevent® will be discontinued in North America from June 2003, ostensibly to be consistent with the Montreal protocol (see http://www.fda.gov/cder/drug/shortages/servent-Letter.pdf).

Note there are no obvious reasons why Serevent® (salmeterol) cannot continue as a CFC-free formulation. This is given that most strengths of both Flixotide® (fluticasone) and Seretide® (fluticasone/salmeterol) are CFC-free.

In addition, newly emerging evidence suggests that Seretide® combination LABA/ICS is no more effective at improving clinically relevant outcomes than concurrent use of separate salmeterol LABA and fluticasone ICS inhalers.[13] Even Seretide®'s improved physiological effects (which are arguably intermediate outcomes of uncertain significance clinically) have been overstated. Also there is no evidence that combination LABA/ICS products improve compliance over concurrent use, and ICS dose titration may be more difficult. Rates of reported adverse events are significantly higher with Seretide®. When compared with salmeterol[14] (and even fluticasone[15]), Seretide® has much smaller changes in physiological effects, reflected in nil

[12] as well as complying with the Montreal Protocol

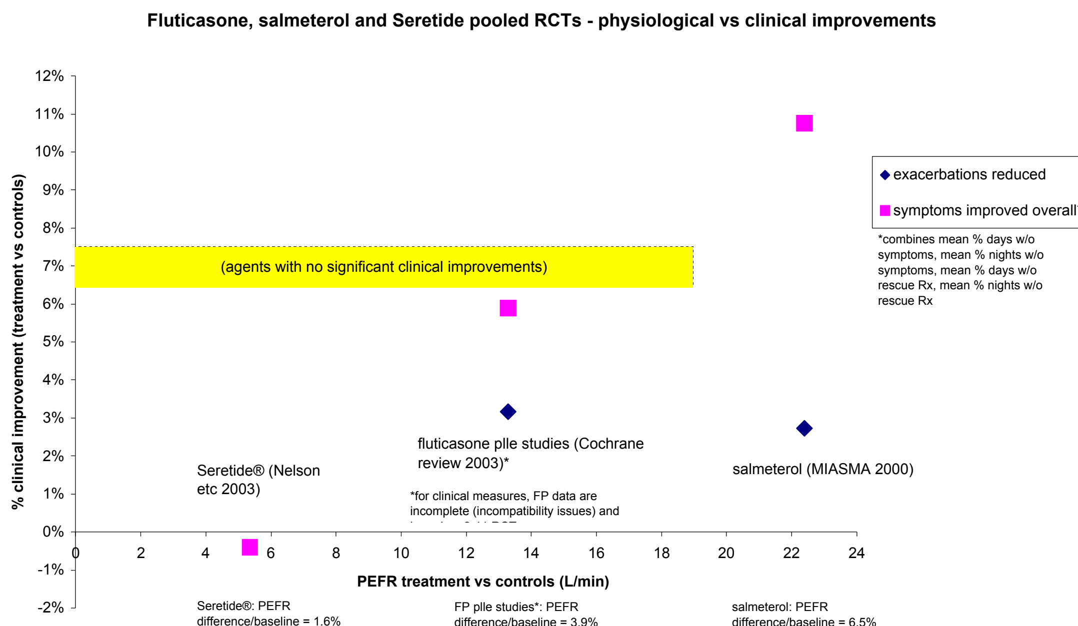
[13] Nelson HS, Chapman KR, Pyke SD, Johnson M, Pritchard JN. Enhanced synergy between fluticasone propionate and salmeterol inhaled from a single inhaler versus separate inhalers. J Allergy Clin Immunol. 2003 Jul;112(1):29-36.

[14] Shrewsbury S, Pyke S, Britton M. Meta-analysis of increased dose of inhaled steroid or addition of salmeterol in symptomatic asthma (MIASMA). BMJ. 2000 May 20;320(7246):1368-73.

[15] Adams N, Bestall JM, Jones PW. Fluticasone versus beclomethasone or budesonide for chronic asthma (Cochrane Review). In: The Cochrane Library, Issue 3, 2003. Oxford: Update Software. CD002310

clinical improvements. Note that neither Seretide® nor fluticasone have been able to demonstrate clinically significant improvements in pooled analyses (figure 21)

Figure 21



Further details are in Appendix 3. Advice from British[16], GINA[17] and New Zealand[18] asthma guidelines has been that there is no difference in clinical efficacy between combination and concurrent (separate devices) LABA/ICS. Such advice still applies.

Yet the Seretide® combination ICS/LABA formulation is priced 2-3 times that of separate equivalent component fluticasone and double-strength salmeterol inhalers (at $531 to $1176 extra per patient per year).[19]

---

[16] British Thoracic Society; Scottish Intercollegiate Guidelines Network. British guideline on the management of asthma. Thorax 2003;58 Suppl 1:i1-94. http://www.sign.ac.uk/guidelines/published/support/guideline63/download.html

[17] National Heart, Lung, and Blood Institute , National Institutes Of Health. Global Strategy for Asthma Management and Prevention, revised 2002. (Scientific information and recommendations for asthma programs. NIH Publication No. 02-3659). p108

[18] Best Practice Evidence-Based Guideline: The Diagnosis and Treatment of Adult Asthma. New Zealand Guidelines Group, 2002. http://www.nzgg.org.nz/library/gl_complete/asthma/index.cfm

[19]

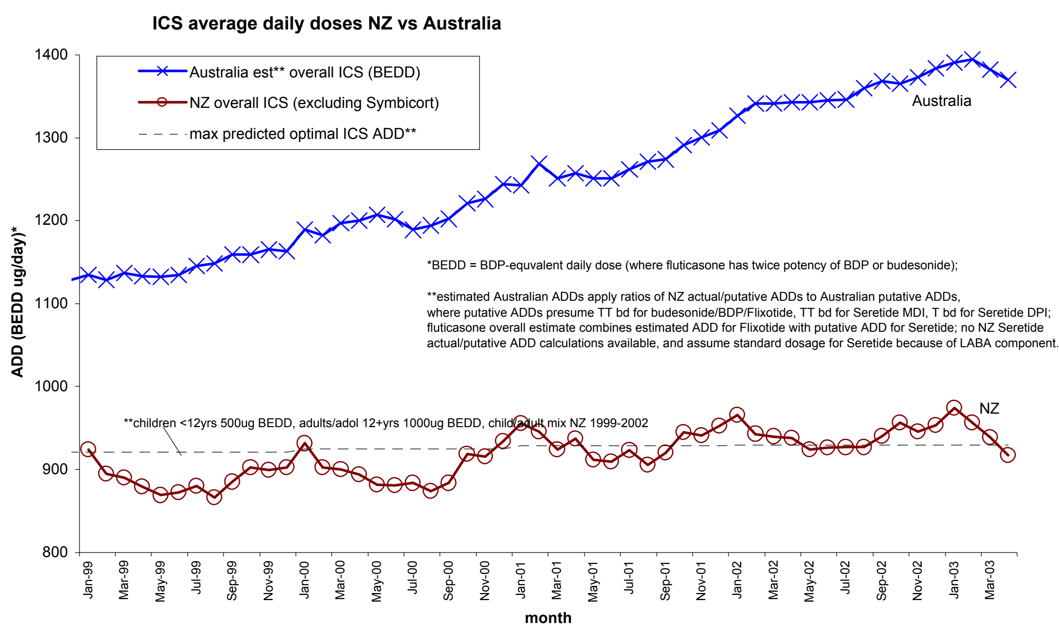
http://www.flixotide.co.nz/seretide/cost.asp price for Seretide, NZ Pharmaceutical Schedule prices for salmeterol and fluticasone (FP):

	cost		difference		RR
	$/device	$/year	$/device	$/year	Seretide®/(FP+salm)
fluticasone 50mcg + salmeterol 50mcg	$43.30	$527			
Seretide® MDI 50/25 (FP 50 mcg/salm 25mcg)	$86.95	$1,059	$43.65	$531	2.0
fluticasone 125mcg + salmeterol 50mcg	$49.40	$601			
Seretide® MDI 125/25 (FP 125 mcg/salm 25mcg)	$108.95	$1,326	$59.55	$725	2.2
fluticasone 250mcg + salmeterol 50mcg	$49.40	$601			
Seretide® MDI 250/25 (FP 250 mcg/salm 25mcg)	$145.95	$1,777	$96.55	$1,175	3.0

Note that Seretide® now dominates the Australian market and is a leading cause of overall pharmaceutical expenditure growth there – with continuing ICS ADDs higher than in New Zealand:

- The presence of Seretide® in Australia has been associated with an increase in the (comparatively high) ICS ADDs there. ADDs in Australia during April 2003 were 52% higher than in New Zealand (1370 µg BEDD for Australia vs. 917 µg New Zealand (excluding Symbicort®)) [20] (figures 22 and 23).

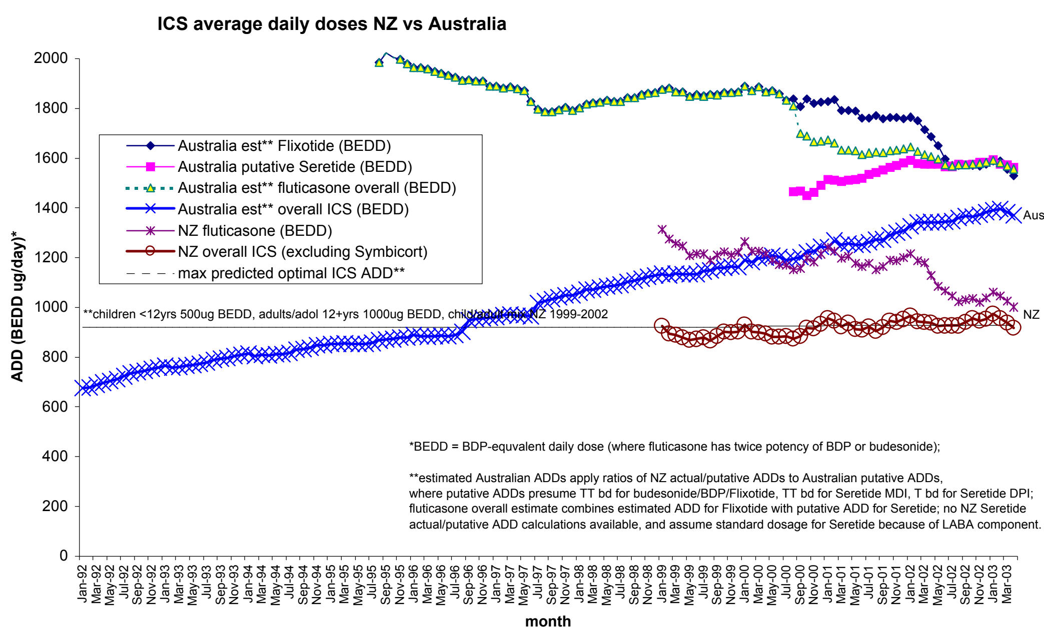
Figure 22



- In particular, Australian fluticasone ADDs were 55% higher (1556 µg BEDD vs. 1001 µg New Zealand) (figure 23).

Figure 23

[20] PHARMAC analysis of PBS data at http://www.hic.gov.au/statistics/dyn_pbs/forms/pbs_tab1.shtml and HealthPAC data.



- Between August 2000 (when Seretide® was introduced into Australia) and April 2003, ADDs in Australia rose 15% (1370 µg BEDD vs. 1194 µg BEDD). Over the same period, ADDs in New Zealand rose 5% (917 µg BEDD vs. 874 µg BEDD, excluding Symbicort®)[21] (figure 22, table 5).

