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Device type and real-world effectiveness of asthma combination therapy: An observational study

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Summary
Background: Selection of inhaler device type appears to influence real-world effectiveness of inhaled corticosteroids (ICS), but data are lacking on the role of inhaler device in ICS and long-acting β2-agonist (LABA) combination therapy for asthma.
Methods: This retrospective matched cohort study compared 1-year asthma outcomes for UK patients initiating fixed-dose combination (FDC) fluticasone–salmeterol delivered by pressurised metered-dose inhaler (pMDI) versus dry powder inhaler (DPI). Patients with asthma aged 4–80 years receiving a first prescription for FDC fluticasone–salmeterol by pMDI or DPI were matched on baseline demographic and asthma severity measures. Co-primary outcomes were asthma control (a composite measure comprising no recorded hospital attendance for asthma, oral corticosteroids, or antibiotics for lower respiratory infection) and exacerbation rate.
Results: Compared with the DPI cohort ($n = 1567$), patients in the pMDI cohort ($n = 1567$) had significantly greater odds of achieving asthma control during the outcome year (odds ratio [OR] 1.19; 95% confidence interval [CI] 1.01 to 1.40). Exacerbation rate was lower but not significantly in the pMDI cohort (adjusted rate ratio for pMDI cohort, 0.82; 95% CI 0.66 to 1.00). The odds of treatment success (defined as no exacerbations and no change in asthma therapy) was significantly greater in the pMDI cohort (OR 1.23; 95% CI, 1.07 to 1.42).

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Conclusions: For UK primary care patients, pMDIs appear to achieve better asthma control outcomes than DPIs for delivery of FDC fluticasone—salmeterol. Pragmatic trials are needed to further investigate real-world outcomes with different inhaler devices for combination therapy.

Introduction

Asthma affects over 300 million people worldwide and has a substantial impact on patients' quality of life and on healthcare resources.[1,2] Much of the social and economic burden of asthma results from poorly controlled disease, often characterised by asthma exacerbations. International surveys reveal that asthma is frequently uncontrolled[3,4]; thus, much work remains to optimise asthma management, particularly in the primary care setting where most asthma care is delivered.[5]

A challenge for clinicians in providing effective therapy for asthma is to ensure that patients are using their inhaler devices correctly. The inhaled route is key for delivery of bronchodilators as well as inhaled corticosteroids (ICS) in persistent asthma. However, many patients have difficulty using their inhalers, and incorrect inhaler technique coupled with poor adherence to therapy are considered common causes of uncontrolled asthma.[5—7] Data are currently lacking on the extent of the roles of inhaler device and technique in delivery of ICS and long-acting β2-agonist (LABA) combination therapy.

Available inhaler device types for combination therapy include pressurised metered-dose inhalers (pMDIs) and dry powder inhalers (DPIs). DPIs are actuated by the patient's inhalation, while the pMDIs currently available for combination therapy require coordination of actuation and inhalation. Device preparation and handling vary greatly according to inhaler brand, particularly among the available types of DPIs. Some generalisations can be made, however, with regard to optimal inhalation manoeuvre for each category of inhaler. Both require a deep inhalation; with pMDIs the inhalation should be slow and steady, whereas with DPIs the inhalation should be sharp and rapid. The very young, the elderly, and those with severe airway obstruction in particular may not be able to reproducibly generate an inhalation rate sufficiently fast for optimal drug delivery with a DPI.[7] Conversely, the most common mistake made with a pMDI is to inhale too fast.[7—11] Difficulty with coordination of actuation and inhalation is also common with pMDIs.

Inhaler prescribing practices differ substantially among countries, with large variation in preferences for pMDIs versus DPIs, likely influenced by availability and habit, as well as by local guidelines. Randomised trials comparing inhalers for license-equivalent combination ICS-LABA are few and report similar outcomes with the two types of inhaler device.[12—14] Likewise, for delivery of ICS monotherapy, comparisons of inhaler device types in randomised controlled trials indicate no consistent differences among devices in asthma outcomes; however, most of these trials were conducted to demonstrate equivalence or non-inferiority of devices for licensing purposes.[15—17] Moreover, enrolled patients were trained and monitored to ensure proper inhaler technique, a situation very dissimilar to that in the real world, where outpatients with asthma commonly make mistakes with their inhalers.[6,18—20] Preliminary data suggest that selection of inhaler device is associated with real-world effectiveness of ICS therapy,[21,22] but data are lacking on the role of inhaler device in real-world effectiveness of combination ICS-LABA therapy.

