

Original Article

Inhaler Errors in the CRITIKAL Study: Type, Frequency, and Association with Asthma Outcomes

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What is already known about this topic? The literature highlights the problem of poor inhaler technique, but to date no study has identified inhaler errors associated with poor outcomes.

How does this article add to our knowledge? Specific inhaler errors, while using either a Diskus or Turbohaler dry-powder inhaler or a metered-dose inhaler, have been identified by their frequency and their adverse impact on asthma outcomes.

How does this study impact current management guidelines? This study provides information on the key errors made when using inhalers. These errors may be targeted in asthma management, to improve inhaler training and potentially improve patient outcomes.

BACKGROUND: Poor inhaler technique has been linked to poor asthma outcomes. Training can reduce the number of inhaler errors, but it is unknown which errors have the greatest impact on asthma outcomes.

OBJECTIVE: The CRITICAL Inhaler mistakes and Asthma control study investigated the association between specific inhaler errors and asthma outcomes.

METHODS: This analysis used data from the iHARP asthma review service—a multicenter cross-sectional study of adults with asthma. The review took place between 2011 and 2014 and captured data from more than 5000 patients on demographic characteristics, asthma symptoms, and inhaler errors observed by purposefully trained health care professionals. People with asthma receiving a fixed-dose combination treatment with inhaled

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corticosteroids and long-acting beta agonist were categorized by the controller inhaler device they used—dry-powder inhalers or metered-dose inhalers: inhaler errors were analyzed within device cohorts. Error frequency, asthma symptom control, and exacerbation rate were analyzed to identify critical errors.

RESULTS: This report contains data from 3660 patients. Insufficient inspiratory effort was common (made by 32%-38% of dry-powder inhaler users) and was associated with uncontrolled asthma (adjusted odds ratios [95% CI], 1.30 [1.08-1.57] and 1.56 [1.17-2.07] in those using Turbohaler and Diskus devices, respectively) and increased exacerbation rate. In metered-dose inhaler users, actuation before inhalation (24.9% of

patients) was associated with uncontrolled asthma (1.55 [1.11-2.16]). Several more generic and device-specific errors were also identified as critical.

CONCLUSIONS: Specific inhaler errors have been identified as critical errors, evidenced by frequency and association with asthma outcomes. Asthma management should target inhaler training to reduce key critical errors. © 2017 American Academy of Allergy, Asthma & Immunology (J Allergy Clin Immunol Pract 2017;■:■-■)

Key words: Inhaler errors; Inhaler technique; Asthma control; Exacerbation

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Abbreviations used*CRITIKAL- CRITical Inhaler mistaKes and Asthma controL**DPI- dry-powder inhaler**iHARP- initiative Helping Asthma in Real-life Patients**MDI- metered-dose inhaler**OR- odds ratio**RR- rate ratio*

Management of asthma is aimed at reducing the risk of exacerbations and controlling symptoms.¹ The effectiveness of treatment may be impaired when inhaler devices are not used correctly. This may lead to poorly controlled asthma, which can reduce quality of life, limit daytime activity, and cause nighttime wakening.^{2,3}

Many studies have shown that errors in inhaler technique are frequent⁴⁻⁹—occurring in both of the main types of inhaler devices: dry-powder inhalers (DPIs) and metered-dose inhalers (MDIs). The link between the occurrence of errors and poor asthma outcomes has been demonstrated,¹⁰⁻¹⁴ and may lead to unnecessary costs to the health care system.¹⁵ Specific types of error may be driving these associations: however, although studies have investigated the impact of poor inhaler technique in general, or the impact of the number of inhaler errors, no study has yet investigated the relative impact of individual inhaler errors on asthma outcomes.

Identifying which specific errors are detrimental could lead to improved outcomes: studies have shown that errors can be corrected/reduced with increased training.^{8,12,16,17} A challenge of patient training is that it relies on the ability of the clinician to teach inhaler technique and to recognize patient errors when they occur. Categorizing critical errors could be the optimal strategy for improving asthma outcomes by facilitating recognition and rectification of these errors.

The objective of the CRITical Inhaler mistaKes and Asthma controL (CRITIKAL) study was to investigate direct relationships between specific inhaler errors and asthma outcomes—including asthma symptom control and exacerbation rate—in both DPIs and MDIs, and to determine the critical errors for each inhaler type.