Table 5
ICS ADDs for Australia and New Zealand

		Aug-00 BEDD	Aug-02 BEDD	% change Aug-02 vs Aug-00	Apr-03 BEDD	% change Apr-03 vs Aug-00*
Australia	Seretide®	1464.4	1566.4	7%	1563.7	7%
	all ICS (incl Seretide®)	1194.2	1346.2	13%	1369.8	15%
New Zealand	all ICS (excl Symbicort®)	873.9	926.7	6%	916.9	5%
	Symbicort®				653.5	
	all ICS (incl Symbicort®)	873.9	912.9	4%	899.9	3%
Australia/NZ	all ICS	1.37	1.47	2.86	1.52	4.95

*note that April vs August comparisons are confounded by season

- Note that for the Australian fluticasone ADD of 1556 µg BEDD, Seretide® ADDs were higher than for Flixotide® (Seretide® 1564 µg BEDD vs. Flixotide® 1530). This possibly reflects gradual movement of those patients with more severe asthma from Flixotide® to Seretide®, given that Flixotide ADDs have fallen contemporaneously (figure 22).

- Seretide® accounted for 51% of patients using ICS and LABAs in Australia during April 2003 (178981 Seretide® pmes / 349970 total ICS/LABA pmes) (figure 20 above).

[21] Note that Symbicort® was fully subsidised in New Zealand from October 2001, and ADDs including Symbicort® have risen 3% since then (900 µg BEDD vs. 874 µg BEDD, including Symbicort®). Symbicort®'s current ADD in New Zealand is 654 µg BEDD.

- At A$144.8 million, Seretide® accounted for 64% of Australia's ICS and LABAs expenditure during the calendar year 2002.

Promotion of Seretide® in New Zealand
In New Zealand, Seretide® is now subject to intense marketing to both prescribers and the general public (including a current televised DTCA campaign and one-month's free supply of Seretide® [22]). GSK recently launched Seretide® in New Zealand (non-funded), coinciding with the publication in the NZ Medical Journal of its POMS study.[23] GSK has heavily promoted POMS,[24] which speculated that PHARMAC restrictions to LABAs and combination LABA/ICS products in New Zealand were an important cause of asthma under-treatment.[25] Such speculation could be but one strategy to ultimately generate sufficient political pressure for Seretide® to be fully funded on the Pharmaceutical Schedule, counter to any arguments of excessive budgetary impact and poor cost-effectiveness (when compared with concurrent separate ICS and LABA devices).

Effects of Flixotide® DTCA on the overall BDP market
In terms of the third of GSK's apparent goals, during the New Zealand Flixotide® DTCA campaign, GSK appeared to be in effect denigrating its own products. This was when stating that the Becotide® and Becloforte® brands of BDP were being withdrawn later in the year because they contained CFCs, and stating that Flixotide® may provide improved control. But in doing so, GSK arguably also damaged the market for other suppliers, particularly that of the new entrant Airflow with its Beclazone® brand of BDP (Beclazone® became fully subsidised in October 2002). This is particularly when the Flixotide® DTCA did not mention that other fully subsidised BDP products would still be available, and omitted to clearly state that one of the Flixotide® formulations too contained CFCs.

The extent of the impact of Flixotide® DTCA on the overall BDP-market - and hence competing generic BDP products - is evident in the 55% decrease in overall BDP dispensings between March 2002 and November 2002 (figure 24).

Figure 24

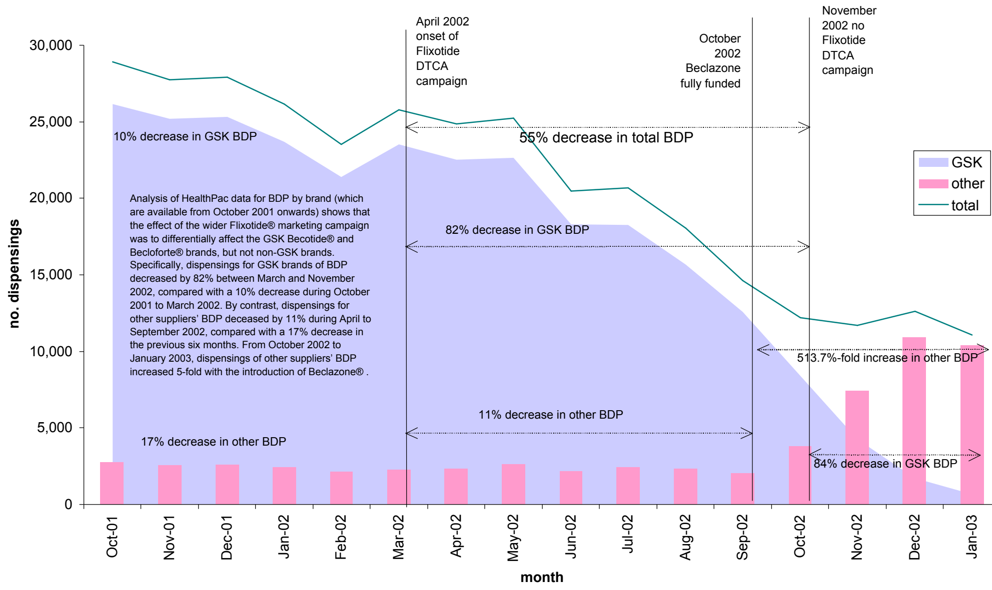
---

[22] http://www.flixotide.co.nz/seretide/try.asp at 30 July 2003

[23] Holt S, Kljakovic M, Reid J, on behalf of the POMS steering Committee. Asthma Morbidity, Control and Treatment in New Zealand: Results of the Patient Outcomes Management Survey. NZ Med J 2003;116:U436. URL: http://www.nzma.org.nz/journal/116-1174/436/.

[24] POMS was co-designed, managed, steered, and fully funded by GSK. Three authors on behalf of a steering committee, which appreciably comprised GSK employees, wrote the published results. The results of the study have been promoted by GSK-sourced media statements, and GSK has hosted the results on its website since late 2002, well before formal publication (and arguably compromising medical publishing convention under the Ingelfinger rule (Wilkes MS, Kravitz RL. Policies, practices, and attitudes of North American medical journal editors. J Gen Intern Med. 1995 Aug;10(8):443-50.)).

[25] POMS did show that half of patients whose asthma was not well controlled and 88% of those whose asthma was markedly out-of-control were under-treated, when compared against BTS-defined best practice. Yet despite stating that it was beyond the scope of that study to determine why there was so much under-treatment, the POMS publication then went on to speculate that it may be in part due to what the authors considered are PHARMAC restrictions on LABAs and combination LABA/ICS products. This argument was repeated in the accompanying editorial (Beasley R, Masoli M. Asthma in New Zealand - time to get control. NZ Med J 2003;116:U434. http://www.nzma.org.nz/journal/116-1174/434/) and in GP Weekly [14 May 2003]. There was no mention of alternative factors such as the ongoing low uptake of eformoterol 6 µg inhaled LABA (Oxis 6) despite being easily available (endorsement only) since mid 2001.



BDP dispensings October 2001-January 2003, by supplier
April 2002 onset of Flixotide DTCA campaign
October 2002 Beclazone fully funded
November 2002 no Flixotide DTCA campaign
30,000
25,000
20,000
15,000
10,000
5,000
0
no. dispensings
10% decrease in GSK BDP
55% decrease in total BDP
82% decrease in GSK BDP
11% decrease in other BDP
17% decrease in other BDP
513.7%-fold increase in other BDP
84% decrease in GSK BDP
GSK
other
total
Analysis of HealthPac data for BDP by brand (which are available from October 2001 onwards) shows that the effect of the wider Flixotide® marketing campaign was to differentially affect the GSK Becotide® and Becloforte® brands, but not non-GSK brands. Specifically, dispensings for GSK brands of BDP decreased by 82% between March and November 2002, compared with a 10% decrease during October 2001 to March 2002. By contrast, dispensings for other suppliers' BDP deceased by 11% during April to September 2002, compared with a 17% decrease in the previous six months. From October 2002 to January 2003, dispensings of other suppliers' BDP increased 5-fold with the introduction of Beclazone® .
Oct-01
Nov-01
Dec-01
Jan-02
Feb-02
Mar-02
Apr-02
May-02
Jun-02
Jul-02
Aug-02
Sep-02
Oct-02
Nov-02
Dec-02
Jan-03
month

Appendix 1: Seasonal variation in dispensings and ADDs, by ICS chemicals and by age-group

Figure 17A.

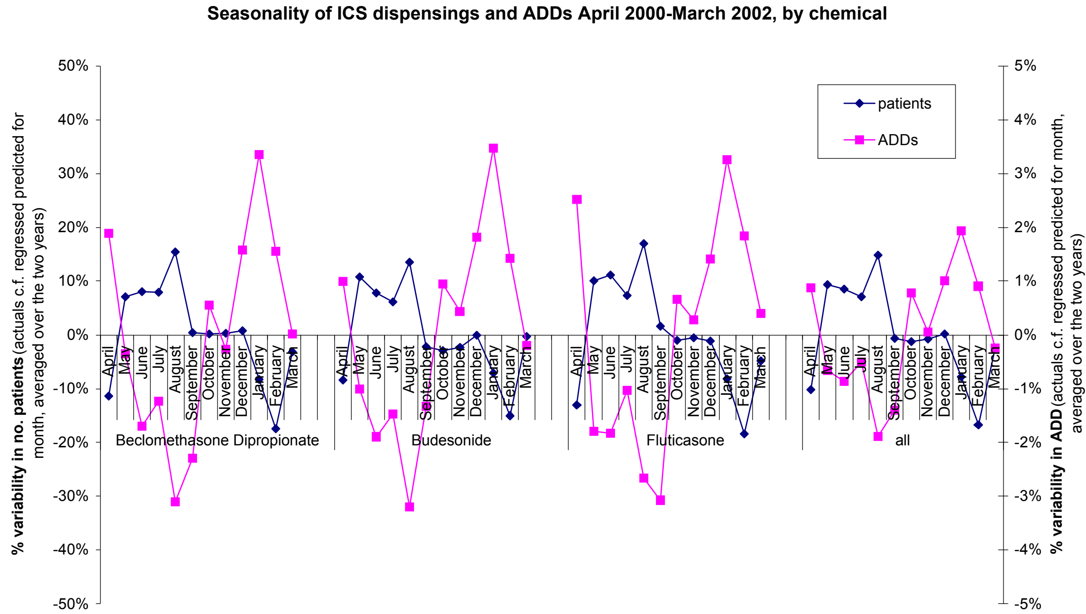


Figure 17B.

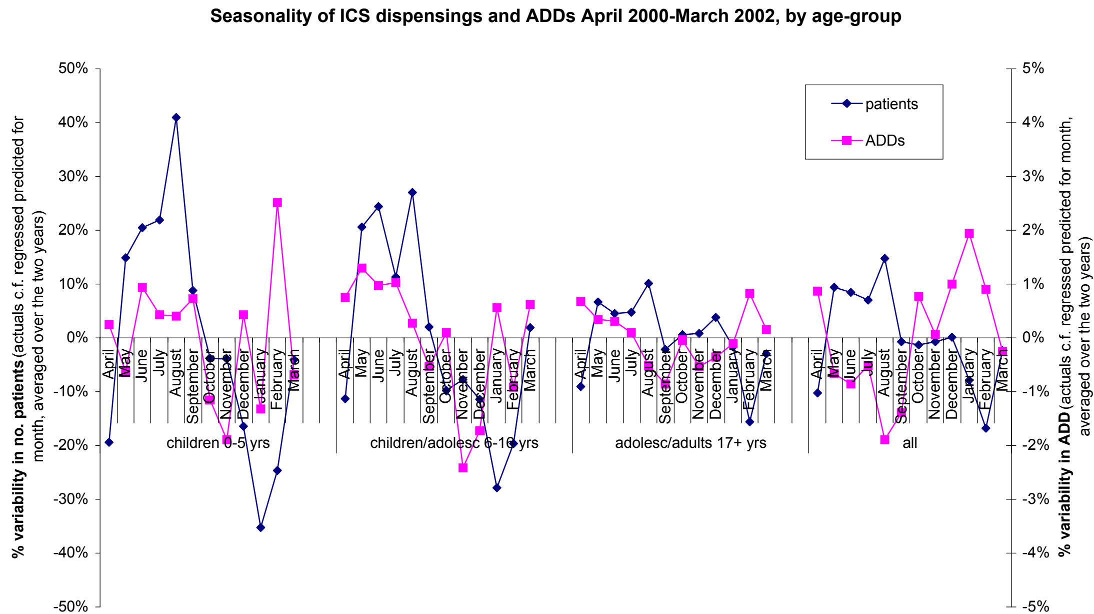


Figure 17C.

