ORIGINAL RESEARCH

Cost saving of switching to equivalent inhalers and its effect on health outcomes

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ABSTRACT

Background Switching inhalers to cheaper equivalent products is often advocated as a necessary cost saving measure, yet the impact on patient's health and healthcare utilisation has not been measured.

Methods We identified asthma and chronic obstructive pulmonary disease (COPD) patients from UK primary care electronic healthcare records between 2000 and 2016. A self-controlled case series was used to estimate incidence rate ratios (IRR); comparing outcome rates during the risk period, 3 months after the exposure (financially motivated switch), and control periods (preswitch and postrisk period). Four outcomes were assessed: disease exacerbation, general practitioner consultation, non-specific respiratory events and adverse-medication events. Medication possession ratio (MPR) was calculated to assess adherence. 2017 National Health Service indicative prices were used to estimate cost differences per equivalent dose.

Results We identified a cohort of 569 901 asthma and 171 231 COPD regular inhaler users, 2% and 6% had been switched, respectively. Inhaler switches between a brand-to-generic inhaler, and all other switches (brand-to-brand, generic-to-generic, generic-to-brand), were associated with reduced exacerbations (brand-to-generic: IRR=0.75, 95% CI 0.64 to 0.88; all other: IRR=0.79, 95% CI 0.71 to 0.88). Gender, age, therapeutic class, inhaler device and inhaler-technique checks did not significantly modify this association (p<0.05). The rate of consultations, respiratory-events and adverse-medication events did not change significantly (consultations: IRR=1.00, 95% CI 0.99 to 1.01; respiratory-events: IRR=0.96, 95% CI 0.95 to 0.97; adverse-medication-events: IRR=1.05, 95% CI 0.96 to 1.15). Adherence significantly increased post-switch (median MPR: pre-switch=54%, post-switch=62%; p<0.001). Switching patients, in the cohort of regular inhaler users, to the cheapest equivalent inhaler, could have saved around £6 million annually.

Conclusion Switching to an equivalent inhaler in patients with asthma or COPD appeared safe and did not negatively affect patient's health or healthcare utilisation.

Key messages

What is the key question?

► Physicians and patients alike are often reticent to switch to an equivalent inhaler to reduce National Health Service (NHS) costs, but it is a commonly encouraged local policy in the UK due to increasing NHS financial pressures; what is the impact of such a policy on patients' health (exacerbations and symptoms) and healthcare utilisation (general practitioner (GP) consultations)?

What is the bottom line?

► The findings from this real-world study support the cost-saving clinical practice of switching to cheaper equivalent inhalers.

Why read on?

► This study assessed four different health outcomes (exacerbations, GP consultations, non-specific respiratory events and adverse-medication events), and multiple factors (eg, inhaler device, inhaler-technique checks) that could influence the impact of this clinical practice.

INTRODUCTION

In the UK, over 5.4 million people receive asthma treatment (estimated in 2012), and over 1.2 million people have a chronic obstructive pulmonary disease (COPD) diagnosis.[1 2] Inhalers incur a large healthcare cost; due to the prevalence of asthma, three of the top five most expensive drugs in the National Health Service (NHS) budget are inhalers. Over £1.1 billion of the NHS budget is spent directly on asthma, the majority of which is due to medication; an additional £800 million is spent directly on COPD.

Pharmaceutical companies have made huge investments in the development of new inhaled medications, resulting in the availability of over 200 different products; expiration of many patents have led to the growth of generic products. Nonetheless, markets become dominated by only a few inhalers, even when cheaper equivalent products are available. Randomised controlled trials have demonstrated that switching inhalers between specified equivalent products results in comparable effectiveness.[3 4] However, trials have optimised participant's inhaler technique and encouraged high levels of adherence, which does not reflect everyday clinical practice and most respiratory patients do not meet typical trial eligibility criteria.[5 6] There is a paucity of real-world studies assessing health outcomes after switching patients to an equivalent inhaler, furthermore, no study has specifically addressed switching for financial gain.[7–11]

In many European countries regulations allow switching of inhalers to cheaper bioequivalent

products, generic or branded, including UK, Germany, Italy, Finland and Netherlands; other countries, including Spain, Belgium and Sweden, regulate against it due to the speculated negative impact on patient's health and healthcare utilisation.[12] In the UK, many local governments strongly advocate switching to cheaper equivalent inhalers, but the effect of this clinical practice on patient's health and their healthcare use is unknown. Physician opinion appears often to be one of reticence, primarily due to apprehension of the interchangeability of inhalers, although the evidence to support this concern is marginal.[13–18] This study aimed to describe the prevalence and health impact of financially motivated inhaler switching, for non-clinical motivation, in the UK and the subsequent health impact.