Database reviews of medical records afford a means of assessing the effectiveness of interventions in the real-world clinical setting and provide longer-term outcome data than are provided by most clinical trials. We undertook this retrospective database study to compare pMDIs with DPIs for the delivery of a fixed-dose combination (FDC) of fluticasone propionate and salmeterol for patients treated in routine UK primary care. Our objective was to examine the impact of inhaler device on real-world effectiveness by comparing the same drug combination delivered by two different inhaler devices.

Methods

Patients and data source

This was a retrospective cohort study using the UK General Practice Research Database (GPRD). The GPRD is a large, well-regarded database containing anonymised, longitudinal medical records for approximately 7% of the UK population, contributed by over 500 participating primary care practices located throughout England, Scotland, Wales, and Northern Ireland.[23] Data from the GPRD are used routinely in epidemiologic research and in evaluations of respiratory medications.[22,24—28]

We studied patients with asthma who had a first prescription recorded in the GPRD from January 1998 to June 2007 for FDC fluticasone—salmeterol delivered by pMDI (Seretide Evohaler, GlaxoSmithKline) or by DPI (Seretide Accuhaler, GlaxoSmithKline). Eligible patients were aged 4—80 years at the time of this index prescription (the index date) and had at least 2 consecutive years' data in the GPRD, including a minimum 1-year baseline period before the index date to establish eligibility and identify possible confounding factors plus 1 year after the index date for outcome evaluation.

We identified patients with asthma as those with a diagnostic code for asthma in the database or at least two prescriptions for asthma medications, including at least one ICS prescription, during the baseline year. Eligible patients had to be on current therapy, defined as at least one asthma prescription during the baseline year. The index prescription was for the initiation of FDC fluticasone—salmeterol, with the fluticasone prescribed at either the same or greater dose relative to the baseline ICS (measured as the beclometasone

dipropionate-equivalent dose). Patients with a prior prescription for a separate LABA in addition to ICS were excluded, as were patients with a diagnostic read code for any chronic respiratory disease other than asthma (e.g., chronic obstructive pulmonary disease). We required that the period of study for each patient be assessed by the GPRD as up-to-standard for their primary care practice.

Permission for use of the data was given by the GPRD Independent Scientific Advisory Committee.

Outcome measures

The two predefined primary outcome measures were a composite proxy for asthma control and exacerbation rate during the outcome year. The asthma control measure was designed to capture available data indicative of control, in accordance with asthma guidelines and international consensus.[29–31] Patients with controlled asthma were defined as meeting all of the following during the outcome year:

1. no recorded hospital attendance for asthma including admission, emergency attendance, out-of-hours attendance, or outpatient department attendance, and
2. no acute prescription for oral corticosteroids, and
3. no consultation, hospital admission, or emergency attendance for lower respiratory tract infection requiring antibiotics.

Any patient not meeting these three criteria was defined as having uncontrolled asthma.

An exacerbation was defined as an unscheduled hospital admission or emergency department attendance for asthma or acute use of oral corticosteroids.

Secondary outcome measures studied over 1 year after the index date included another composite measure—treatment success—defined as no exacerbation and no change in therapy, where a change in therapy could be any of the following:

1. an increase in dose of ICS,
2. a change in ICS-LABA combination,
3. a change in inhaler device, or
4. use of additional therapy in the form of theophylline or leukotriene receptor antagonist.

We assessed adherence as the percentage of medication issued relative to the amount that should have been issued over the year according to the initial prescribing instructions.

Statistical analyses

All analyses took account of confounding variables using multiple regression methods. Data were analysed using SPSS version 17 (SPSS Inc, Chicago, Illinois, USA), STATA version 11 (StataCorp LP, College Station, Texas, USA), and SAS version 9.2 (SAS Software, Ltd, Marlow, Buckinghamshire, UK). Differences in outcomes between cohorts were considered significant if $p < 0.05$ and as trends if $0.05 \leq p < 0.10$.

Baseline characteristics were compared between unmatched treatment cohorts using the Mann–Whitney test for continuous data and χ^2 test for categorical variables. Baseline differences between treatment cohorts were considered possibly important if $p < 0.10$. Variables meeting this criterion were examined for collinearity as well as clinical importance to select those used for regression modelling on outcomes. Continuous variables showing a skewed distribution were categorised appropriately. We categorised short-acting β2-agonist (SABA) daily dose (as 0, 1–100, 101–200, 201–300, 301–400, and >400 μg); prescribed ICS daily dose at the index date and during the baseline period (as 1–100, 101–250, 251–500, and >500 μg); and counts of oral corticosteroid prescriptions and hospitalisations (as 0, 1, 2, ≥3).