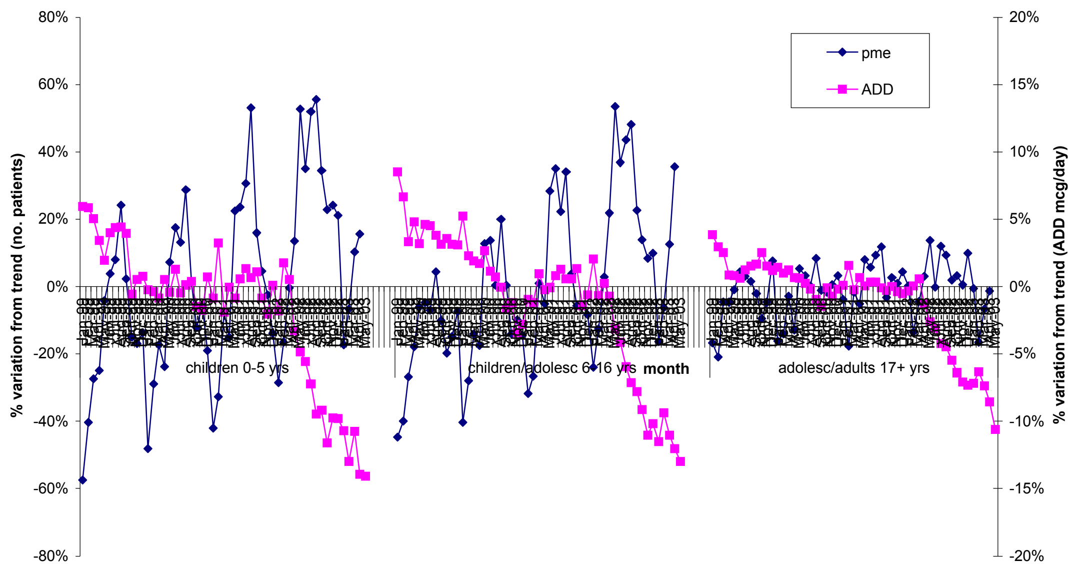


Figure 17D

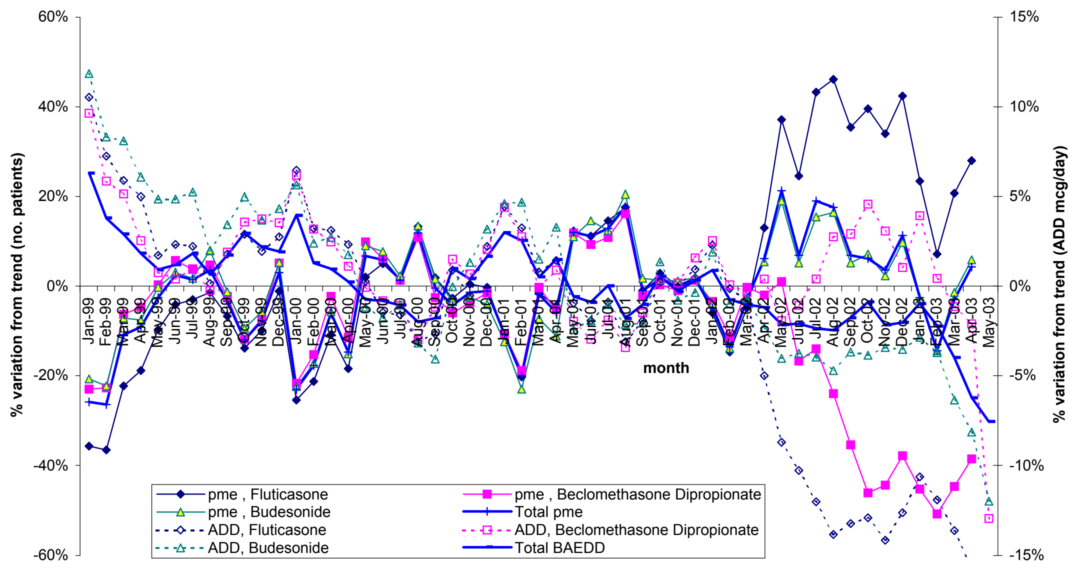
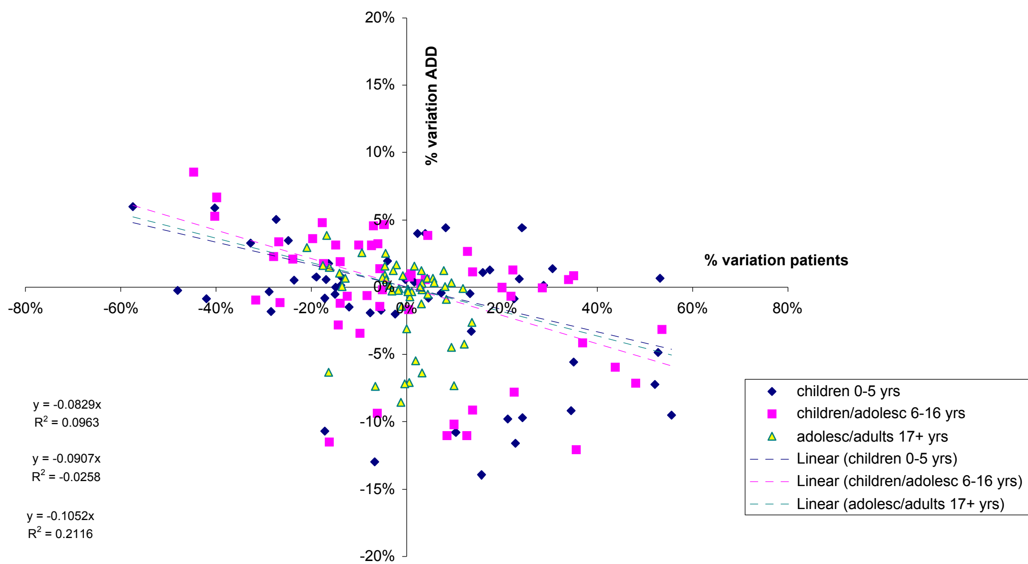


Figure 17E


Variability in patients numbers and ICS ADDs by season
% variation ADD
% variation patients
20%
15%
10%
5%
0%
-5%
-10%
-15%
-20%
-80%
-60%
-40%
-20%
0%
20%
40%
60%
80%
y = -0.0829x
R2 = 0.0963
y = -0.0907x
R2 = -0.0258
y = -0.1052x
R2 = 0.2116
children 0-5 yrs
children/adolesc 6-16 yrs
adolesc/adults 17+ yrs
Linear (children 0-5 yrs)
Linear (children/adolesc 6-16 yrs)
Linear (adolesc/adults 17+ yrs)

Appendix 2. Bradford Hill criteria for causation

The Bradford Hill criteria, proposed for attributing disease causation to environmental factors, have been used widely in epidemiology and are applicable to pharmacovigilance and pharamacoepidemiology (http://www.dsru.org/publications/DSRU_143.html).

Criteria include strength, consistency, specificity, temporality, biological gradient, plausibility, coherence, experimental evidence and analogy. Note the criteria are said to serve as a general guide, and are not meant to be an inflexible list. Not all criteria must be fulfilled to establish scientific causation.

Note there are important limitations with the criteria-based approach to causation (see Rothman KJ. Epidemiology: An Introduction. Oxford; OUP, 2001. Chapter 2 What is causation? at http://www.oup-usa.org/sc/0195135547/downloads.html).

In full, the nine criteria are:

1. Strength of association. Two aspects: the frequency with which the factor is found in the disease, and the frequency with which it occurs in the absence of the disease. The larger the relative risk, the more the hypothesis is strengthened. Is the risk so large that we can easily rule out other factors?

2. Consistency. Confirmation of the association by different investigators, in different populations, using different methods. Have the results have been replicated by different researchers and under different conditions?

3. Specificity. If the determinant being studied can be isolated from others and shown to produce changes in the incidence of the disease, e.g., if thyroid cancer can be shown to have a higher incidence specifically associated with fluoride, this is convincing evidence of causation. Is the exposure associated with a very specific disease as opposed to a wide range of diseases?

4. Temporal sequence. Exposure to the factor must occur before onset of the disease. In addition, if it is possible to show a temporal relationship, as between exposure to the factor in the population and frequency of the disease, the case is strengthened. Did the exposure precede the disease?

5. Biological gradient (dose-response relationship). Finding a quantitative relationship between the factor and the frequency of the disease. The intensity or duration of exposure may be measured. Are increasing exposures associated with increasing risks of disease?

6. Plausibility. The statistically significant association fits well with previously existing knowledge. Is there a credible scientific mechanism that can explain the association?

7. Coherence. The evidence must fit the facts that are thought to be related, e.g., the rising incidence of dental fluorosis and the rising consumption of fluoride are coherent. Is the association consistent with the natural history of the disease?

8. Experimental evidence. This aspect focuses on what happens when the suspected offending agent is removed. Is there improvement? The evidence of remission - or even resolution of significant medical symptoms - following explanation would strengthen the case. Does a physical intervention show results consistent with the association?

9. Reasoning by analogy. Is there a similar result that we can draw a relationship to?

Appendix 3. Effectiveness of combined ICS/LABAs delivery devices versus concurrent ICS and LABA via separate inhalers

- There is little evidence that combination LABA/ICS products improve compliance over concurrent use of separate ICSA and LABA inhalers.

- There is newly emerging evidence that combination LABA/ICS products may be physiologically more effective than concurrent use of ICSs and LABAs.

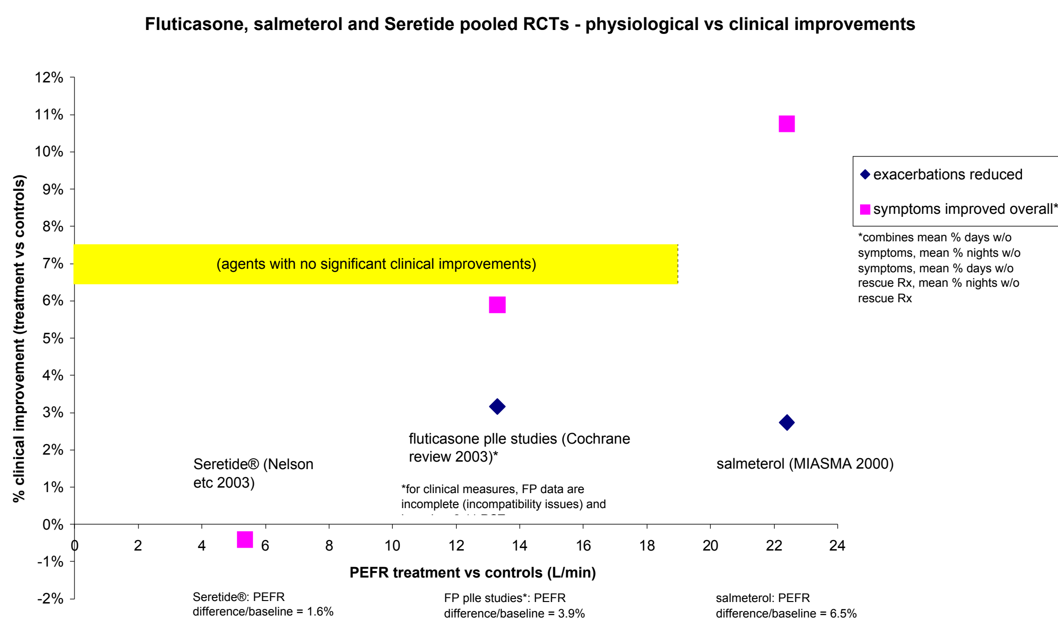
- However, the extent of these improvements in physiological measures (which are but intermediate or surrogate outcomes) has been overstated. The true extent of peak expiratory flow rate (PEFR) reduction is 11% (using relative risk, not odds ratio).