METHODS**Data source and permissions**

This study, labeled the CRITIKAL study, used data from the iHARP (initiative Helping Asthma in Real-life Patients¹⁸) database—an asthma review service supported by the Respiratory Effectiveness Group.¹⁹ iHARP collected data prospectively between June 2011 and December 2014 in participating primary care practices in Australia and 7 European countries (United Kingdom, Italy, Spain, the Netherlands, France, Norway, and Sweden). Each of these practices received an identical iHARP asthma review service. Patients were included if they had a diagnosis of asthma, and excluded if they had a diagnosis of chronic obstructive pulmonary disease or any other chronic respiratory disease other than asthma. The iHARP review used questionnaire-led and practitioner-led assessments to collect extensive information about the patients' demographic characteristics, asthma symptoms, lung function, inhaler technique, and occurrence of exacerbations. The iHARP database collected anonymized data from more than 5000 patients with asthma.

Practices participating in the iHARP asthma review obtained ethics approval according to the requirements specific to their country and gave permission for their anonymized data to be used for research purposes. Permission to link UK data to electronic medical records was obtained from the Health Research Authority for clinical research use (REC reference 15/EM/0150). The iHARP database is governed by the Anonymous Data Ethics Protocols and Transparency committee, an independent body of experts and regulators commissioned by the Respiratory Effectiveness Group¹⁹ to govern the standard of research conducted on internationally renowned databases. The Anonymous Data Ethics Protocols and Transparency committee gave approval for the CRITIKAL study to use iHARP data. Individual ethics approvals were granted in most countries. The CRITIKAL study was registered with the European Network of Centers for Pharmacoepidemiology and Pharmacovigilance²⁰ (as ENCePP/SDPP/9651).

Study design and cohorts

The CRITIKAL study was a cross-sectional, observational analysis using data collected for the iHARP asthma review. Patients were allocated to device cohorts, according to which inhaler device they were using for their controller/preventer medication, that is, a specific type of DPI or MDI. Analyses were then carried out within device cohorts.

Inclusion and exclusion criteria

Patients were included in the analysis if all the following criteria were met: they were 16 years or older at the date of their iHARP review; they were receiving combined asthma therapy as fixed-dose combination with inhaled corticosteroids and long-acting beta agonist via a DPI or MDI (evidenced by at least 1 prescription in the year before their iHARP review); and their iHARP review contained all study-relevant data and met standards of the International Primary Care Respiratory Group,²¹ Global Initiative for Asthma guidelines,²² and Quality and Outcomes Framework²³ recommendations.

Patients were excluded from the study if they had received oral corticosteroids and/or antibiotics for a lower respiratory tract condition in the 2 weeks preceding their iHARP review, or they had received long-term systemic treatments for asthma, including maintenance, theophylline, leukotriene receptor antagonist, or anti-IgE therapy. These exclusions were specified to minimize any potential confounding by additional medications.

All types of device were considered for inclusion, but were included in the analysis only if the total number of patients using that device met the sample size requirement for a single device cohort. Details of the power calculation and sample size requirements are given in the Statistical Analysis section.

Record of inhaler errors

In the iHARP review, inhaler technique was assessed and number and type of inhaler error were recorded for each inhaler device against predefined checklists. Technique was assessed by purposefully trained medical professionals. Observation of errors was standardized as much as possible by having assessors watch dedicated inhaler videos for the relevant device types, as part of their training. The final list of potential errors for each device was provided by clinical experts in the steering committee, after grouping similar errors from original lists (see [Tables E1-E3](#) in this article's Online Repository at www.jaci-inpractice.org).

Outcome measures

The primary outcome measure for this study was asthma symptom control. Patients were categorized into the following 3 categories: controlled, partly controlled, and uncontrolled. These categories were defined according to Global Initiative for Asthma guidelines (Global Initiative for Asthma),²² using responses from the iHARP review questionnaire. The questionnaire asked patients if they experienced the following during the previous week:

- Daytime symptoms (more than twice/week)
- Any night waking due to asthma
- Needed reliever inhaler (more than twice/week)
- Any limitation to daytime activity

The presence of these 4 symptoms determined the asthma symptom control category as follows:

- None of above → *controlled*
- 1 or 2 of above → *partly controlled*
- 3 or 4 of above → *uncontrolled*

The primary outcome was estimated as an odds ratio (OR) for the likelihood of being in the uncontrolled asthma category. This OR compared patients who made a specific inhaler error with those who did not make that error.