The baseline analysis highlighted significant differences between patients in the two cohorts (see online Supplemental information). Therefore, we elected to use two different approaches—a matched analysis and an adjusted but unmatched analysis—to better account for and examine differences between treatment cohorts in line with our *a priori* study protocol.

For the matched analysis, patients were matched at baseline on a 1:1 basis using key clinically relevant characteristics so as to minimise the potential for confounding in the outcomes. We matched patients on five baseline criteria: age, sex, average daily SABA dose, number of oral corticosteroid prescriptions, and average daily ICS dose. The former two criteria were chosen to provide comparable demographic groups; the latter three, as non-collinear measures of disease severity during the baseline period. Patient ages were matched within 1 year for those aged 4–5 years, within 3 years for those aged 6–12 years, and within 5 years for those aged 13 and older.

Comparisons between treatment cohorts were carried out using conditional logistic and Poisson regression models to account for patient matching. Odds ratios (ORs) for the dichotomised definitions of asthma control and treatment success were calculated using conditional logistic regression, with control or treatment success as the dependent variable and inhaler type and residual confounding variables as explanatory variables. Exacerbation rates in the outcome period were compared using a conditional Poisson regression model (using empirical standard errors for more robust confidence intervals [CIs]), with the number of exacerbations as the dependent variable and inhaler type and residual confounding variables as explanatory variables. For both models, variables that remained potentially different on univariate analysis between the matched cohorts at baseline ($p < 0.10$) were included as confounding factors.

For the unmatched analyses, ORs for asthma control and treatment success were calculated using multiple logistic regression models, and exacerbation rates were compared using a Poisson regression model, adjusted for overdispersion using robust standard errors (see online Supplement). All models were adjusted for potential baseline confounders.

Results

Matched analysis

We identified 3966 patients who were initiated on fluticasone–salmeterol by pMDI and 1843 patients initiated on

fluticasone–salmeterol by DPI. The matching process resulted in 1567 patients in each matched treatment cohort (see Figure in online supplement). Several baseline variables remained significantly different between cohorts after matching, but most differences were small and deemed not clinically meaningful (Tables 1 and 2). Most patients (95%; Table 2) had a diagnosis of asthma recorded in the database, and, of the 157 patients without a recorded asthma diagnosis, all had two or more prescriptions for asthma during the baseline year, and 83% had four or more during the 2-year study.

Similar numbers of patients in each cohort met the criteria for asthma control at baseline (Table 2). The year of the index date was significantly different between cohorts ($p < 0.001$; data not shown), generally earlier for patients receiving a DPI, as DPIs were licensed earlier in the UK. When differences between matched cohorts were clinically significant or had a significant effect on the outcome variable, we adjusted for their effect in the regression modelling.

Approximately three quarters of patients achieved asthma control by our composite measure during the outcome year (Table 3). The unadjusted OR showed significantly higher odds of achieving control with fluticasone–salmeterol by pMDI than by DPI device (Fig. 1). Adjustment for confounding factors, including ICS dose at the index date, did not change the direction or statistical significance of the result. The exacerbation rate was lower in the pMDI cohort, although not significantly different between cohorts ($p = 0.054$) (Table 3; Fig. 1).

The odds of meeting the composite measure of treatment success were significantly higher for the pMDI cohort (Table 3; Fig. 1). Significantly more patients in the DPI cohort had a change in therapy during the outcome year (Table 3; Fig. 2). Percentages of patients with increases in ICS dose or changes in ICS-LABA or inhaler device are depicted in Fig. 2. Adherence with FDC fluticasone–salmeterol therapy was significantly lower ($p = 0.022$) in the pMDI cohort, as <50% adherence was recorded for 697 [53%] patients in the pMDI cohort and for 633 [49%] patients in the DPI cohort.

As their device type for SABA reliever therapy during the outcome year, the majority of patients in both cohorts were prescribed a pMDI (81% and 51% in pMDI and DPI cohorts,

Table 1 Baseline demographic and clinical characteristics of a matched population of patients prescribed fixed-dose combination fluticasone–salmeterol by pressurised metered-dose inhaler (FP-Sal by pMDI) or dry powder inhaler (DPI).