METHODS

Data source

We used the Clinical Practice Research Database (CPRD), a nationally representative database of de-identified electronic healthcare records. CPRD holds data on diagnoses, symptoms, and prescriptions on more than 11 million patients across the UK.[19] Globally, it is one of the largest longitudinal healthcare databases, and has been extensively validated.[19] Secondary care and mortality information was obtained from the Hospital Episode Statistics (HES) database and Office of National Statistics (ONS), respectively. HES contains information on all admissions to English NHS hospitals. Approximately 60% of practices in CPRD have individual level linkage to HES and ONS, and to socioeconomic data (Index of Multiple Deprivation).

Study design

We conducted a self-controlled case series (SCCS) analyses (figure 1). SSCS is an increasingly popular study design,[20–22] it allows each individual to act as their own control (comparing outcome rates during periods of exposure to periods of non-exposure) to therefore implicitly control for confounding factors that do not vary with time. This approach significantly reduces the bias that can occur in observational studies; for example, a cohort or case-control could suffer from confounding by indication which would be an issue with this research question. SCCS is also statistically more efficient than traditional cohort and case-control designs. The SCCS method is the most suitable when there are acute outcomes (eg, exacerbation) and transient exposures (eg, inhaler switch), and that exact timings of these are available.[23] Incidence rate ratios (IRR) are calculated, comparing the rate of events during exposed periods (defined as the 'risk period') with that during all other observed periods (defined as the 'control period'). To ensure valid and unbiased estimates, certain assumptions should be met.[24] First, the outcome should not affect the occurrence of a further outcome event. As exacerbations are not independent, we studied only the first exacerbation outcome[24]; therefore, all patients had to have a 12-month exacerbation-free period before entering the SCCS-exacerbation cohort (prior to the control period). The other outcomes were considered to be independent. A second assumption is that the outcome does not affect the probability of exposure. This potential bias is common and simply reduced by using a pre-exposure period that is then not included in the analysis.[24] Third, the outcome should not increase the probability of death; the typical approach to deal with this is to carry out a sensitivity analysis excluding patients that died.[24]

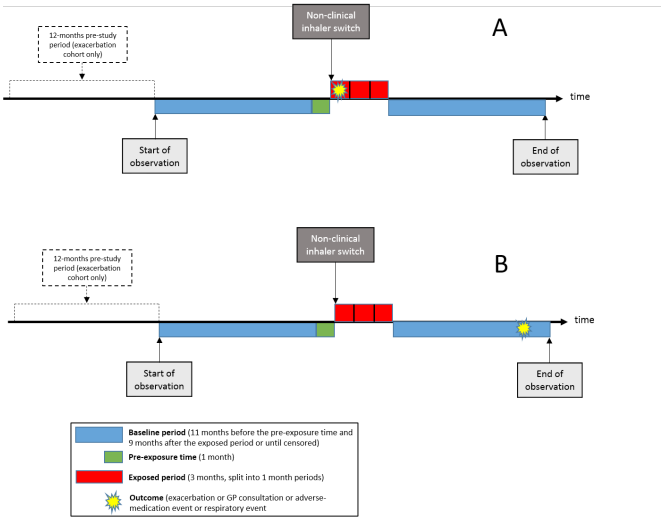

Figure 1 Pictogram (A) represents a patient that exacerbated during the 3-month risk period after their inhaler switch. Pictogram (B) represents a patient that exacerbated during the control period. The study assessed the relative incidence of the outcome during the risk period as compared with the control period.

Study population

Patients were identified as having asthma or COPD using validated algorithms.[25 26]

Study population: regular inhaler users

Only patients that were on a regular maintenance inhaler were included; this was defined as ≥3 consecutive prescriptions of the same inhaler class, each within 3 months of the next one. Maintenance inhaler classes were inhaled corticosteroid (ICS), long-acting beta agonist (LABA), combination LABA-ICS, long-acting muscarinic antagonist (LAMA), or combination LAMA-LABA. Prescription data were included from the latest date of the following: 1 January 2000, patient's data were research acceptable (CPRD quality control), patient started a continuous CPRD record, 18th birthday (asthma) or 35th birthday (COPD), or first validated asthma/COPD read code. Follow-up was censored at the earliest date of the following: patient transferred out of CPRD, death, last data collection date, or 31 December 2016.