- In addition, there were no differences in clinically relevant outcomes for combination LABA/ICS products.

- Separate analysis of withdrawals and adverse events (not performed in the industry-funded Seretide® meta-analysis) shows significantly higher rates of reported adverse events with Seretide®.

- Compared with salmeterol (and even fluticasone), Seretide® has much smaller changes in physiological effects, reflected in nil clinical improvements. Note that neither Seretide® nor fluticasone have been able to demonstrate clinically significant improvements in pooled analyses (figure A5.1).

Figure A5.1



- Hence, the advice from the British, GINA and New Zealand asthma guidelines, that there is no difference in clinical efficacy between combination and concurrent (separate devices) LABA/ICS, still applies.

Compliance with combination LABA/ICS devices

The recently updated joint British Thoracic Society/Scottish Intercollegiate Guidelines Network asthma guidelines (BTS/SIGN guidelines) (section 11.2.2, page i59) state "Combination inhalers have not been shown to improve compliance in the medium to long term."[26]

The BTS/SIGN guidelines cite as evidence for the above statement as from a double-blind RCT comparing nedocromil/salbutamol combination with nedocromil alone[27], an open-label RCT of combination vs. concurrent terbutaline (short-acting beta2 agonist) and budesonide (ICS)[28], and 70% long-term compliance in a fluticasone RCT[29] (a somewhat curious citation, but perhaps because compliance was higher than in the other two studies).

In three out of four identified RCTs for Seretide® (Bateman etc 1998, Chapman etc 1999, Van den Berg 2000 below), mean compliance (actual use/expected) was respectively reported at 91%, 96% and 93% for combination LABA/ICS versus 89%, 95% and 93% for concurrent LABA/ICS use via separate inhalers. These formally combine to give a non-significant 1% difference in (already high) compliance (Peto one-step relative risk (RR) 1.01, 95% CI 0.99-1.03) (detailed in table A5.3 below). In the other RCT (Aubier 1999), compliance was stated to be high in all patients (regardless of regime).

These Seretide® RCT data were however complicated by Seretide® patients needing to use concurrent placebo inhaler, in order to maintain participant's blinding (double dummy design). Hence they do not allow for differences in convenience,[30] nor fully answer the question "Does the use of a single combination LABA/ICS inhaler improve compliance, beyond that gained using concurrent two separate inhalers?"

That said, compliance rates in the control groups in the Seretide® clinical trials were high, suggesting the need to use two inhalers at the same time is not necessarily a key cause of poor compliance with asthma preventive inhalers.

The 2002 revised Global Strategy for Asthma Management and Prevention (GINA) guidelines state "Fixed combination inhalers are more convenient for patients, may increase compliance, ensure that the long-acting beta2-agonist is always accompanied by a glucocorticosteroid"[31] Note however that no evidence was given to support the claims of either greater convenience (although this does have face validity) nor increased compliance.

---

[26] British Thoracic Society; Scottish Intercollegiate Guidelines Network. British guideline on the management of asthma. Thorax 2003;58 Suppl 1:i1-94. http://www.sign.ac.uk/guidelines/published/support/guideline63/download.html

[27] Braunstein GL, Trinquet G, Harper AE. Compliance with nedocromil sodium and a nedocromil sodium/salbutamol combination. Compliance Working Group. Eur Respir J. 1996 May;9(5):893-8.

[28] Bosley CM, Parry DT, Cochrane GM. Patient compliance with inhaled medication: does combining beta-agonists with corticosteroids improve compliance? Eur Respir J. 1994 Mar;7(3):504-9.

[29] van Grunsven PM, van Schayck CP, van Deuveren M, van Herwaarden CL, Akkermans RP, van Weel C. Compliance during long-term treatment with fluticasone propionate in subjects with early signs of asthma or chronic obstructive pulmonary disease (COPD): results of the Detection, Intervention, and Monitoring Program of COPD and Asthma (DIMCA) Study. J Asthma. 2000 May;37(3):225-34.

[30] Eisen SA, Miller DK, Woodward RS, Spitznagel E, Przybeck TR. The effect of prescribed daily dose frequency on patient medication compliance. Arch Intern Med. 1990 Sep;150(9):1881-4.

[31] National Heart, Lung, and Blood Institute , National Institutes Of Health. Global Strategy for Asthma Management and Prevention, revised 2002. (Scientific information and recommendations for asthma programs. NIH Publication No. 02- 3659). p108

International guidelines re efficacy of combination LABA/ICS devices

The recent New Zealand adult asthma guidelines[32] (page 40) state "Dry powder devices that combine both LABA and ICS in one unit are now available. Such combination dry powder devices have similar but not improved clinical effectiveness as giving the same medication via separate devices [1+]" (citing one RCT[33]). "Although combination dry powder devices may appear more convenient, the fixed dosing of such devices makes titration of the ICS portion of the dose more difficult."

The BTS/SIGN guidelines (section 4.4.3, page i22) cite grade 1++ evidence in an evidence table[34] detailing four identified RCTs for Seretide®.[35 36 37 38] On this basis they state "There is no difference in efficacy in giving inhaled steroid and long-acting beta2 agonist in combination or in separate inhalers".

Note however that there was no attempt with the BTS/SIGN guidelines to pool the results of the four Seretide® RCTs.

The 2002 revised GINA guidelines (p 108) state "Controlled studies have shown that delivering glucocorticosteroids and long-acting beta2- agonists together in a combination inhaler is as effective as giving each drug separately (Evidence B)."

Note the evidence cited for the GINA statement is misreferenced as three montelukast publications.[39 40 41] GINA also states "fixed combination inhalers … are usually less expensive than giving the two drugs separately." In New Zealand, Seretide® is priced 2-3 times that of separate fluticasone and salmeterol inhalers.

---

[32] Best Practice Evidence-Based Guideline: The Diagnosis and Treatment of Adult Asthma. New Zealand Guidelines Group, 2002. http://www.nzgg.org.nz/library/gl_complete/asthma/index.cfm

[33] Bateman E, Britton M, Carrillo J, Almeida J, Wixon C. Salmeterol/fluticasone combination inhaler. A new, effective and well tolerated treatment for asthma. Clin Drug Invest 1998;16(3):193-201

[34] Evidence table 4.22: Combined therapy of inhaled steroids and long acting B2 agonist http://www.sign.ac.uk/guidelines/published/support/guideline63/table4.22.html

[35] Bateman et al 1998, op cit.

[36] Van den Berg NJ, Ossip MS, Hederos CA, Anttila H, Ribeiro BL, Davies PI. Salmeterol/fluticasone propionate (50/100 microg) in combination in a Diskus inhaler (Seretide) is effective and safe in children with asthma. Pediatr Pulmonol 2000;30(2):97-105.

[37] Chapman KR, Ringdal N, Backer V, Palmqvist M, Saarelainen S, Briggs M. Salmeterol and fluticasone propionate (50/250 microg) administered via combination Diskus inhaler: as effective as when given via separate Diskus inhalers. Can Respir J 1999;6(1):45-51.

[38] Aubier M, Pieters WR, Schlosser NJ, Steinmetz KO. Salmeterol/fluticasone propionate (50/500 microg) in combination in a Diskus inhaler (Seretide) is effective and safe in the treatment of steroid-dependent asthma. Respir Med 1999;93(12):876-84.

[39] Bleecker ER, Welch MJ, Weinstein SF, Kalberg C, Johnson M, Edwards L, et al. Low-dose inhaled fluticasone propionate versus oral zafirlukast in the treatment of persistent asthma. J Allergy Clin Immunol 2000;105:1123-9.

[40] Laviolette M, Malmstrom K, Lu S, Chervinsky P, Pujet JC, Peszek I, et al. Montelukast added to inhaled beclomethasone in treatment of asthma. Montelukast/Beclomethasone Additivity Group. Am J Respir Crit Care Med 1999;160:1862-8.

[41] Lofdahl CG, Reiss TF, Leff JA, Israel E, Noonan MJ, Finn AF, et al. Randomised, placebo controlled trial of effect of a leukotriene receptor antagonist, montelukast, on tapering inhaled corticosteroids in asthmatic patients. BMJ 1999;319:87-90. Cochrane Database Syst Rev 2000;2.

Recently published meta-analysis of Seretide® (Nelson et al 2003)

More recently, an industry co-written meta-analysis has been published (Nelson et al 2003[42]) pooling the results of the four Seretide® RCTs behind the above BTS/SIGN statement of no difference in efficacy.

With pooling, this meta-analysis reported a significant advantage with Seretide® combination therapy over concurrent salmeterol and fluticasone therapy in morning peak expiratory flow rates (PEFR). "Odds of achieving a greater than 15 or greater than 30 L/min improvement with combination therapy were increased by approximately 40% compared with those after concurrent therapy, representing an additional 7% to 9% and 5% to 14% more patients, respectively, on combination therapy responding compared with those on concurrent therapy."

In the meta-analysis, >30 L/min improvements in PEFR with combination treatment occurred in 9% more patients (54% minus 45%), being a 19% improvement relative to concurrent controls (9%/45%).

Likewise, >15 L/min improvements occurred in an additional 7% of combination treatment patients (73% versus 66%), a relative increase of 11% (7%/66%).

These changes were reflected similarly in improvements to mean baseline morning PEFRs, where combination treatment caused on average an extra crude 5.8 L/min in PEFR over concurrent controls (38.2 vs. 32.8 L/min improvements, 5.4 L/min difference formally reported (Nelson et al 2003)).

[42] Nelson HS, Chapman KR, Pyke SD, Johnson M, Pritchard JN. Enhanced synergy between fluticasone propionate and salmeterol inhaled from a single inhaler versus separate inhalers. J Allergy Clin Immunol. 2003 Jul;112(1):29-36.

Limitations with the Seretide® meta-analysis

However, the Seretide® meta-analysis had important limitations in its data and interpretation, materially affecting its key reported findings:

1. *Selective reporting of key findings*

Statistically significant results in the Seretide® meta-analysis were confined to most but not all physiological variables, and there were no significant differences in more clinically-relevant outcomes (tables A5.1, A5.2 and A5.4, below):

- There were statistically significant change in self-reported mean morning and evening PEFR over weeks 1-12 (continuous variable), and achieving greater than 15 and 30 l/min improvements in morning PEFR (dichotomous variables);

- There was no significant change in mean change in objective clinic FEV1 at week 12 (continuous variable);

- There were no significant changes in the clinically relevant secondary outcomes of median % days and nights symptom- and reliever-free (median % days symptom-free, median % nights symptom-free, median % days reliever-free, median % nights reliever-free).