Characteristic	FP-Sal by pMDI ($n = 1567$)	FP-Sal by DPI ($n = 1567$)	p value[a]
Female sex, no. (%)	940 (60.0)	940 (60.0)	n/a
Age, median (IQR)	42 (20–57)	44 (19–57)	0.037
4–11 y, no. (%)	165 (10.5)	188 (12.0)	<0.001
12–69 y, no. (%)	1293 (82.5)	1280 (81.7)	
70–80 y, no. (%)	109 (7.0)	99 (6.3)	
Weight (kg), mean (SD)[b]	72.2 (22.7)	71.9 (23.0)	0.535
Height (m), mean (SD)[b]	1.62 (0.16)	1.62 (0.16)	0.993
Body mass index (kg/m^2), mean (SD)[b]	26.7 (7.1)	26.6 (6.8)	0.535
Socioeconomic status, median (IQR)[c]	18 (10–33)	18 (9–33)	0.725
Charlson comorbidity index, no. (%)[c]			
0	1382 (88.2)	1387 (88.5)	0.904
1	122 (7.8)	109 (7.0)	
≥2	63 (4.0)	71 (4.5)	
Smoking status, no./total no. (%)			
Current	310/1263 (24.5)	292/1091 (26.8)	0.092
Former	271/1263 (21.5)	257/1091 (23.6)	
Never	682/1263 (54.0)	542/1091 (49.7)	
Recorded comorbidity, no. (%)			
Rhinitis	329 (21.0)	322 (20.5)	0.760
Cardiac disease	81 (5.2)	89 (5.7)	0.514
Gastroesophageal reflux disease	146 (9.3)	171 (10.9)	0.130
1 + prescription in 12 mo, no. (%)			
NSAID	384 (24.5)	335 (21.4)	0.027
Beta blocker[d]	69 (4.4)	70 (4.5)	0.928
Paracetamol	376 (24.0)	362 (23.1)	0.552

IQR = interquartile range; n/a = p value is not applicable for matching criteria; NSAID = nonsteroidal anti-inflammatory drug.

[a] Conditional logistic regression.

[b] Not all patients had recorded weight and height data. For weight, $n = 1396$ and 1381; height $n = 1474$ and 1475; BMI $n = 1380$ and 1362 for pMDI versus DPI cohort, respectively.

[c] Socioeconomic status was that assigned, in quintiles, by the General Practice Research Database to each practice using the Index of Multiple Deprivation as a proxy measure. The Charlson comorbidity index is a weighted index that accounts for number and severity of comorbidities, each assigned a score depending on the associated risk of dying.

[d] Most prescribed beta blockers were topical.

Table 2 Asthma-related medical resource use during the baseline year for matched population of patients prescribed fixed-dose combination fluticasone—salmeterol by pressurised metered-dose inhaler (FP-Sal by pMDI) or dry powder inhaler (DPI).