Main exposure and the four outcomes

Financially motivated inhaler switch (main exposure)

An inhaler switch was defined as at least three consecutive prescriptions of the same inhaler, followed by a subsequent prescription of a different inhaler, in the same therapeutic class, each within 3 months of the previous. For the switch to be defined as financially motivated it must be (1) between the same bioequivalent dosage, (2) occurred on a day without a respiratory symptom or adverse-medication symptom/event and (3) not on the day of another new inhaler. Switches were further broken down into those between brand-to-generic inhaler (financial motivation was the only objective), all other switches (financial motivation was highly likely). Three months use was arbitrarily defined as the time point by which the switch itself would have impacted on the patient's health as it expected the effect of the 'switch' would be reasonably immediate. This was also further broken down by 1-monthly periods to look for any dose affect over time.

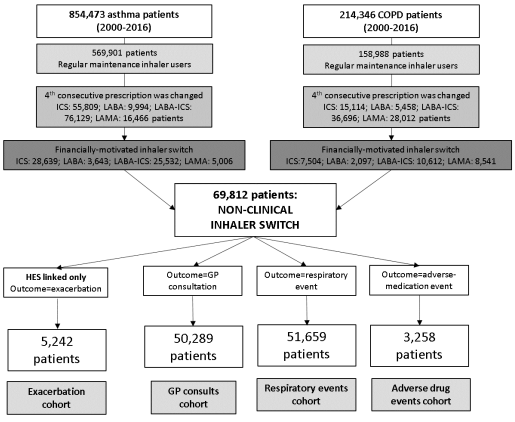

Figure 2 Consort diagram of study inclusion and exclusion.

Outcomes

The main outcome of interest was exacerbations. COPD exacerbations were identified using a validated algorithm for CPRD data.[27 28] Asthma exacerbations were identified as previously defined,[29] a short course of oral corticosteroids, a hospital admission for asthma or death secondary to asthma. The other three outcomes were primary care consultations, non-specific respiratory events (including respiratory symptoms, inhaler technique, and other asthma and COPD specific events; online supplementary table 1), and adverse-medication events (online supplementary table 2).

Populations used in the SCCS-cohorts

The SCCS analysis requires that each included patient should have the outcome (at some point during either the risk or control period), and the exposure—as those without both would not contribute towards the rate ratio estimate (patient exposed but without an outcome would have a rate of zero in all time periods); therefore, four different cohorts were identified for the four different outcomes described above (figure 2). The SCCS cohorts were: (1) exacerbations, (2) general practitioner (GP) consultations, (3) non-specific respiratory events and (4) adverse-medication events. Study follow-up was a maximum of 2 years. All patients entered the SCCS analysis 12 months before the non-clinical inhaler switch, and were censored at the earliest date of: 12 months after the inhaler switch, death, transferred out of CPRD, or last data collection. The exacerbation SCCS-cohort only comprised of patients with linked HES/ONS data (to ensure inclusion of hospital treated exacerbations).

Measuring adherence

Adherence was calculated using the medication possession ratio (MPR); the sum of the days medication was prescribed, divided by the total number of days between the first and the last prescription plus the duration of the last prescription; this number is then expressed as a percentage. MPR was compared between preswitch (12 months before the switch) and postswitch (from the switch until follow-up ended).

Statistical and sensitivity analyses

Event rates were compared during the risk period (for 3 months after exposure) and the control periods (11 months before the pre-exposure 1-month period, and from the end of the risk period until censored) (figure 1). IRRs were also measured for each consecutive 1-month period during the 3-month risk period. The exacerbation analysis was stratified by the type of inhaler that was switched between; switches from a branded to a generic inhaler were analysed separately, as these should only be carried out for financial gain. Other scenarios (switches between: generic to branded, branded to branded, or generic to generic) were analysed separately as it is possible some of these switches may have been carried out for an undocumented clinical reason. IRRs were estimated using fixed effects conditional Poisson regression models. The effect was adjusted for age using age bands (years: 18–45, 45–55, 55–65, 65–75, 75–85, 85–110). Evidence of interaction was assessed using likelihood ratio tests for several time-invariant variables: respiratory condition, gender, therapeutic class, generic/brand switch, device switch, kept/not kept on same inhaler. The effects were reported by stratifying the analysis for each variable. A negative control analysis was also carried out, such that the 'exposure' date was a random consecutive inhaler prescription; patients also had to fulfil all eligibility criteria of the SCCS cohort. Stata V.14.0 was used for all analysis.

Cost analysis of switching inhalers

Inhaler prices were obtained using 2017 NHS indicative prices from the NHS Dictionary of Medicines and Devices (dm +d). All costs were calculated per bioequivalent medication dose. Assumptions about how many inhalers could be switched to generic inhalers used NHS product availability in 2017. Cost differences were based on the inhaler cost only.