Table A5.1

Combination (Seretide) vs concurrent ICS/LABA - results of individual RCTs in Nelson et al 2003 (fixed effects model, Peto one-step method)

		PEFR combination LABA/ICS	concurrent separate LABA/ICS	% combination LABA/ICS	concurrent separate LABA/ICS	difference	measures of effect OR(+/- 95%CI)	RR(+/- 95%CI)	RRI	ARI*	NNT (-ve = NNH)
physiological measures											
baseline PEFR		347.9	341.7								
>30 l/min morning PEFR increase				54.0%	45.2%	8.7%	1.42 (1.13-1.78)	1.19 (1.07-1.32)	19%	8.7%	11
clinical impact of >30 l/min increase			8.7%								
>15 l/min morning PEFR increase				72.6%	65.4%	7.2%	1.41 (1.10-1.80)	1.11 (1.03-1.18)	11%	7.2%	14
clinical impact of >15 l/min increase			4.4%								
adjusted mean change from baseline in mean morning		39.9	32.8			7.1		1.22	22%	2.1%	
WMD as published						5.4		1.16	16%	1.6%	
% change in PEFR		11.0%	9.6%			**1.4%**					
(adjusted mean change from baseline in mean morning		43.1	36.6			6.5		1.18	18%	1.9%	
WMD as published						4.7		1.13	13%	1.4%	
clinical measures											
days w/o sympts	Pharmac calculations			41.0%	39.5%	1.5%		1.04	4%	1.5%	65
median % days symptom free	WMD as published					0.0%		1.00	0%	0.0%	-
nights w/o sympts	Pharmac calculations			57.4%	53.7%	3.7%		1.07	7%	3.7%	27
median % nights symptom free	WMD as published					-1.2%		0.98	-2%	-1.2%	-87
days w/o rescue Rx	Pharmac calculations			49.7%	47.6%	2.1%		1.05	5%	2.1%	47
median % days reliever free	WMD as published					-0.4%		0.99	-1%	-0.4%	-278
nights w/o rescue Rx	Pharmac calculations			69.3%	65.4%	3.9%		1.06	6%	3.9%	26
median % nights reliever free	WMD as published					-0.1%		1.00	0%	-0.1%	-909

source: Pharmac analysis of: Nelson HS, Chapman KR, Pyke SD, Johnson M, Pritchard JN. Enhanced synergy between fluticasone propionate and salmeterol inhaled from a single inhaler versus separate inhalers. J Allergy Clin Immunol. 2003 Jul;112(1):29-36.

- There were significantly higher rates of adverse events reported for Seretide®, otherwise no differences in withdrawal rates/withdrawals for adverse effects.

The withdrawal and adverse events were not measured in the Seretide® meta-analysis, requiring other analysis (table A5.2) (further details below).

Table A5.2

Combination (Seretide) vs concurrent ICS/LABA - results of individual RCTs in Nelson et al 2003 (fixed effects model, Peto one-step method)

	% combination LABA/ICS	concurrent separate LABA/ICS	difference	measures of effect OR(+/- 95%CI)	RR(+/- 95%CI)	RRI	ARI*	NNT (-ve = NNH)
compliance								
compliance (Pharmac calculations)	93.0%	92.1%	0.9%	1.16	1.01 (0.99-1.03)	1%	0.9%	107
withdrawals and adverse events								
total withdrawals (Pharmac calculations)	14.6%	12.6%	2.0%	1.18	1.16 (0.84-1.57)	16%	2.0%	50
withdrawals from adverse events (Pharmac calculations)	8.4%	7.1%	1.2%	1.19	1.17 (0.76-1.79)	17%	1.2%	81
reported adverse events (+/- considered by investigators to be Rx-related) (Pharmac calculations)	59.0%	46.7%	12.4%	1.59	1.26 (1.09-1.44)	26%	12.4%	8

source: Pharmac analysis of: Nelson HS, Chapman KR, Pyke SD, Johnson M, Pritchard JN. Enhanced synergy between fluticasone propionate and salmeterol inhaled from a single inhaler versus separate inhalers. J Allergy Clin Immunol. 2003 Jul;112(1):29-36.

Note that the Seretide® meta-analysis stated a prospective sole primary outcome measure, that of morning PEFR. However, PEFR was not stated to be the primary efficacy measure for one of the RCTs (Aubier etc 1999).

Secondary measures in all the RCTs included FEV_1, and the clinically relevant outcomes.

Withdrawals and adverse events were reported for all the individual RCTs.

Withdrawals affect analysis of physiological and clinical outcomes, are themselves clinical outcomes, and should similarly at least have been reported. Withdrawals and adverse effects were all reported in meta-analyses of other asthma treatments, e.g. the Cochrane review of fluticasone.[43]

[43] Adams N, Bestall JM, Jones PW. Fluticasone versus beclomethasone or budesonide for chronic asthma (Cochrane Review). In: The Cochrane Library, Issue 3, 2003. Oxford: Update Software. CD002310

2. Reporting overstates the magnitude of physiological effects

In addition, Nelson et al's reporting of odds ratios (ORs) in the Seretide® meta-analysis overstates the magnitude of PEFR improvement; using relative risk (RR) gives much lower estimates of true relative effect:

- ORs (as reported by Nelson et al) are the measure used when combining results of individual trials into a weighted summary measure able to demonstrate statistically significant effects.

- Odds and ORs however do not necessarily equate to risk and relative risk (RR). If the OR is interpreted as a RR it will always overstate any effect size – particularly when baseline risk is high.[44]

- Such potential for overstatement due to high baseline risk certainly occurs with the PEFR improvements in the Seretide® meta-analysis, with 45-73% prevalence rates for both treatments and controls.

- RRs can be derived from adjusted baseline event rates and pooled odds ratios, with associated confidence limits, according to the formula[45]:

  $$RR = 1 - \frac{(1-aEc).(1-OR)}{1 - [aEc.(1-OR)]}$$

  where RR = relative risk; aEc =adjusted baseline event rate (i.e. control incidence rate, weighted according to inverse variance); OR = pooled odds ratio (weighted according to inverse variance)

- Recalculating relative risks from the published ORs and calculating baseline risks gives an 11% likelihood of patients gaining ≥15 L/min improvement in PEFR using Seretide® rather than concurrent ICS/LABA (RR 1.11 (95% CI 1.03-1.18)).

  The likelihood for a ≥30 L/min PEFR improvement becomes 19% (RR 1.19 (1.07-1.32)).

  These results using RRs contrast sharply with the ORs of 1.40 and 1.42 as reported by Nelson et al.

[44] Davies HT, Crombie IK, Tavakoli M. When can odds ratios mislead? BMJ. 1998 Mar 28;316(7136):989-91.

[45] algebraic transformation of formulae in Sackett D, Straus S, Richardson WS, Rosenberg W, Haynes B. Evidence-based medicine: how to practice and teach EBM, 2nd edition. Oxford: Churchill Livingstone, 2000. p136 Table 5.1 Formulae to convert odds ratios (ORs) and relative risks (RRs) to NNTs.

3. No difference in clinically relevant outcomes

The lack of statistically-significant clinically-relevant outcomes in the Seretide® meta-analysis reflects both (1) low variation relating to relatively small numbers of events and (2) little difference in clinically relevant outcomes:

- A 15 L/min improvement in PEFR represented just a 4.4% increase in PEFR over baseline (where patients had PEFRs averaging 344 L/min at baseline). A 30 L/min represented an 8.7% increase over baseline.

- In other words, an extra 9% of patients had a 9% or more improvement in morning PEFR through using combination treatment (and an extra 7% had a 4% or more improvement).

- Likewise, the magnitude of average improved PEFR was in the region of just 1.4% ([5.4 L/min crude mean difference in PEFR between combination and concurrent] / [344 L/min mean baseline PEFR]).

- These seemingly low physiological changes may be reflected in the very low rates of reductions in days or nights without symptoms or reliever drugs (0.0 to 1.15% reductions, all statistically insignificant).

4. No analysis of withdrawals and adverse events, where these show significantly higher rates of reported adverse events with Seretide®

The Seretide® meta-analysis could equally have analysed then reported (but did not) all withdrawals being *prima facie* 16% higher in combination than concurrent LABA/ICS users. Likewise, withdrawals due to adverse effects were *prima facie* higher at 17% with Seretide®.

Although neither measure of withdrawal showed differences that were statistically significant, reported adverse events in Seretide® patients were significantly higher. Seretide® users had *prima facie* one quarter (26%) more reported adverse events or events considered by investigators to be drug-related (289 in Seretide® patients (59%) vs. 263 in concurrent LABA/ICS users (47%), RR 1.26, 95% CI 1.09 – 1.44) (table A5.3).

Table A5.3

Combination (Seretide) vs concurrent ICS/LABA - results of individual RCTs in Nelson et al 2003
(fixed effects model, Peto one-step method)

	duration (weeks)	no. patients		no.		%				measures of effect				(variance wgts)
		combination LABA/ICS	concurrent separate LABA/ICS	combination LABA/ICS	concurrent separate LABA/ICS	combination LABA/ICS	concurrent separate LABA/ICS	difference	OR	RR(+/- 95%CI)	RRI	ARI*	NNT (-ve = NNH)	
compliance														
compliance														
Bateman etc 1998	12	121	121	110	108	91%	89%	2%		1.02	2%	1.7%	61	0.3965
Chapman etc 1999	28	180	191	173	181	96%	95%	1%		1.01	1%	1.3%	74	0.2968
Aubier etc 1999														0.0000
Van den Berg etc 2000	12	125	132	116	123	93%	93%	0%		1.00	0%	-0.4%	-262	0.3067
total or weighted average	16.7	426	444	399	412	93.0%	92.1%	0.9%	1.16	1.01 (0.99-1.03)	1%	0.9%	107	1.0000
withdrawals and adverse events														
total withdrawals														
Bateman etc 1998	12	121	121	18	17	14.9%	14.0%	0.8%		1.06	6%	0.8%	121	0.2482
Chapman etc 1999	28	180	191	20	16	11.1%	8.4%	2.7%		1.33	33%	2.7%	37	0.2689
Aubier etc 1999	28	167	171	31	28	18.6%	16.4%	2.2%		1.13	13%	2.2%	46	0.4033
Van den Berg etc 2000	12	125	132	5	5	4.0%	3.8%	0.2%		1.06	6%	0.2%	471	0.0796
total or weighted average	22.8	593	615	74	66	14.6%	12.6%	2.0%	1.18	1.16 (0.84-1.57)	16%	2.0%	50	1.0000
withdrawals from adverse events														
Bateman etc 1998				11	9	9.1%	7.4%	1.7%		1.22	22%	1.7%	61	0.2585
Chapman etc 1999				12	9	6.7%	4.7%	2.0%		1.41	41%	2.0%	51	0.2785
Aubier etc 1999				16	16	9.6%	9.4%	0.2%		1.02	2%	0.2%	446	0.4076
Van den Berg etc 2000				2	2	1.6%	1.5%	0.1%		1.06	6%	0.1%	1,179	0.0554
total or weighted average				41	36	8.4%	7.1%	1.2%	1.19	1.17 (0.76-1.79)	17%	1.2%	81	1.0000
withdrawals from asthma adverse events														
Bateman etc 1998				4	3	3.3%	2.5%	0.8%		1.33	33%	0.8%	121	0.3677
Chapman etc 1999				5	5	2.8%	2.6%	0.2%		1.06	6%	0.2%	625	0.5251
Aubier etc 1999				0	0	0.0%	0.0%	0.0%		#DIV/0!	######	0.0%	-	0.0000
Van den Berg etc 2000				1	1	0.8%	0.8%	0.0%		1.06	6%	0.0%	2,357	0.1072
total or weighted average				10	9	2.7%	2.4%	0.4%	1.16	1.15 (-95% CI-+95% CI)	15%	0.4%	276	1.0000
reported adverse events (+/- considered by investigators to be Rx-related)														
Bateman etc 1998				88	69	72.7%	57.0%	15.7%		1.28	28%	15.7%	6	0.3499
Chapman etc 1999				160	164	88.9%	85.9%	3.0%		1.04	4%	3.0%	33	0.2598
Aubier etc 1999				28	24	16.8%	14.0%	2.7%		1.19	19%	2.7%	37	0.2788
Van den Berg etc 2000				13	6	10.4%	4.5%	5.9%		2.29	129%	5.9%	17	0.1115
total or weighted average				289	263	59.0%	46.7%	12.4%	1.59 (1.16-2.17)	1.26 (1.09-1.44)	26%	12.4%	8	1.0000

source: Nelson HS, Chapman KR, Pyke SD, Johnson M, Pritchard JN. Enhanced synergy between fluticasone propionate and salmeterol inhaled from a single inhaler versus separate inhalers. J Allergy Clin Immunol. 2003 Jul;112(1):29-36.