Characteristic	FP-Sal by pMDI (n = 1567)	FP-Sal by DPI (n = 1567)	p value[a]
Recorded asthma diagnosis, no. (%)	1498 (95.6)	1479 (94.4)	0.114
Mean SABA dose, no. (%)[b]			
0	60 (3.8)	60 (3.8)	n/a
1—100 μg/d	290 (18.5)	290 (18.5)	
101—200 μg/d	512 (32.7)	512 (32.7)	
201—300 μg/d	222 (14.2)	222 (14.2)	
301—400 μg/d	127 (8.1)	127 (8.1)	
≥401 μg/d	356 (22.7)	356 (22.7)	
Oral corticosteroid courses, no. (%)			
0	1173 (74.9)	1173 (74.9)	n/a
1	290 (18.5)	290 (18.5)	
2	66 (4.2)	66 (4.2)	
3—5	38 (2.4)	38 (2.4)	
Total exacerbations, no. (%)[c]			
0	1173 (74.9)	1170 (74.7)	0.234
1	289 (18.4)	292 (18.6)	
2	67 (4.3)	67 (4.3)	
≥3	38 (2.4)	38 (2.4)	
Mean ICS dose during baseline year, no. (%)			
None	52 (3.3)	52 (3.3)	n/a
1—199 μg/d	819 (52.3)	819 (52.3)	
200—399 μg/d	394 (25.1)	394 (25.1)	
400—599 μg/d	141 (9.0)	141 (9.0)	
600—799 μg/d	79 (5.0)	79 (5.0)	
800—1199 μg/d	59 (3.8)	59 (3.8)	
1200—1599 μg/d	13 (0.8)	13 (0.8)	
≥1600 μg/d	10 (0.6)	10 (0.6)	
Spacer device used, no. (%)	326 (20.8)	206 (13.1)	<0.001
Mixed ICS device types—baseline yr, no. (%)	76 (5.0)	121 (8.0)	0.001
ICS device type during baseline yr, no. (%)			
pMDI	1221 (77.9)	761 (48.6)	<0.001
Breath-actuated MDI	217 (13.8)	369 (23.5)	
DPI	77 (4.9)	386 (24.6)	
None/missing data	52 (3.3)	51 (3.3)	
ICS dose at index date, no. (%)			
1—200 μg/d	51 (3.3)	57 (3.6)	<0.001
201—500 μg/d	499 (31.8)	669 (42.7)	
501—1000 μg/d	718 (45.8)	636 (40.6)	
≥1000 μg/d	299 (19.1)	205 (13.1)	
Asthma consultations, no. (%)			
0	469 (29.9)	452 (28.8)	<0.001
1	508 (32.4)	472 (30.1)	
2	311 (19.8)	300 (19.1)	
≥3	279 (17.8)	343 (21.9)	
Courses of antibiotics for lower respiratory tract infection, no. (%)			
0	1218 (77.7)	1203 (76.8)	0.750
1	248 (15.8)	268 (17.1)	
≥2	101 (6.4)	96 (6.1)	
≥1 Hospitalisation for asthma, no. (%)	1 (0.1)	3 (0.2)	0.306
Asthma control status, no. (%)[d]	968 (61.8)	970 (61.9)	0.913

ICS = inhaled corticosteroid; n/a = p value is not applicable for matching criteria; SABA = short-acting β2-agonist.

[a] Conditional logistic regression.

[b] The SABA dose is the albuterol dose equivalent (standard dose in UK is 100 μg). The ICS dose is the chlorofluorocarbon-beclomethasone dose equivalent.

[c] An exacerbation was defined as an occurrence of unscheduled hospital admission or emergency room attendance for asthma or prescription for oral corticosteroids; exacerbations on the index date were included in the baseline data.

[d] Asthma control was defined as no recorded hospital attendance for asthma, oral corticosteroid course, or antibiotics for lower respiratory infection.

Table 3 Outcomes over 1 year after prescription for fixed-dose combination fluticasone–salmeterol by pressurised metered-dose inhaler (FP-Sal by pMDI) or dry powder inhaler (DPI).

Outcome	FP-Sal by pMDI (n = 1567)	FP-Sal by DPI (n = 1567)	p value[a]
Asthma control,[b] no. (%)	1176 (75.0)	1127 (71.9)	
Treatment success, no. (%)	896 (57.2)	815 (52.0)	
Asthma exacerbations,[c] no. (%)			
0	1329 (84.8)	1289 (82.3)	0.054
1	169 (10.8)	201 (12.8)	
2	44 (2.8)	46 (2.9)	
≥3	25 (1.6)	31 (2.0)	
Asthma consultations, median (IQR)	0 (0–1)	0 (0–2)	<0.001
SABA daily dose (μg), median (IQR)	164 (55–329)	164 (55–329)	0.648
Average ICS daily dose (μg) 0	1 (0.1)	0 (0)	0.390
1–99	379 (24.2)	412 (26.3)	
100–199	329 (21.0)	344 (22.0)	
200–299	266 (17.0)	257 (16.4)	
300–399	167 (10.7)	120 (7.7)	
400–599	268 (17.1)	255 (16.3)	
600–799	81 (5.2)	95 (6.1)	
≥800	76 (4.9)	84 (5.4)	
Disaggregated outcomes of the composite measures			
≥1 hospital admission, no. (%)	1 (0.0)	1 (0.0)	1.0
≥1 oral corticosteroid course, no. (%)	238 (15.2)	278 (17.7)	0.051
≥1 course of antibiotics for LRTI, no. (%)	236 (15.1)	261 (16.7)	0.209
≥1 change in therapy, no. (%)	548 (35.0)	616 (39.3)	0.011

ICS = inhaled corticosteroid; IQR = interquartile range; LRTI = lower respiratory tract infection; SABA = short-acting β2-agonist.
[a] Conditional logistic regression.
[b] Asthma control was defined as no recorded hospital attendance for asthma, oral corticosteroid course, or antibiotics for lower respiratory infection.
[c] An exacerbation was defined as an occurrence of unscheduled hospital admission or emergency room attendance for asthma or prescription for oral corticosteroids.

respectively); 14% and 24%, respectively, received a breath-actuated MDI; and the remainder (4% and 22%, respectively) a DPI (1% and 2% received no SABA prescription during the outcome year).