Ethical approval

Linked pseudonymised data were provided for this study by CPRD. Data are linked by NHS Digital, the statutory trusted third party for linking data, using identifiable data held only by NHS Digital. Select practices consent to this process at a practice level with individual patients having the right to opt-out.

RESULTS

Temporal changes in UK generic and device prescriptions

There has been a fall in the proportion of generic prescriptions for all therapeutic classes in asthma and COPD; most notable in ICS prescriptions (online supplementary figure 1). The proportion of dry powder inhaler (DPI) used in asthma dropped from 50% in 2000 to 30% in 2016, but remained around 50% in COPD (online supplementary figure 2).

Low prevalence of inhaler switching

Over the last decade the proportion of patient's that had their inhalers switched within the same therapeutic class was low, although it slightly increased over time (2006–2016: asthma N=5 69 901, 2%–6% switched; COPD N=171 321, 3%–10% switched) (online supplementary figure 3). Around two-thirds of switches were for non-clinical reasons, the majority were between branded and generic products, and around one-third were for increases in medication dose or adverse-medication effects. Inhaler switching peaks were in 2001 (Becotide, a phased-out ICS), 2007/2008 (chlorofluorocarbons, phased out MDIs), and 2014 onwards (LAMA and combination LABA-ICS inhalers).

SCCS-cohorts were similar to the regular inhaler users

Of those with a non-clinical inhaler switch, 5242 patients met eligibility criteria for the exacerbation SCCS-cohort, 50 289

Table 1 Description of the demographics and characteristics of each of the SCCS cohorts, and the study population of patients that they were drawn from

	Exacerbation cohort		All non-clinical switchers HES linked		Non-urgent GP consults cohort		Respiratory events cohort		Adverse inhaler events cohort		All non-clinical switchers	
	N	%	N	%	N	%	N	%	N	%	N	%
Total	5242	100	23488	100	50289	100	51659	100	3258	100	69812	100
Patient characteristics												
Respiratory condition												
Asthma	4232	80.7	18185	77.4	43653	86.8	45318	87.7	2821	86.6	59909	85.8
COPD	1010	19.3	5303	22.6	6636	13.2	6341	12.3	437	13.4	9903	14.2
Gender												
Male	2377	45.3	10663	45.4	21613	43.0	21848	42.3	1190	36.5	29925	42.9
Female	2865	54.7	12825	54.6	28676	57.0	29811	57.7	2068	63.5	39887	57.1
Age at switch, years (median, IQR)	68.2 (58–76)		69.6 (62–77)		63.6 (50–73)		63.4 (50–73)		67.0 (57–75)		62.7 (49–73)	
Socioeconomic status												
1 (least deprived)	597	11.4	2663	11.3	3829	13.6	3733	13.3	177	10.2	5085	13.5
2	1018	19.4	4557	19.4	5010	17.8	5184	18.5	372	21.4	7114	18.9
3	1011	19.3	4689	20.0	5292	18.8	5217	18.6	268	15.4	7245	19.2
4	1147	21.9	4998	21.3	5813	20.7	5957	21.2	356	20.4	7751	20.5
5	1469	28.0	6581	28.0	8158	29.0	7987	28.4	569	32.7	10544	27.9
Smoking												
Never	1281	24.4	6104	26.0	10923	21.7	11860	23.0	686	21.1	16264	23.3
Ex-smoker	2678	51.1	5916	25.2	14382	28.6	14219	27.5	884	27.1	19288	27.6
Current	1283	24.5	11468	48.8	24984	49.7	25580	49.5	1688	51.8	34260	49.1
COPD, inhaler use preswitch												
ICS alone	119	11.8	764	14.4	822	12.4	748	11.8	41	9.4	1291	13.0
LABA alone	23	2.3	91	1.7	117	1.8	103	1.6	3	0.7	180	1.8
LAMA alone	63	6.2	481	9.1	537	8.1	515	8.1	23	5.3	971	9.8
LABA and ICS	219	21.7	1165	22.0	1382	20.8	1296	20.4	90	20.6	2029	20.5
LABA and LAMA	17	1.7	137	2.6	164	2.5	162	2.6	12	2.7	259	2.6
LAMA and ICS	41	4.1	1165	22.0	267	4.0	264	4.2	25	5.7	363	3.7
Triple therapy	528	52.3	2464	46.5	3347	50.4	3253	51.3	243	55.6	4810	48.6
Asthma, inhaler use preswitch												
ICS only	1374	32.5	6466	35.6	16069	36.8	16473	36.3	829	29.4	21847	31.3
ICS and LABA	1710	40.4	6946	38.2	17992	41.2	18997	41.9	1157	41.0	25519	36.6
ICS and LABA and Add on*	1020	24.1	4264	23.4	8615	19.7	8856	19.5	770	27.3	11335	16.2
Non-guideline treatment	128	3.0	509	2.8	977	2.2	992	2.2	65	2.3	1208	1.7
Inhaler technique checked												
Yes	2003	38.2	7867	33.5	19010	37.8	21341	41.3	1369	42.0	25025	35.8
No	3239	61.8	15621	66.5	31279	62.2	30318	58.7	1889	58.0	44787	64.2
Adverse medication events												
Yes	135	2.6	676	2.9	1335	2.7	1567	3.0	1435	44.0	1975	2.8
No	5107	97.4	22812	97.1	48954	97.3	50092	97.0	1823	56.0	67837	97.2