[To be consistent with the Nelson etc reporting of PEFR improvements in the Seretide® meta-analysis as odds ratios, the odds of reporting an adverse effect with Seretide® were increased by 59% *prima facie* compared with those after concurrent therapy (OR 1.59, 95% CI 1.16-2.17).

We are not advocating the use of ORs here. Rather the *prima facie* 1.59 OR for reported adverse events places the use of 1.40-1.42 ORs for PEFRs in context, re-emphasising how these overstate actual increases in likelihood.]

5. Seretide®'s physiological and clinical improvements were comparatively low

Contextually, Seretide®'s physiological and clinical improvements were low relative to those seen in other relevant ICS/LABA meta-analyses.

Patterns of Seretide® clinical improvements relative to physiological improvement were consistent with the relative patterns seen for salmeterol LABA and fluticasone (when respectively compared with increasing the dose of ICS and compared with BDP or budesonide):

- The above 5.4 L/min morning PEFR improvement with Seretide® was much less than the 22.4 L/min improvement occurring with salmeterol (when compared with increased doses of ICS – MIASMA meta-analysis[46]) or even the 13.3 L/min improvement calculable for fluticasone (when compared with BDP or budesonide) (calculating from data in figures in Cochrane review[47]).

- In the salmeterol MIASMA meta-analysis, the above 22.4 L/min magnitude of PEFR improvement was associated with a 5 to 20% relative reduction in days or nights without symptoms or reliever drugs over 3 or 6 months.

- If we assume that baseline PEFRs were similar in both MIASMA and the Seretide® meta-analyses, then the 16% relative increase in PEFR in the Seretide® meta-analysis[48] would translate to a 68% relative improvement with salmeterol in MIASMA[49].

- Yet such a relatively large putative relative improvement for salmeterol PEFR (RRI 68%) translates to a much smaller clinical effect (salmeterol 11% overall reduction in days or nights without symptoms or reliever drugs at 3 months, range 5 to 17%).

- This discrepancy between salmeterol's physiological and clinical effects is consistent with the contrasts seen with Seretide® between its statistically significant 5.4 L/min added PEFR improvement and its negligible clinical impacts. Incidentally, both Seretide®'s PEFR and clinical effects were appreciably lower than those of salmeterol in MIASMA.

- Likewise with fluticasone, the above 13.3 L/min improvement in PEFR translates to maybe 3% reduction in exacerbations and 6% improvement in symptom/reliever-free days (with neither overall clinical outcome statistically significant) (figure A5.2, table A5.4).

Figure A5.2

[46] Shrewsbury S, Pyke S, Britton M. Meta-analysis of increased dose of inhaled steroid or addition of salmeterol in symptomatic asthma (MIASMA). BMJ. 2000 May 20;320(7246):1368-73.

[47] Adams N, Bestall JM, Jones PW. Fluticasone versus beclomethasone or budesonide for chronic asthma (Cochrane Review). In: The Cochrane Library, Issue 3, 2003. Oxford: Update Software. CD002310

[48] relative increase in PEFR with Seretide® = ([5.4 L/min difference between combined and concurrent ICSA/LABA use] / [32.8 L/min improvement with concurrent use]) = 16%

[49] relative increase in PEFR with salmeterol = ([16% Seretide® PEFR RRI] x [22.4 L/min PEFR added PEFR improvement in MIASMA] / [5.4 L/min added improvement with Seretide®]) = 69%

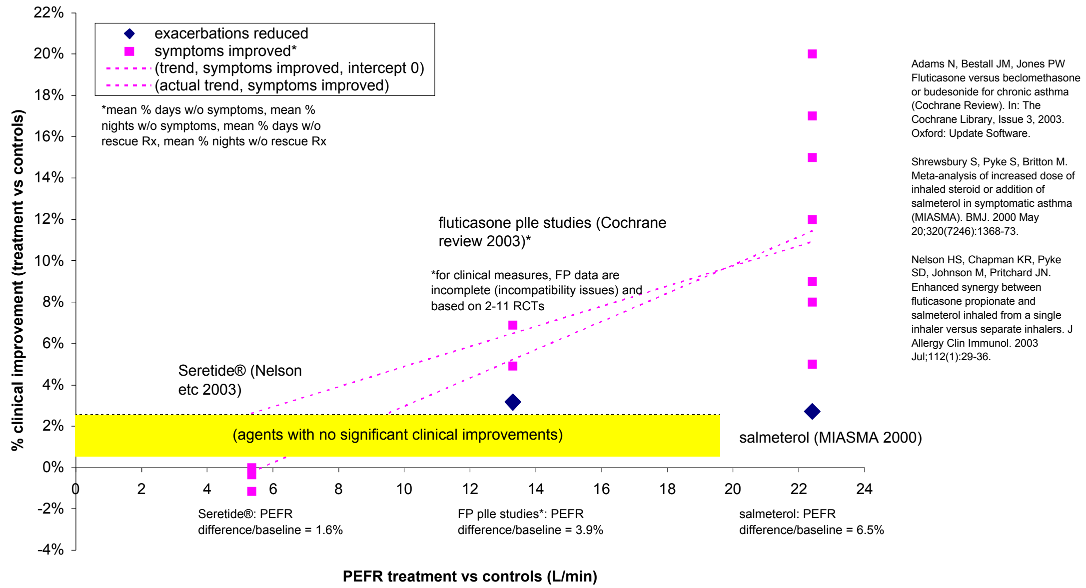


Table A5.4

Comparison between FP vs. BDP/bud RCTs (Cochrane review), Salmeterol vs. increased ICS RCTs (MIASMA), and Seretide® combination vs. concurrent FP/Salmeterol RCTs (Nelson 2003 meta-analysis)

		difference (ARR/ARI)			relative effects (RRR/RRI)		
		FP plle studies*	salmeterol	Seretide®	FP plle studies*	salmeterol	Seretide®
physiological measures							
baseline morning PEFR (L/min)		340.4	(n/avail)	344.8			
mean difference PEFR tmt vs. cntrl (L/min)	at 3 months		22.4	5.35		68%	16%
	at 6 months		27.7				
	not stated	13.3			41%		
mean difference FEV_1 tmt vs. cntrl (ml)	at 3 months		100	40			
	at 6 months		80				
	not stated	120					
extrapolated, using Seretide® 32.8 and 38.1 L/min improvements in cntrl and trmt groups (5.35 L/min difference, 16% RRI)							
clinical measures							
all exacerbations		-3.2%	-2.7%		-20%	-9%	
moderate/severe exacerbations			-2.4%				
withdrawals due to exacerbations		-1.2%		0.4%	-22%		15%
mean % days w/o symptoms	at 3 months		12%	0.00%		21%	0.00%
	at 6 months		15%				
	not stated	4.9%			15%		
mean % nights w/o symptoms	at 3 months		5%	-1.15%		19%	-2.14%
	at 6 months		5%				
mean % days w/o rescue Rx	at 3 months		17%	-0.36%		34%	-0.76%
	at 6 months		20%				
	not stated, change	6.9%			108%		
mean % nights w/o rescue Rx	at 3 months		9%	-0.11%		45%	-0.17%
	at 6 months		8%				
all exacerbations		-3.2%	-2.7%		-20%	-9%	
unweighted average symptom improvement (at 3 months, or not stated)		6%	11%	-0.41%	61%	15%	-0.38%
composite exacbns/symptoms		4.5%	6.7%	-0.2%	40.5%	12.2%	-0.2%
clinical vs. PEFR							
difference PEFR/baseline		3.9%	6.5%	1.6%			
clinical/PEFR		0.003	0.003	0.000	1.000	0.179	-0.012

*for clinical measures, FP data are incomplete (incompatibility issues) and based on 2-11 RCTs

Note that of the three ICS/LABA meta-analyses, only salmeterol has demonstrated significant clinical improvements.[50]

6. Quality of individual RCTs and meta-analysis

The above analysis has not critically appraised the four individual contributing RCTs, nor systematically appraised the meta-analysis.[51]

The four RCTs were each stated to be double-dummy double-blind randomised parallel-group controlled trials. Patients were children and adults with similar levels of asthma severity. The RCTs all measured both physiological and clinically relevant outcomes and included withdrawals and adverse events.

However, there was some ambiguity with reporting around the quality of the individual RCTs:

- None of the RCTs clearly described blinding;
- Three of the four RCTs did not describe the process of randomisation nor whether (and how) allocation was concealed;
- The randomisation process was described in one RCT (Bateman etc 1998), but concealment was not explicit and must be implied from computer block randomisation;
- All patients were accounted for, but whether analysis of effectiveness was by intention-to-treat or on-treatment was unclear for one RCT (Bateman 1998), with strong inference that it was on-treatment analysis. This would mean missing out patients withdrawing because of asthma exacerbations, hence unable to contribute to data re PEFR changes;
- All were multicentre trials, but no details were given on oversight/controls across sites.

The Nelson etc 2003 Seretide® meta-analysis did not describe how its component RCTs were identified (formal search strategies etc.). That said, the separate search presumably undertaken for the BTS/SIGN guidelines' evidence table and searching PubMed revealed/reveals no other relevant RCTs. It is assumed the Nelson meta-analysis, being authored by GSK employees, would have systematically and comprehensively identified all Seretide® RCTs known to the manufacturer, but this was not made explicit in the publication.

Note again the Seretide® meta-analysis chose not to pool then report on withdrawal and adverse events rates.

[50] Although clinically relevant improvements were not statistically significant with fluticasone, there were problems with study incomparability, hence possible type 1 error i.e. falsely ascribing no effect when a true effect exists.

[51] formal appraisal tools from EPIQ http://www.health.auckland.ac.nz/comhealth/epiq/epiq.htm for individual RCTs are at http://www.health.auckland.ac.nz/comhealth/ElectronicGateInterV12.doc, for meta-analyses at http://www.health.auckland.ac.nz/comhealth/epiq/GateSRChklstV3.doc

Message of international guidelines remains unchanged.

Hence in view of the above limitations with the Nelson et al Seretide® meta-analysis, the advice from the BTS/SIGN, GINA and New Zealand asthma guidelines still applies, viz. that there is no difference in clinical efficacy between combination and concurrent (separate devices) LABA/ICS.

Further detail of the results of the four component Seretide® RCTs and overall pooled effects are in table A5.5.