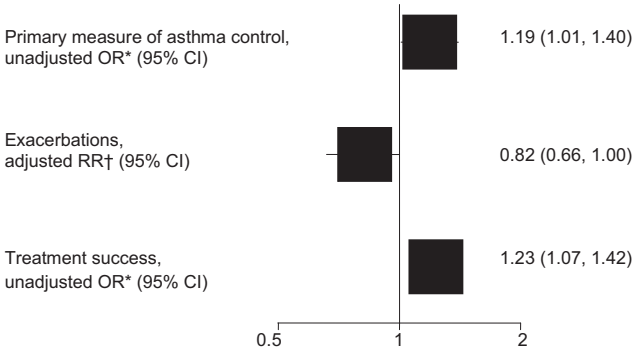

Figure 1 ORs for asthma control and treatment success, and RR for exacerbations, for the pMDI cohort. Data represent outcomes for patients in the pMDI cohort as compared with those in DPI cohort (ORs and RR of 1.0) over 1 year after prescription for fixed-dose combination fluticasone–salmeterol. *No significant effects (ie, no confounders identified). †adjusted for baseline confounders and inhaled corticosteroid dose at the index date. OR = odds ratio; RR = rate ratio; pMDI = pressurised metered dose inhaler; DPI = dry powder inhaler.

Unmatched analysis

Baseline data and outcomes for the unmatched pMDI and DPI cohorts are summarised in the online supplement (Supplemental Tables 1–4). The adjusted odds ratio for achieving asthma control was significantly higher, and exacerbation rate ratio significantly lower, for patients prescribed a pMDI (Supplemental Table 4).

Discussion

In this real-world observational study, the proportion of patients meeting the asthma control criterion increased from baseline in both cohorts receiving FDC therapy with fluticasone and salmeterol for 1 year. Asthma control over the outcome year was more likely for the patients who initiated combination therapy by pMDI rather than by DPI. The exacerbation rate ratio trended in the same direction as the control measure, as exacerbations were less frequent in the pMDI cohort, although the difference in exacerbation rates was not statistically significant. The likelihood of patients meeting the composite measure of treatment success (which incorporated the absence of exacerbations as well as no change in asthma therapy) was significantly greater in the pMDI cohort.

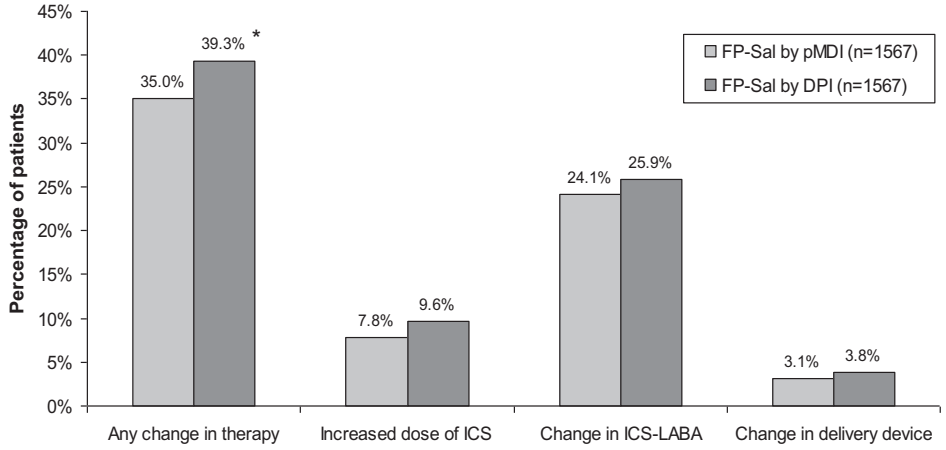

Figure 2 Percentage of patients with change in therapy during the outcome year. $*p = 0.011$ for overall comparison between treatment cohorts. No patients in either cohort were prescribed additional asthma therapy. FP-Sal = fluticasone—salmeterol; pMDI = pressurised metered dose inhaler; DPI = dry powder inhaler; ICS = inhaled corticosteroid; LABA = long-acting β2-agonist.