Continued

Table 1 Continued

	Exacerbation cohort		All non-clinical switchers HES linked		Non-urgent GP consults cohort		Respiratory events cohort		Adverse inhaler events cohort		All non-clinical switchers	
Inhaler switch characteristics												
Drug class												
ICS	2164	41.3	9928	42.3	22138	44.0	22624	43.8	1353	41.5	30053	43.0
LABA	377	7.2	1629	6.9	3411	6.8	3189	6.2	225	6.9	4881	7.0
LABA/ICS	1850	35.3	7926	33.7	19244	38.3	20441	39.6	1279	39.3	27118	38.8
LAMA	851	16.2	4005	17.1	5496	10.9	5406	10.5	401	12.3	7760	11.1
Switch between same drug(s)												
No	540	10.3	2413	10.3	6169	12.3	6443	12.5	416	12.8	8731	12.5
Yes	4702	89.7	21075	89.7	44119	87.7	45215	87.5	2841	87.2	61083	87.5
Type												
Brand to generic	1719	32.8	9517	40.5	20411	40.6	20376	39.4	1411	43.3	27111	38.8
Generic to generic	274	5.2	1186	5.0	2590	5.2	2634	5.1	169	5.2	3722	5.3
Generic to brand	2433	46.4	9739	41.5	20626	41.0	21654	41.9	1258	38.6	29086	41.7
Brand to brand	816	15.6	3037	12.9	6662	13.2	6995	13.5	420	12.9	9893	14.2
Device												
MDI to DPI	411	10.1	1973	11.2	3884	10.3	3948	10.2	279	11.0	5170	9.7
DPI to DPI	1418	34.7	7101	40.5	14209	37.6	14291	36.9	890	35.2	20493	38.6
DPI to MDI	601	14.7	2408	13.7	5317	14.1	5529	14.3	348	13.8	7398	13.9
MDI to MDI	1655	40.5	6058	34.5	14381	38.1	15013	38.7	1012	40.0	20058	37.8
Kept new inhaler												
Yes	5015	95.7	22135	94.2	47486	94.4	48795	94.5	3042	93.4	65947	94.5
No	227	4.3	1353	5.8	2803	5.6	2864	5.5	215	6.6	3865	5.5

*Add on therapy included a LAMA, leucotriene receptor antagonist or slow release theophylline.
COPD, chronic obstructive pulmonary disease; DPI, dry powdered inhaler; GP, general practitioner; HES, Hospital Episode Statistics; ICS, inhaled corticosteroid; LABA, long-acting beta agonist; LAMA, long-acting muscarinic antagonist; MDI, metered-dose inhaler; SCCS, self-controlled case series.

for the consultations SCCS-cohort, 51659 for the respiratory events SCCS-cohort and 3258 for the adverse-medication events SCCS-cohort (figure 2). The four SCCS-cohorts were broadly similar in characteristics to the populations they were derived from table 1). The SCCS-cohorts were also similar to the much larger population of regular inhaler users (online supplementary table 3). The SCCS-cohorts were equivalent in terms of inhalers prescribed, frequency of inhaler technique checks (around 40%) and proportion that had experienced adverse-medication events (around 2%) (table 1); except for the adverse-medication events SCCS-cohort, as would be expected.

Most non-clinical inhaler switches occurred with ICS and LABA-ICS. Around 90% were between an identical drug (table 1), approximately three-quarters were between the same device type, and around 80% were between generic and brand. Around 95% of patients kept the inhaler that they were switched to.