The secondary outcome measure was a rate ratio (RR) for exacerbations, comparing the number of exacerbations experienced in a fixed period by patients who made a specific inhaler error with the number experienced by patients who did not make that error. The number of exacerbations was taken from the 12-month period preceding the iHARP review and exacerbations were identified by 1 of the following patient-reported events: hospital admission with breathing or chest problems; accident and emergency attendance related to asthma; or an acute course of oral steroids for worsening asthma.

Statistical analysis

Summary statistics of patient characteristics were computed for the total study sample, including demographic variables, inhaler device used, and number of exacerbations in the previous year. These were compared across the 3 categories of asthma symptom control using chi-square tests. Frequency of inhaler errors was computed. Correlations between errors of the same device were investigated using Spearman rank correlation coefficient.

The primary analysis used ordinal logistic regression to examine the association between specific types of inhaler error and uncontrolled asthma. The ORs represented the odds of patients being in the uncontrolled category, over the partly controlled and controlled categories. Univariable models (with a single error only) were fitted for each type of error, within device cohorts. For errors that were significant at this stage, multivariable models were fitted. The first multivariable model included all errors that were significant in the univariable case. The second multivariable model added relevant patient factors to the previous multivariable model. Final models were arrived at following a backwards elimination procedure, where the full model was fitted and then nonsignificant variables removed one by one. A list of the variables in the iHARP database that were investigated as potential confounders in the multivariable models can be found in the [Methods](#) section in this article's Online Repository at www.jaci-inpractice.org. Poisson regression models were fitted for the secondary analyses, to estimate exacerbation RRs for the important inhaler errors identified in primary analyses.

Sensitivity analyses were carried out in which the above models were further adjusted by patient adherence. This is a potential confounder when comparing asthma outcomes because poor outcomes may be an indication of poor adherence to treatment. Patient adherence was recorded in the iHARP database using the Medication Adherence Rating Scale,²⁴ and in this case was categorized into the following groups: poor, borderline, and good (more details can be found in the [Methods](#) section in this article's Online Repository). This variable was not used as adjustment in the main analysis because it may not be a strong measure of adherence.²⁵

The level of statistical significance was set at 5% (ie, $P < .05$). A power calculation was carried out to determine the number of patients required to detect an OR of 1.25 in the main analysis (more details in the [Methods](#) section in this article's Online Repository). If individual device cohorts did not meet the sample size requirement to achieve 80% power, they were not included in the study. All categorization and coding of variables were approved by the steering committee. Analyses were carried out using STATA version 14 (StataCorp, College Station, Texas).

RESULTS

Patients

After applying inclusion and exclusion criteria, 4276 patients with asthma were available for study in the iHARP database. Six device cohorts were formed, on the basis of the type of inhaler device used by patients. Three of these cohorts were excluded from the final study sample because they did not have a sufficient sample size for the main analysis. The excluded device cohorts were Seretide MDI with spacer (Glaxo Wellcome Operations, Ware, UK) ($n = 242$), Fostair MDI (Chiesi Farmaceutici, Parma, Italy) ($n = 304$), and Fostair MDI with spacer ($n = 76$). Hence, the final study sample ($N = 3660$) contained 3 device cohorts: 2 DPI cohorts—Turbohaler-Symbicort (AstraZeneca, Södertälje, Sweden) ($n = 2074$ [49% of total eligible cohort]) and Diskus-Seretide (Glaxo Wellcome Operations) ($n = 826$ [19%])—and 1 MDI cohort—MDI Seretide (Glaxo Wellcome Operations) ($n = 760$ [18%]) (see [Figure E1](#) in this article's Online Repository at www.jaci-inpractice.org).

Most patients were aged 41 to 60 years (46%) and female (60%). Approximately 45% were current or ex-smokers, and 65% had mild or significant rhinitis. Younger age, being female, high body mass index, smoking, rhinitis, and paracetamol use were all significantly associated with a higher proportion of uncontrolled asthma ([Table I](#)). These variables, including paracetamol use, were among those considered as potential confounders in the main analysis. Of the total study sample, approximately 46% had controlled asthma, 34% had partly controlled asthma, and 19% had uncontrolled asthma. There was no significant difference in these proportions across devices.