The difference in statistical findings for asthma control and exacerbation measures could be explained by the fact that asthma control is a dichotomy (yes versus no) and thus one hospitalisation, corticosteroid prescription, or antibiotic use is effectively the same as 100. Instead, the exacerbation rate is a continuum and thus distinguishes between 1 and 100 'events'. Moreover, the composite measure of asthma control was constructed to capture antibiotic prescribing for lower respiratory tract infection, together with oral corticosteroids and unplanned visits or hospitalisations for asthma, because treatment with antibiotics is commonly reported for patients presenting for acute asthma exacerbations.[32,33]

The findings of this study reflect the real-world outcomes of therapy with FDC fluticasone—salmeterol for asthma. Different from the perspective of a randomised controlled trial, where patient progress is closely monitored and treatment adherence encouraged, a database assessment such as this one captures the effects of actual prescribing practices and takes into account patient and physician preferences, patient education, and adherence with therapy (or lack thereof). This enabled us to study the comparative effectiveness of inhaler devices as used by real-world patients in real-world settings. Our main analysis matched patients at baseline for demographic and asthma-related characteristics to provide a more rigorous comparison of the effects of therapy for patients with similar asthma severity at baseline. Because patient subgroups could potentially be excluded by the matching process, we also performed an unmatched analysis adjusted for confounders, the results of which were similar to and thus provide support for the matched analyses.

The effectiveness of inhaled therapy depends not only on the drug(s) delivered, but also, and perhaps more importantly, on the delivery device and the patient's ability to use it correctly. We can only speculate why pMDIs were associated with better asthma control outcomes than DPIs for FDC fluticasone—salmeterol. It is important to note that DPIs are prescribed less frequently than pMDIs in the UK, a fact supported by our finding of more patients with a recorded prescription for a pMDI at baseline and on the index date. Thus, it is possible there may be a prescribing preference that biases the type of patient for whom DPIs are prescribed. We tried to eliminate any such bias by matching patients on demographic characteristics and baseline characteristics indicative of asthma severity and control, with statistical adjustments for any remaining confounding factors. While matching is never perfect, we believe the process addressed baseline differences as completely as was feasible without over-matching or losing too many patient numbers.

As DPIs are prescribed less frequently in the UK, it is possible that the differences between inhaler cohorts arose because UK practitioners are less proficient at teaching DPI technique. Another possibility is that patients prescribed a pMDI were still using it because they could use it properly, whilst those in the DPI cohort had been switched because of poor pMDI technique, and they also had poor DPI technique. This theory is supported by the fact that 80% of patients in the pMDI cohort were prescribed a pMDI device for ICS during the baseline year, while only 25% of patients in the DPI cohort were prescribed a DPI device at baseline. Therefore, on the index date, less than one fifth of patients in the pMDI cohort had a device switch, whilst three quarters of patients in the DPI cohort had a device switch from a pMDI or a breath-actuated MDI to a DPI for FDC fluticasone—salmeterol therapy.

In addition, patients in the DPI cohort were more likely to have mixed inhaler types for maintenance and reliever therapies during the outcome year and thus could have confused inhaler technique because of switching between devices. Our ability to separate out the role of mixing device types from that of the ICS-LABA device itself was limited by the high correlation (and subsequent collinearity) between ICS-LABA device type used and use of same versus mixed devices for reliever therapy. However, an earlier study looking at the effect of prescribing mixed inhaler types for maintenance and reliever therapies reported a higher percentage of patients making inhaler technique errors where pMDI and DPI devices were used in combination as compared with use of two different DPI devices.[34]

Another possibility, purely speculative, is that the additional benefit of the bronchodilator in the combination might have helped patients who made mistakes with their ICS monotherapy pMDI to recognise their coordination issues, and this helped them to improve their inhalation technique with the FDC pMDI. In theory, of course, the presence of the bronchodilator would also help patients to self-train with a DPI, although their ability to generate the correct inspiratory acceleration and velocity with a DPI would remain a limiting factor.