Health impact of non-clinical inhaler switching

The IRR of an exacerbation was significantly lower after switching (brand-to-generic: crude IRR=0.74, 95%CI 0.63 to 0.87, age-adjusted IRR=0.75, 95%CI 0.64 to 0.88; all other switches: crude IRR=0.78, 95%CI 0.70 to 0.87, age-adjusted=0.79, 95%CI 0.71 to 0.88). Differences in patient characteristics, or differences in measured factors related to the inhalers, did not significantly modify the rate of exacerbations; these characteristics were differences in patient condition (COPD/asthma), gender, therapeutic class (ICS, LABA-ICS, LABA, LAMA), device switch (MDI/DPI) and inhaler technique check (LRT p>0.05, tables 2 and 3). Exacerbation rates were not significantly different each consecutive month of the 3 months after the inhaler switch (p<0.05, online supplementary tables 4 and 5). A sensitivity analysis excluding patients who died (N=80) showed negligible difference in the IRRs.

There was no significant association between the rate of consultations and switching (age-adjusted IRR=1.00, 95%CI 0.99 to 1.01; table 4). There was a very slight reduction in respiratory events (age-adjusted IRR=0.96, 95%CI 0.94 to 0.97). There was a non-significant minor increase in the risk of adverse events (age-adjusted IRR=1.05, 95%CI 0.96 to 1.15); the risk decreased with each consecutive month, during the 3-month risk period (online supplementary table 6).

The negative control analyses found no effect on exacerbations (age-adjusted IRR=0.99, 95%CI 0.96 to 1.02).

Impact of switching on adherence

Inhaler adherence improved after the inhaler switch. The median MPR (IQR) for the 12 months preinhaler switch was 54.8% (39.1–78.2), compared with 62.6% postinhaler switch (47.0–93.9) (p<0.001). Postinhaler switch adherence was not different between patients that were switched on the day of a GP consultation or not (median MPR=62.6%, p>0.05).

Table 2 Age-adjusted incidence rate ratios (IRR) of exacerbations, in the 3-month risk period after a brand-to-generic inhaler switch, compared with stable periods

	Patients (N)	Exacerbations in risk period	Exacerbations in control period	IRR	95% CI	
3-month risk period	1719	168	1483	0.75	0.64 to 0.88	
Variable association may be modified by	**Patients (N)**	**Exacerbations in risk period**	**Exacerbations in control period**	**IRR**	**95% CI**	**P value**
Disease						0.09
COPD	332	41	332	0.78	0.57 to 1.09	
Asthma	1151	127	1151	0.74	0.61 to 0.89	
Gender						0.22
Male	809	88	693	0.85	0.68 to 1.06	
Female	910	80	790	0.67	0.53 to 0.84	
Medication class switched						0.12
ICS	363	35	314	0.76	0.53 to 1.07	
LABA	182	18	160	0.77	0.47 to 1.27	
LABA-ICS	826	67	722	0.61	0.48 to 0.78	
LAMA	348	48	287	1.10	0.80 to 1.48	
Switch between MDI and DPI						0.61
Yes	311	263	121	0.85	0.60 to 1.22	
No	1239	34	1074	0.75	0.62 to 0.90	
Inhaler check in prior year						0.22
Yes	606	535	117	0.64	0.47 to 0.85	
No	1113	948	51	0.81	0.67 to 0.99	

COPD, chronic obstructive pulmonary disease;DPI, dry powdered inhaler; ICS, inhaled corticosteroid; LABA, long-acting beta agonist; LAMA, long-acting muscarinic antagonist; MDI, metered-dose inhaler.

Potential cost saving of switching to cheaper inhalers

In the exacerbation SCCS cohort, 1184 of the 5242 switches (23%) could have been switched to a cheaper equivalent generic product in 2017. This could have saved an estimated £14 308, or annual saving of around £172 000 (assuming an inhaler prescribed per month) (online supplementary table 7). In the same cohort, 2125 of the 5242 switches (41%) could have been switched to a cheaper bioequivalent branded product (same therapeutic class and bioequivalent dose, although drug may differ). This could have saved £28 231, or annual saving of around £339 000 (online supplementary table 8).

In the total cohort of 665 105 regular inhaler users, there was an alternative cheaper equivalent generic inhaler available for 28% of prescriptions (LABA-ICS or LAMA) in 2016; switching to these could have saved approximately £1.97 million. An estimated additional £4.1 million could have been saved if all inhalers had been switched to the cheapest bioequivalent product (including generic or branded products), assuming all patients were suitable for switching to the alternative.

CPRD represents at least 5% of the UK population, extrapolating our findings indicates that, if implemented across the UK, switching to the cheapest available bioequivalent product (generic or branded), could have saved the NHS approximately £112 million (1.5% of the total primary care annual prescribing costs).