Type and frequency of inhaler errors

For each type of device, a list of 14 inhaler error types was created ([Tables E1-E3](#)) and the frequencies of each error may be seen in [Table II](#). Errors related to inspiratory effort were frequent in all 3 device cohorts. In the DPI cohorts, the inhalation was insufficiently fast and forceful in 32.1% of patients using Turbohaler and in 38.4% of patients using Diskus. In the MDI cohort, the inspiratory effort was not slow and deep enough in 47.2% of patients. In the Turbohaler cohort, the most frequent errors were "twist errors," made by 49% of patients. These included not holding the inhaler device in the upright position (as is required), and not twisting the base of the device twice

TABLE I. Patient characteristics of total study sample, and their association with asthma symptom control

Demographic factors	Asthma symptom control			Total (N = 3660)	P value*
	Controlled, n = 1690 (46.2%)	Partly controlled, n = 1258 (34.4%)	Uncontrolled, n = 712 (19.4%)		
Age (y), n (%)					<.001
16-24	90 (5.3)	65 (5.2)	59 (8.3)	214 (5.9)	
25-40	292 (17.3)	253 (20.1)	151 (21.2)	696 (19.0)	
41-60	762 (45.1)	583 (46.3)	331 (46.5)	1676 (45.8)	
61+	546 (32.3)	357 (28.4)	171 (24.0)	1074 (29.3)	
Sex, n (%)					<.001
Male	731 (43.3)	461 (36.6)	260 (36.5)	1452 (39.7)	
Female	959 (56.7)	797 (63.4)	452 (63.5)	2208 (60.3)	
BMI†, n (%)					<.001
<18.5	63 (3.7)	52 (4.1)	28 (3.9)	143 (3.9)	
18.5-24.99	484 (28.6)	330 (26.2)	175 (24.6)	989 (27.1)	
25-29.99	670 (39.6)	426 (33.9)	224 (31.5)	1320 (36.2)	
≥30	472 (27.9)	444 (35.3)	281 (39.5)	1197 (32.8)	
Smoking status‡, n (%)					<.001
Nonsmoker	990 (58.6)	644 (51.2)	362 (50.8)	1996 (54.6)	
Current smoker	172 (10.2)	180 (14.3)	129 (18.1)	481 (13.1)	
Ex-smoker	528 (31.2)	432 (34.3)	221 (31.0)	1181 (32.3)	
Rhinitis severity‡, n (%)					<.001
No rhinitis	656 (38.8)	395 (31.4)	180 (25.3)	1231 (35.2)	
Mild rhinitis	604 (35.7)	479 (38.1)	278 (39.0)	1361 (38.9)	
Significant rhinitis	338 (20.0)	329 (26.2)	240 (33.7)	907 (25.9)	
Paracetamol use§, n (%)					<.001
Yes	141 (8.3)	146 (11.6)	117 (16.4)	404 (11.0)	
No	1549 (91.7)	1,112 (88.4)	595 (83.6)	3256 (89.0)	
Inhaler device type, n (%)					.159
Turbohaler-Symbicort	964 (57.0)	727 (57.8)	383 (53.8)	2074 (56.7)	
Diskus-Seretide	391 (23.1)	259 (20.6)	176 (24.7)	826 (22.6)	
MDI-Seretide	335 (19.8)	272 (21.6)	153 (21.5)	760 (20.8)	
Number of exacerbations¶					<.001
0	1399 (82.8)	928 (73.8)	393 (55.2)	2720 (74.3)	
1	188 (11.1)	201 (16.0)	135 (19.0)	524 (14.3)	
2+	98 (5.8)	124 (9.9)	183 (25.7)	405 (11.1)	

BMI, Body mass index.

*P value from chi-square test.

†Variables contained missing observations (161 missing for rhinitis, 11 missing for BMI, and 2 missing for smoking status).

‡Details of rhinitis comorbidity found in the [Methods](#) section in this article's Online Repository.

§Regular or intermittent paracetamol use during the last year.

¶Number of exacerbations recorded during year before iHARP review. Details of exacerbation criteria found in the [Methods](#) section.