Table A5.5

Combination (Seretide) vs concurrent ICS/LABA - results of individual RCTs in Nelson et al 2003
(fixed effects model, Peto one-step method)

physiological measures	duration (weeks)	no. patients		baseline PEFR		no.		%			measures of effect					(variance wgts)
		combination LABA/ICS	concurrent separate LABA/ICS	combination LABA/ICS	concurrent separate LABA/ICS	combination LABA/ICS	concurrent separate LABA/ICS	combination LABA/ICS	concurrent separate LABA/ICS	difference	OR(+/- 95%CI)	RR(+/- 95%CI)	RRI	ARI*	NNT	
>30 l/min morning PEFR increase																
Bateman etc 1998	12	121	121	368	365	75	66	62.0%	54.5%	7.4%		1.14	14%	7.4%	13	0.1973
Chapman etc 1999	12	180	191	398	391	100	89	55.6%	46.6%	9.0%		1.19	19%	9.0%	11	0.3101
Aubier etc 1999	12	167	171	359	345	82	75	49.1%	43.9%	5.2%		1.12	12%	5.2%	19	0.2815
Van den Berg etc 2000	12	125	132	241	243	63	48	50.4%	36.4%	14.0%		1.39	39%	14.0%	7	0.2112
total or weighted average	12	593	615	347.9	341.7	320	278	54.0%	45.2%	8.7%	1.42	1.19	19%	8.7%	11	1.0000
clinical impact of >30 l/min increase					8.7%						(1.13-1.78)	(1.07-1.32)				
>15 l/min morning PEFR increase																
Bateman etc 1998						96	87	79.3%	71.9%	7.4%		1.10	10%	7.4%	13	0.1752
Chapman etc 1999						135	130	75.0%	68.1%	6.9%		1.10	10%	6.9%	14	0.2966
Aubier etc 1999						115	106	68.9%	62.0%	6.9%		1.11	11%	6.9%	15	0.3000
Van den Berg etc 2000						87	81	69.6%	61.4%	8.2%		1.13	13%	8.2%	12	0.2282
total or weighted average						433	404	72.6%	65.4%	7.2%	1.41	1.11	11%	7.2%	14	1.0000
clinical impact of >15 l/min increase					4.4%						(1.10-1.80)	(1.03-1.18)				
adjusted mean change from baseline in mean morning PEFR over weeks 1-12, ITTA																
Bateman etc 1998						42	33			9.0		1.27	27%	2.5%		0.2413
Chapman etc 1999						43	36			7.0		1.19	19%	1.8%		0.2892
Aubier etc 1999						35	33			2.0		1.06	6%	0.6%		0.2529
Van den Berg etc 2000						33	28			5.0		1.18	18%	2.1%		0.2167
total or weighted average				347.9	341.7	39.9	32.8			7.1		1.22	22%	2.1%		1.0000
WMD as published						38.1	32.8			5.4		1.16	16%	1.6%		
% change in PEFR						11.0%	9.6%			**1.4%**						
(adjusted mean change from baseline in mean morning PEFR over weeks 1-12, per protocol)																
Bateman etc 1998						51	42			9.0		1.21	21%	2.5%		0.1997
Chapman etc 1999						43	36			7.0		1.19	19%	1.8%		0.3125
Aubier etc 1999						40	36			4.0		1.11	11%	1.1%		0.2753
Van den Berg etc 2000						34	33			1.0		1.03	3%	0.4%		0.2125
total or weighted average						43.1	36.6			6.5		1.18	18%	1.9%		1.0000
WMD as published						41.2	36.6			4.7		1.13	13%	1.4%		

*ARI for x l/min morning PEFR increase is a measure of population impact,
= (% treatment group patients achieving xx increase) minus (% control group patients achieving xx increase).
ARI for mean changes in baseline morning PEFR is a measure of average individual clinical impact (improvement in lung function),
= (mean improvement) / (mean baseline)

clinical measures

	duration (weeks)	no. patients		no.		%			measures of effect				(variance wgts)
		combination LABA/ICS	concurrent separate LABA/ICS	combination LABA/ICS	concurrent separate LABA/ICS	combination LABA/ICS	concurrent separate LABA/ICS	difference	RR	RRI	ARI*	NNT (-ve = NNH)	
days w/o sympts													
Bateman etc 1998		121	121	48	52	39.7%	43.0%	-3.3%	0.92	-8%	-3.3%	-30	0.2299
Chapman etc 1999		180	191	39	29	21.7%	15.2%	6.5%	1.43	43%	6.5%	15	0.2171
Aubier etc 1999		167	171	63	65	38.0%	38.0%	0.0%	1.00	0%	0.0%	-	0.3116
Van den Berg etc 2000		125	132	75	79	60.0%	60.0%	0.0%	1.00	0%	0.0%	-	0.2414
total or weighted average		593	615	225	225	41.0%	39.5%	1.5%	1.04	4%	1.5%	65	1.0000
WMD as published	median % days symptom free					39.5%	39.5%	0.0%	1.00	0%	0.0%	-	
nights w/o sympts													
Bateman etc 1998				58	69	47.9%	57.0%	-9.1%	0.84	-16%	-9.1%	-11	0.2224
Chapman etc 1999				84	80	46.7%	41.9%	4.8%	1.11	11%	4.8%	21	0.3364
Aubier etc 1999				95	94	57.0%	55.0%	2.0%	1.04	4%	2.0%	50	0.3065
Van den Berg etc 2000				114	99	91.0%	75.0%	16.0%	1.21	21%	16.0%	6	0.1348
total or weighted average		593	615	351	342	57.4%	53.7%	3.7%	1.07	7%	3.7%	27	1.0000
WMD as published	median % nights symptom free					52.6%	53.7%	-1.2%	0.98	-2%	-1.2%	-87	
days w/o rescue Rx													
Bateman etc 1998				75	68	62.0%	56.2%	5.8%	1.10	10%	5.8%	17	0.2159
Chapman etc 1999				73	64	40.6%	33.5%	7.0%	1.21	21%	7.0%	14	0.3182
Aubier etc 1999				63	65	38.0%	38.0%	0.0%	1.00	0%	0.0%	-	0.2935
Van den Berg etc 2000				91	104	73.0%	79.0%	-6.0%	0.92	-8%	-6.0%	-17	0.1724
total or weighted average		593	615	303	301	49.7%	47.6%	2.1%	1.05	5%	2.1%	47	1.0000
WMD as published	median % days reliever free					47.2%	47.6%	-0.4%	0.99	-1%	-0.4%	-278	
nights w/o rescue Rx													
Bateman etc 1998				82	87	67.8%	71.9%	-4.1%	0.94	-6%	-4.1%	-24	0.2446
Chapman etc 1999				126	118	70.0%	61.8%	8.2%	1.13	13%	8.2%	12	0.3999
Aubier etc 1999				117	111	70.0%	65.0%	5.0%	1.08	8%	5.0%	20	0.3555
Van den Berg etc 2000													
total or weighted average		468	483	325	316	69.3%	65.4%	3.9%	1.06	6%	3.9%	26	1.0000
WMD as published	median % nights reliever free					65.3%	65.4%	-0.1%	1.00	0%	-0.1%	-909	

source: Nelson HS, Chapman KR, Pyke SD, Johnson M, Pritchard JN. Enhanced synergy between fluticasone propionate and salmeterol inhaled from a single inhaler versus separate inhalers. J Allergy Clin Immunol. 2003 Jul;112(1):29-36.

Appendix 4: Age group-specific results

Changes in ICS use and average daily doses (BAEDDs) by age-group, April to October 2002

Patients

		from age-specific unadjusted analyses														from formal analysis		age-specific unadjusted
		children 0-5 yrs		children/adolesc 6-16 yrs		young children 0-5 + older children/adolesc 6-16 yrs		adolesc/adults 17+ yrs		RR children / adults		(unadjusted total)*		(All)		Total (BEDDS, incl Symbicort)		[children/adolesc 0-16] / total
		actual	(seasonally-adj counterfactual)	actual	(seasonally-adj counterfactual)	actual	(seasonally-adj counterfactual)	actual	(seasonally-adj counterfactual)	actual	(seasonally-adj counterfactual)	actual	(seasonally-adj counterfactual)	actual	(seasonally-adj counterfactual)	actual	(seasonally-adj counterfactual)	actual
no.																		
fluticasone	no.	7,364	5,019	11,808	8,093	19,173	13,108	57,707	47,468	0.33	0.28	76,880	60,581	76,641	59,922	76,660	61,276	25%
	% variation	47%		46%		46%		22%		2.15		27%		28%		25%		
BDP	no.	2,361	3,013	4,082	4,627	6,443	7,641	26,042	33,791	0.25	0.23	32,485	41,430	32,538	41,801	33,727	43,099	20%
	% variation	-22%		-12%		-16%		-23%		0.68		-22%		-22%		-22%		
budesonide (excl Symbicort)	no.	163	135	3,698	3,311	3,861	3,448	19,579	18,828	0.20	0.18	23,440	22,274	23,362	22,181	26,216	23,059	16%
	% variation	20%		12%		12%		4%		3.00		5%		5%		14%		
total	no.	9,932	8,097	19,944	16,335	29,876	24,435	104,716	101,352	0.29	0.24	134,592	125,784	134,617	125,678	136,603	127,840	22%
	% variation	23%		22%		22%		3%		6.71		7%		7%		7%		
excess fluticasone and BDP																		
excess fluticsasone (a=d+e)		2,345		3,715		6,065		10,239		0.59		16,300		16,719		15,385		37%
excess BDP (b)		-651		-545		-1,198		-7,748		0.15		-8,945		-9,263		-9,372		13%
net excess (c=a+b)		1,694		3,171		4,867		2,490		1.95		7,355		7,456		6,012		66%
[[net excess all ICS (including budesonides**)]]		1,835		3,610		5,441		3,364		1.62		8,808		8,939		8,763		62%
[net excess fluticasone] (d)		1,694		3,171		4,867		2,490		1.95		7,355		7,456		6,012		66%
[excess from additional switching BDP to fluticasone*] (e)		651		545		1,198		7,748		0.15		8,945		9,263		9,372		13%
% switching of excess fluticasone (e/a)		28%		15%		20%		76%		0.26		55%		55%		61%		
change patients (slope)																		
fluticasone	slope (mean change no./month)	1	37	5	37	2	257	-2,148	-8,109	0.00	-0.03			-4,083	-21,232			
	difference	-36		-32		-255		5,961		-0.04				17,149				
BDP	slope (mean change no./month)	-16	-59	63	-499	94	-945	2,026	10,001	0.05	-0.09			6,955	30,272			
	difference		43.5		562.0		1038.6		-7975.7		-0.13				-23317.5			
budesonide (excl Symbicort)	slope (mean change no./month)	-1	-2	16	-104	17	-137	194	187	0.09	-0.73			951	1,610			
	difference	1		120		153		7		23.44				-658				
total	slope (mean change no./month)	-16	-21	81	-543	111	-776	-121	1,801	-0.92	-0.43			3,296	9,612			
	difference	5		624		887		-1,922		-0.46				-6,316				

*unadjusted totals and (All) from age-specific unadjusted analyses may conflict with totals from formal analysis. This reflects anomalies caused by averaging processes and sloping.
Age-specific and formal analyses are not directly comparable. Age-specific analyses use BAEDDs, whereas formal analysis uses BEDDs (hence lower values). Formal analyses include Symbicort.
Age-specific BAEDDs are averages for the period April-October 2002, wheras formal analysis BEDDs are averages for April'02 to Jnuary'03.

net excess (c=a+b) = from new patients beyond cf increases
net excess all ICS (including budesonides**) = from new naïve patients beyond counterfactual increases
net excess fluticasone (d) = from new naïve patients beyond counterfactual increases
excess from additional switching from BDP to fluticasone (e) = beyond switch occurring already
** budesonides - only budesonide for age-specific analyses, includes Symbicort for total formal analysis

ICS daily dose (BAEDD)