Other possible explanations for the differences between cohorts seem less likely. While the index date ICS dose was higher in the pMDI cohort, the average ICS dose during the outcome year was similar in the two cohorts; moreover, adjusting for index ICS dose did not significantly affect outcomes. Better adherence in the pMDI cohort can be ruled out as a possibility because, in fact, adherence was worse in the pMDI than the DPI cohort. Overall, approximately half of patients showed <50% adherence. Poor levels of adherence with asthma maintenance therapy have been recorded in all real-world studies on this topic.[35–39]

The apparent superiority of pMDI in producing better asthma control with FDC fluticasone–salmeterol was an unexpected finding. In a prior, similarly designed cohort study, we found that DPIs were consistently more effective than pMDIs for patients initiating ICS monotherapy.[22] It is possible that, in the present study, the LABA in the pMDI drove better technique or the effects of device mixing were more prominent. Randomised trials comparing pMDIs and DPIs for FDC fluticasone–salmeterol report similar outcomes with the two types of inhaler device.[12–14] The differences between cohorts in the present study, while statistically significant, were not large, as reflected in the relatively low odds ratios. In cross-sectional observational studies of inhaler technique, no clear pattern emerges: patients assessed in the clinic make mistakes of different types and to varying degrees with both pMDIs and DPIs.[9,19,40–44]

The use of a large database has enabled us to study real-world outcomes with asthma inhaler devices in a representative UK primary care population. We studied outcomes over a full year to balance seasonal influences on outcome measures. A major limitation of this study, inherent to observational studies, is the possibility of unrecognised confounding factors or influences on prescribing that we have not accounted for, e.g., inhaler technique, and, as for any retrospective study, the analyses are susceptible to bias. While the GPRD is a well-validated and well-maintained database, we cannot rule out the possibility of inaccurate or missing data. Moreover, study analyses are based on recorded prescriptions for FDC salmeterol–fluticasone; we cannot be certain that medications were actually dispensed or taken as prescribed. Finally, only one type of DPI was evaluated in this study; thus, our findings apply to the pMDI-Accuhaler comparison and may not be applicable to other types of DPI.

Conclusions

In this retrospective database analysis, asthma control and treatment success were significantly more likely for primary care patients who were prescribed a pMDI rather than a DPI device for a fixed-dose combination of fluticasone–salmeterol. Exacerbations were less frequent in the pMDI cohort but not statistically different between cohorts. For real-world ICS-LABA FDC therapy in the UK, pMDIs appear to achieve better asthma control outcomes than DPIs for delivery of FDC fluticasone–salmeterol. Despite careful matching and adjustments, an effect of confounding factors such as baseline severity cannot be ruled out. Therefore, pragmatic trials are required to investigate real-world outcomes with different inhaler devices for combination therapy. In addition, further work remains to investigate the effects of device mixing and practice preferences on inhaler technique and asthma-related outcomes.

Conflict of interest

D.P. has consultant arrangements with Boehringer Ingelheim, GlaxoSmithKline, Merck, Mundipharma, Novartis, and Teva. He or his research team have received grants and support for research in respiratory disease from the following organisations in the last 5 years: UK National Health Service, Aerocrine, AstraZeneca, Boehringer Ingelheim, GlaxoSmithKline, Merck, Mundipharma, Novartis, Nycomed, Pfizer, and Teva. He has spoken for AstraZeneca, Boehringer Ingelheim, Chiesi, GlaxoSmithKline, Merck, Mundipharma, Pfizer, and Teva. He has shares in AKL Ltd which produces phytopharmaceuticals. He is the sole owner of Research in Real Life Ltd.

N.R. has received fees for attending scientific meetings, speaking, educational activities, organizing research or consulting from Almirall, AstraZeneca, Boehringer Ingelheim, Chiesi, GlaxoSmithKline, Hoffman la Roche, Mundipharma, MEDA, Novartis, Nycomed/Altana, Pfizer, and Teva.

J.C.V. has lectured for and received honoraria from Asche-Chiesi, AstraZeneca, Avontec, Bayer, Bencard, Bionorica, Boehringer Ingelheim, Essex/Schering-Plough, GSK, Janssen-Cilag, Leti, MEDA, Merck, MSD, Mundipharma, Novartis, Nycomed/Altana, Pfizer, Revotar, Sandoz-Hexal, Stallergens, Teva, UCB/Schwarz-Pharma, and Zydus/Cadila. He has served on advisory boards for Asche-Chiesi, Avontec, Boehringer Ingelheim, Essex/Schering-Plough, GSK, Janssen-Cilag, MSD, Mundipharma, Novartis, Revotar, Sandoz-Hexal, and UCB/Schwarz-Pharma and has received research funding from GSK and Merck/MSD.

A.B., M.A., A.C., and J.vZ. are employees of Research in Real Life and have no conflicts of interest to declare.

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Supplementary material

Supplementary data associated with this article can be found, in the online version, at doi:10.1016/j.rmed.2011.04.010.

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