DISCUSSION

Principal findings

From this study of over 0.65 million asthma patients and just under 0.2 million COPD patients, it was observed that inhaler switching for financial-motivation was uncommon; in keeping with the only other nationally representative study of inhaler switching.[7] The increase in switches from generic to branded inhalers is likely due to the increase in the availability of cheaper branded inhalers in the UK; the cheapest LABA-ICS in 2017 was a branded inhaler. We found that switching slightly reduced the risk of an exacerbation. This risk was not significantly affected by the patient's age, gender, type of respiratory disease, whether the switch was between MDI/DPI devices or not, whether the patient had a documented inhaler check that year, or the medication class that was switched. Around 95% of the patients remained on their switched inhaler. Interestingly, adherence to the switched inhaler was significantly higher than adherence to the pre-switch equivalent inhaler. This may partially explain the observed reduction in exacerbations as, although the study was not designed to measure adherence as a primary outcome, the increase was only slightly below the considered clinically minimal important difference of 10%.[30] Further analyses, of over 50 000 patients, showed that non-clinical inhaler switching did not affect the rate of GP consultations, but slightly decreased the rate of non-specific respiratory events (including symptoms) and slightly increased the rate of adverse medication events, however, these effects were not statistically significant. Overall this clinical practice appears to occur infrequently in the UK. The cost analyses estimated significant savings could potentially be gained from switching expensive popular inhalers to bioequivalent cheaper (generic or branded) ones.

A less commonly advocated, but arguably as important, reason to switch an inhaler, is to reduce the large environmental impact that MDI inhalers produce.[31] Hydrofluorocarbon inhalers are estimated to contribute 4% of the NHS's entire carbon footprint, with MDIs identified as a 'carbon hotspot' in the NHS.[32]

Table 3 Age-adjusted incidence rate ratios (IRR) of exacerbations, in the risk period compared with stable periods, after an inhaler switch (brand-to-brand, generic-to-generic or generic-to-brand)

	Patients (N)	Exacerbations in risk period	Exacerbations in control period	IRR	95% CI	
3-month risk period	3523	362	2980	**0.79**	**0.71 to 0.88**	
Variable association may be modified by	**Patients (N)**	**Exacerbations in risk period**	**Exacerbations in control period**	**IRR**	**95% CI**	**P value**
Disease						0.09
COPD	625	55	534	0.64	0.48 to 0.85	
Asthma	2898	307	2446	0.82	0.73 to 0.93	
Gender						0.48
Male	1568	155	1338	0.75	0.63 to 0.89	
Female	1955	207	1642	0.82	0.71 to 0.95	
Medication class switched						0.20
ICS	1801	200	1522	0.87	0.75 to 1.00	
LABA	195	18	170	0.73	0.45 to 1.20	
LABA-ICS	1024	97	860	0.72	0.58 to 0.89	
LAMA	503	47	428	0.70	0.52 to 0.95	
Switch: generic/ branded						0.35
Generic to brand	274	247	2071	0.78	0.68 to 0.89	
Generic to generic	2433	23	236	0.61	0.39 to 0.94	
Brand to brand	816	92	673	0.87	0.70 to 1.09	
Switch between MDI and DPI						0.11
Yes	918	76	786	0.64	0.50 to 0.81	
No	1617	175	1354	0.83	0.71 to 0.97	
Inhaler check in prior year						0.89
Yes	1397	34	276	0.80	0.56 to 1.13	
No	2126	328	2704	0.79	0.70 to 0.88	

COPD, chronic obstructive pulmonary disease;DPI, dry powdered inhaler; ICS, inhaled corticosteroid; LABA, long-acting beta agonist; LAMA, long-acting muscarinic antagonist; MDI, metered-dose inhaler.

Switching from a MDI to a DPI is thought to decrease the carbon footprint by a factor of 18.[31] Discerningly, our observations suggest only around a third of inhalers prescribed for asthma patients, and half of those prescribed for COPD patients, are DPIs; yet switching between MDIs and DPIs did not seemingly impact on exacerbations, adverse medication events or respiratory events.