		from age-specific unadjusted analyses														from formal analysis		age-specific unadjusted
		children 0-5 yrs		children/adolesc 6-16 yrs		young children 0-5 + older children/adolesc 6-16 yrs		adolesc/adults 17+ yrs		RR children / adults		(unadjusted total)*		(All)		Total (BEDDS, incl Symbicort)		[children/adolesc 0-16] / total
		actual	(seasonally-adj counterfactual)	actual	(seasonally-adj counterfactual)	actual	(seasonally-adj counterfactual)	actual	(seasonally-adj counterfactual)	actual	(seasonally-adj counterfactual)	actual	(seasonally-adj counterfactual)	actual	(seasonally-adj counterfactual)	actual	(seasonally-adj counterfactual)	actual
ICS nominal average daily dose (ADD)																		
fluticasone	mcg (nominal)	153.4	158.7	312.6	350.3	252.3	276.3	619.6	662.0									
	new ICS-naïve patients	142.0		230.6		200.3		422.7										
BDP	mcg (nominal)	218.4	215.1	349.1	340.3	299.0	291.8	702.1	691.1									
	switching patients	203.4		274.2		253.0		654.1										
budesonide (excl Symbicort)	mcg (nominal)	364.3	324.3	524.8	524.2	511.2	507.4	1000.2	1026.0									
Age/chemical-adjusted ADD (BAEDD)																		
fluticasone	mcg (BAEDD)	613.4	634.6	862.4	966.3	767.4	840.5	1239.2	1324.1	0.62	0.63	1121.4	1219.2	1124.1	1232.3	1053.8	1186.6	68%
	% variation	-3%		-11%		-9%		-6%		1.36		-8%		-9%		-11%		108%
	new ICS-naïve patients	568.1		636.1		609.3		845.4				757.8		736.2		549.4		
	new/c.f.	0.90		0.66		0.72		0.64		1.14		0.62		0.60		0.46		117%
BDP	mcg (BAEDD)	436.7	430.3	481.5	469.3	465.2	453.9	702.1	691.1	0.66	0.66	655.1	647.4	655.6	643.2	626.0	615.3	71%
	% variation	1%		3%		2%		2%		1.55		1%		2%		2%		207%
	switching patients	406.9		378.2		393.6		654.1		0.60		619.3		599.5		591.8		64%
	lost/c.f.	0.95		0.81		0.87		0.95		0.92		0.96		0.93		0.96		91%
budesonide (excl Symbicort)	mcg (BAEDD)	728.7	648.7	723.9	723.0	723.8	718.3	1000.2	1026.0	0.72	0.70	954.7	978.7	956.3	980.5	901.4	952.6	76%
	% variation	12%		0%		1%		-3%		-0.30		-2%		-2%		-5%		-31%
total	mcg (BAEDD)	572.7	550.3	760.8	767.2	698.3	695.2	1067.9	1072.8	0.65	0.65	985.9	999.5	986.0	1000.1	925.9	950.9	71%
	% variation	4%		-1%		0%		0%		-0.97		-1%		-1%		-3%		-33%
% variation fluticasone new patients/BDP "lost" patients (BAEDD)		39.6%		68.2%		54.8%		29.3%				22.4%		22.8%		-7.2%		
change BAEDD (slope)																		
fluticasone	slope (mean mcg change/month)	-0.5	-1.0	-0.3	-16.8	0.3	-16.4	13.3	65.0	0.02	-0.25			8.9	140.0			
	difference	0.6		16.5		16.7		-51.6		-0.32				-131.1				
BDP	slope (mean mcg change/month)	-0.2	0.4	0.7	1.5	0.6	2.0	6.1	-4.0	0.10	-0.51			8.6	-31.3			
	difference	-0.6		-0.8		-1.4		10.1		-0.14				39.9				
budesonide (excl Symbicort)	slope (mean mcg change/month)	-1.0	2.0	0.6	0.8	0.6	1.4	1.3	17.1	0.49	0.08			0.5	17.9			
	difference	-2.9		-0.2		-0.8		-15.8		0.05				-17.4				
total	slope (mean mcg change/month)	-0.2	0.5	-0.5	-1.8	-0.1	-1.4	-7.8	-10.2	0.02	0.14			-21.7	-22.6			
	difference	-0.7		1.4		1.3		2.3		0.56				1.0				

*unadjusted totals and (All) from age-specific unadjusted analyses may conflict with totals from formal analysis. This reflects anomalies caused by averaging processes and sloping.
Age-specific and formal analyses are not directly comparable. Age-specific analyses use BAEDDs, whereas formal analysis uses BEDDs (hence lower values). Formal analyses include Symbicort.
Age-specific BAEDDs are averages for the period April-October 2002, wheras formal analysis BEDDs are averages for April'02 to Jnuary'03.

ADDs for new fluticasone patients by age-group, April-October 2002

	from age-specific unadjusted analyses: children 0-5 yrs			children/adolesc 6-16 yrs			young children 0-5 + older children/adolesc 6-16 yrs			adolesc/adults 17+ yrs			RR children / adults			from formal analysis: Total (BEDDS, incl Symbicort)		
	no. patients	BAEDD ug/day	ADD fluticasone ug/day	no. patients	BAEDD ug/day	ADD fluticasone ug/day	no. patients	BAEDD ug/day	ADD fluticasone ug/day	no. patients	BAEDD ug/day	ADD fluticasone ug/day	no. patients	BAEDD ug/day	ADD fluticasone ug/day	no. patients	BEDD ug/day	ADD fluticasone ug/day
if all pts switch at approriate dose equivalence																		
new ICS-naïve patients, beyond counterfactual increases	1,694	630.1	157.5	3,171	680.5	246.7	4,867	662.3	217.8	2,490	1440.7	720.4	1.95	0.46	0.30	6,012	483.3	241.7
patients additional switching from BDP*	651	406.9	101.7	545	378.2	137.1	1,198	393.6	129.4	7,748	654.1	327.1	0.15	0.60	0.40	9,372	591.8	295.9
total new fluticasone patients	2,345	568.1	142.0	3,715	636.1	230.6	6,065	609.3	200.3	10,239	845.4	422.7	0.59	0.72	0.47	15,385	549.4	274.7
if 10% of pts switching have inappropriately 1:1 dosing																		
new ICS-naïve patients, beyond counterfactual increases	1,694	614.4	153.6	3,171	674.0	244.3	4,867	652.6	214.6	2,490	1237.2	618.6	1.95	0.53	0.35	6,012	391.1	195.5
patients additional switching from BDP*	651	447.6	111.9	545	416.0	150.8	1,198	433.0	142.4	7,748	719.5	359.8	0.15	0.60	0.40	9,372	651.0	325.5
total new fluticasone patients	2,345	568.1	142.0	3,715	636.1	230.6	6,065	609.3	200.3	10,239	845.4	422.7	0.59	0.72	0.47	15,385	549.4	274.7
if 20% of pts switching have inappropriately 1:1 dosing																		
new ICS-naïve patients, beyond counterfactual increases	1,694	598.8	149.7	3,171	667.5	242.0	4,867	643.0	211.4	2,490	1033.7	516.9	1.95	0.62	0.41	6,012	298.8	149.4
patients additional switching from BDP*	651	488.3	122.1	545	453.8	164.5	1,198	472.4	155.3	7,748	784.9	392.5	0.15	0.60	0.40	9,372	710.1	355.1
total new fluticasone patients	2,345	568.1	142.0	3,715	636.1	230.6	6,065	609.3	200.3	10,239	845.4	422.7	0.59	0.72	0.47	15,385	549.4	274.7

* assumes that patients switching from BDP are placed on an appropriate equivalent dose of fluticasone (i.e. a straight 2:1 change in µg dose)

Appendix 5: Overall results

ICS use and costs April 2002 to January 2003

	No. dispensings			No. patients		Costs		
	total 4/02 to 10/02	increase/month 4/02-10/02 (non-seasonal regressions)	total 4/02 to 1/03	average 4/02 to 10/02	average 4/02 to 1/03	total 4/02 to 10/02	total 4/02 to 1/03	annualised costs at 10/02
fluticasone								
- actual (changes since April 2002)	436,841	1,720	625,188	76,660	77,327	$12,619,678	$18,100,548	$21,633,734
- predicted counterfactual (if no change since March 2002)	349,261	310	493,815	61,276	61,056	$10,551,177	$14,823,479	$18,087,732
- difference	87,580	1,410	131,373	15,385	16,271	$2,068,501	$3,277,068	$3,546,003
- excess/predicted	1.25	4.55	1.27	1.25	1.27	1.20	1.22	1.20
BDP								
- actual (changes since April 2002)	136,095	-2,167	171,502	33,727	30,240	$2,313,590	$2,963,520	$3,966,154
- predicted counterfactual (if no change since March 2002)	173,447	-478	236,015	43,099	41,886	$2,810,458	$3,791,144	$3,791,144
- difference	-37,352	-1,690	-64,513	-9,372	-11,646	-$496,868	-$827,624	$175,010
- excess/predicted	0.78	3.54	0.73	0.78	0.72	0.82	0.78	1.05
budesonide incl Symbicort								
- actual (changes since April 2002)	97,461	213	140,020	26,216	26,144			
- predicted counterfactual (if no change since March 2002)	85,705	-19	119,997	23,059	22,422			
- difference	11,756	232	20,023	3,157	3,722			
- excess/predicted	1.14	-12.05	1.17	1.14	1.17			
other ICS (BDP/budesonide/Symbicort combined)								
- actual (changes since April 2002)	233,556	-1,954	311,522	59,943	56,384	$5,826,124	$8,289,046	$9,987,641
- predicted counterfactual (if no change since March 2002)	259,153	-497	356,011	66,564	64,515	$6,003,585	$8,562,322	$10,291,860
- difference	-25,597	-1,457	-44,489	-6,621	-8,131	-$177,461	-$273,276	-$304,219
- excess/predicted	0.90	2.93	0.88	0.90	0.87	0.97	0.97	0.97
total ICS								
- actual (changes since April 2002)	670,397	-234.4	936,710	136,603	133,711	$18,445,802	$26,389,593	$31,621,375
- predicted counterfactual (if no change since March 2002)	608,413	-186.8	849,826	127,840	125,571	$16,554,762	$23,385,801	$28,379,591
- difference	61,984	-48	86,884	8,763	8,140	$1,891,040	$3,003,792	$3,241,784
- excess/predicted	1.10	0.25	1.10	1.07	1.06	1.11	1.13	1.11

Excess ICS use and costs

	No. dispensings		No. patients		Costs	
	total 4/02 to 10/02	total 4/02 to 1/03	average 4/02 to 10/02	average 4/02 to 1/03	total 4/02 to 10/02	total 4/02 to 1/03
Excess fluticasone and BDP, April 2002 to January 2003:						
excess fluticsasone (a=d+e)	87,580	131,373	15,385	16,271	$2,068,501	$3,277,068
excess BDP (b)	-37,352	-64,513	-9,372	-11,646	-$599,921	-$1,025,683
net excess (= from new patients beyond cf increases) (c=a+b)	**50,228**	**66,861**	**6,012**	**4,625**	**$1,468,580**	**$2,251,385**
[[net excess all ICS (including budesonides) (= from new naïve patients beyond counterfactual increases)]]			8,763	8,140		
[net excess fluticasone (= from new naïve patients beyond counterfactual increases)] (d)			6,012	4,625	$946,135	$1,351,896
[excess from additional switching from BDP to fluticasone*] (e)			9,372	11,646	$522,445	$899,490
*(beyond switch occurring already						
% switching of excess fluticasone (e/a)			61%	72%	25%	27%
[predicted increase in fluticasone under counterfactual**]	8,859	17,397	1,690	2,324		
**i.e. if there had been no DTCA), i.e. switching from other ICS at ongoing rate						

ICS ADDs since April 2002

	ADD ug/day 4/02-1/03			ADD ug/day at 10/02		
	actual (changes since April 2002)	predicted cf	new/"lost" pts	actual (changes since April 2002)	predicted cf	new/"lost" pts
fluticasone	526.9	593.3	274.7	517.5	597.5	278.4
(BDP-equivalent DD)	1053.8	1186.6	549.4	1035.0	1195.1	556.9
- difference	-66.4			-80.0		
- actual/predicted	0.89			0.87		
BDP	626.0	615.3	591.8	643.7	621.4	593.5
- difference	10.7			22.3		
- actual/predicted	1.02			1.04		
budesonide	901.4	952.6	599.0	894.5	962.3	592.1
- difference	-51.2			-67.8		
- actual/predicted	0.95			0.93		
other ICS (BDP/budesonide)	754.7	732.7	591.1	781.5	742.0	596.3
- difference	22.1			39.5		
- actual/predicted	1.03			1.05		
total ICS (BDP-equivalents)	925.9	950.9		940.9	965.8	
- difference	-25.0			-25.0		
- actual/predicted	0.97			0.97		
% variation fluticasone new patients/BDP "lost" patients (BEDD)			-7.2%			-6.2%

ADDs for new fluticasone patients, April-October 2002

	no. patients	if all pts switch at approriate dose equivalence		if 10% of pts switching have inappropriately 1:1 dosing	
		BEDD ug/day	ADD fluticasone ug/day	BEDD ug/day	ADD fluticasone ug/day
new ICS-naïve patients, beyond counterfactual increases	6,012	483.3	241.7	391.1	195.5
patients additional switching from BDP*	9,372	591.8	295.9	651.0	325.5
* assumes that patients switching from BDP are placed on an appropriate equivalent dose of fluticasone (i.e. a straight 2:1 change in µg dose)					
total new fluticasone patients	15,385	549.4	274.7	549.4	274.7