Comparison to previous studies

There have been few real-world studies addressing switching inhaler therapy of equivalent medication and dose. A small UK asthma study, 1993–2003, looked at ICS switching of 824 patients, at GP practice-level, not individual-level; they found no change in exacerbations.[11] Another UK study, considered 979 asthma patients, switching from any ICS to a particular inhaler, the reason was not reported and may have often been clinical; they found no worsening of clinical outcomes.[8] A more recent observational UK study addressed switching of 382 asthma patients from one commonly used LABA-ICS inhaler to the cheapest one.[10] Although the product drugs differed, the study found a decline in exacerbations, improvement in asthma control, and reduction in healthcare costs; however, the reason for the switches was not described, and due to the design there may have been confounding by indication. One large Dutch study, including 70 053 patients, investigated adherence to inhaler medication after switching to generic products; this study found an increase in adherence in patients switched between a branded to a generic inhaler.[7] Our findings in respect to adherence levels are also in keeping with previous studies.[7 33] Evidence is even sparser for COPD patients,[15] with only a small retrospective

Table 4 The incidence rate ratios (IRR) of general practitioner (GP) consultations, respiratory events, and adverse-medication events, in the risk period after an inhaler switch compared with stable periods

Event	Number of patients	Number of events in 3-month risk period	Number of events in control period	IRR	95% CI
GP consultation	50 289	143 602	926 991	1.00	0.99 to 1.01
Non-specific respiratory	51 659	27 772	187 618	0.96	0.94 to 0.97
Adverse-medication	3258	573	3520	1.06	0.97 to 1.15

Switches could be between brand-to-generic, brand-to-brand, generic-to-generic or generic-to-brand.
DPI, dry powdered inhaler; MDI, metered-dose inhaler.

Japanese observational study of 57 patients that had switched between specific LAMA inhalers.[9] None of these studies comprehensively addressed the overall impact of non-clinical inhaler switching, nor directly examined the impact of switching from a branded to a generic inhaler.

Strengths and weaknesses of the study

One advantage was the use of real-world data; whereas in most trials, inhaler technique is optimised, and adherence is encouraged. The SCCS cohorts were similar to the large nationally representative population that they were drawn from. Therefore, these two features provide results likely to be generalisable to the UK, and other similar populations. However, it is also probable that most patients were only switched if deemed appropriate by their GP practice, therefore, these results would only be generalisable to such patients. Switching may also have led to improved adherence and/or inhaler technique if the GP practice or patient's pharmacist provided education at the time of the switch.

Another advantage was that the SCCS design is less prone to confounding and statistically more efficient than traditional cohort designs. To prevent violation of the SCCS assumptions, in the exacerbation cohort alone, an eligibility criterion of a 12-month period of no exacerbations prior to the observation period was set. This could have reduced generalisability (as a patient must have 1-year exacerbation-free period), but, the SCCS-exacerbation cohort was very similar to the reference population and analyses with the three other outcomes, which did not have this eligibility stipulation, showed comparable findings. It's also possible that the effect of inhaler switching had a shorter or more prolonged affect than 3 months, however, this would only have underestimated the relative risk. Although the prescription data quality was high, we did not know if the prescription was dispensed or taken. However, a very low proportion did not stay on the switched prescription (suggesting the medication was dispensed). The respiratory and adverse-medication events measured were only those that were recorded, potentially some were not. If such under recording was equally likely throughout follow-up, this would only lead to reduced power, rather than generating a biassed estimate. Mild exacerbations were not included as an outcome as identifying these from the data would not have been accurate. However, the assessment of symptom changes, should have identified milder clinical effects. The potential cost savings, depended on the assumption that all patients were suitable; but, we recognise this is unlikely as not all inhaler devices suit everyone. The cost analysis did not take into account savings from reductions in exacerbations. Since 2016 it is possible switching prevalence has changed, although this would not affect the effect estimates from switching.

Implications of these findings

Treatment with combination inhalers is increasing; as these are some of the most expensive products, this will continue the escalation in respiratory spending. Our findings suggest that financially driven inhaler switching occurs infrequently. This is likely due to physician reticence, related to concern that switching is detrimental to a patient's health. This apprehension has been discussed in several reviews, and questionnaires found that doctors across Europe believe that inhalers are not interchangeable.[12–18 34–36] Reassuringly, we have shown here, that exacerbations, respiratory symptoms, and adverse-medication events did not increase; in fact, only 5% of patients did not stay on their new inhaler. We propose that the temporary decrease in exacerbations could be related to a temporary increase in inhaler adherence, due to intensified medication awareness or related to adherence discussion at the time of the inhaler switch. There may have been, predictable or unpredictable, reasons why inhaler switching was successful in these patients, but the parameters we were able to consider did not reveal any influencing characteristics. Further studies are therefore needed to determine the factors that will ensure a successful outcome, and which patients and circumstances are not suitable.

These findings have important implications and could help inform national policy; they suggest that switching inhalers is safe, if implemented correctly (which should include appropriate patient selection and mandating the importance of providing inhaler education), and could help to redirect the respiratory healthcare budget towards more effective use.

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