(1 time in each direction). An error common to all devices was not having the head tilted with chin up during inhalation: 34.3% of patients made this error in the Turbohaler cohort, 34.6% in the Diskus cohort, and 34.1% in the MDI cohort. Another error common to all 3 cohorts was not breathing out to empty lungs before inhalation (error rate was 26.2% in the Turbohaler cohort, 32.4% in the Diskus cohort, and 25.4% in the MDI cohort).

The total number of errors made by patients varied significantly by device type ($P < .001$). The proportion of patients making no errors was greatest in the Diskus cohort (29.7% vs 19.5% and 13.4% in the Turbohaler and MDI cohorts, respectively), whereas the proportion of patients making 5+ errors was greatest in the MDI cohort (17.2% vs 8.1% and 5.9% in the Turbohaler and Diskus cohorts, respectively; see [Table E4](#) in this article's Online Repository at www.jaci-inpractice.org).

Association with uncontrolled asthma

In unadjusted analysis, many of the inhaler errors were significantly associated with asthma symptom control, that is, were associated with increased odds of being in the uncontrolled asthma category. In the Turbohaler and MDI cohorts, 8 of 14 errors had a significant association, whereas 4 of 14 errors in the Diskus cohort had a significant association ([Table III](#)).

DPI cohorts. For the DPI cohorts, associations that remained significant when all errors were included in the model are presented in [Figure 1](#). Further adjustment was made by the following patient factors: age, sex, body mass index, smoking, rhinitis, and paracetamol use. Other potential confounders, listed in the [Methods](#) section in this article's Online Repository, were found to be unimportant in the final multivariable models. After adjusting for patient factors, “insufficient inspiratory effort” was

TABLE II. Frequency of inhaler errors, by type of inhaler device

Inhaler error/n (%), by inhaler device type (and decreasing order of frequency)					
Turbohaler-Symbicort (n = 2074)		Diskus-Seretide (n = 826)		MDI-Seretide (n = 760)	
Twist errors (Device not held upright, base not twisted until it clicks or turn back to original position)	1012 (48.8)	Insufficient inhalation effort	317 (38.4)	Inspiratory effort not slow and deep	359 (47.2)
Did not have head tilted such that chin is slightly upward	712 (34.3)	Did not have head tilted such that chin is slightly upward	286 (34.6)	Did not have head tilted such that chin is slightly upward	259 (34.1)
Insufficient inspiratory effort	666 (32.1)	Did not breathe out to empty lungs before inhalation	268 (32.4)	Lack of device knowledge, or incorrect second dose preparation, timing, or inhalation	257 (34.7)
Did not breathe out to empty lungs before inhalation	544 (26.2)	No breath-hold following inhalation (or holds breath for <3 s)	204 (24.7)	No breath-hold following inhalation (or holds breath for <3 s)	254 (33.4)
No breath-hold following inhalation (or holds breath for <3 s)	459 (22.1)	Compromised dose after preparation because of holding downward	98 (11.9)	Did not breathe out to empty lungs before inhalation	193 (25.4)
Incorrect second dose preparation, timing, or inhalation	327 (20.8)	Incorrect second dose preparation, timing, or inhalation	44 (6.3)	Actuation did not correspond with inhalation, actuation before inhalation	189 (24.9)
Dose compromised after preparation because of shaking or tipping	71 (3.4)	Did not put inhaler in mouth and seal lips around mouthpiece	39 (4.7)	Did not remove cap or shake device before actuation	144 (19)
Patient had an empty inhaler	57 (2.75)	Exhaled into device before inhalation	38 (4.6)	Exhaled into the inhaler or did not hold inhaler upright	109 (14.3)
After inhalation did not replace cover	55 (2.65)	Did not slide cover fully open	33 (4)	Actuation did not correspond with inhalation, actuation after inhalation	92 (12.1)
Did not put device in mouth and seal lips around mouthpiece	44 (2.1)	Dose compromised after preparation because of shaking or tipping	29 (3.5)	Did not seal lips around the mouthpiece	78 (10.3)
Exhaled into the inhaler before inhalation	36 (1.74)	After inhalation did not replace cover	17 (2.1)	Did not actuate or did not inhale through mouth	30 (3.9)
Patient has expired inhaler	24 (1.16)	Patient had an empty inhaler	16 (1.9)	Patient had an empty inhaler	23 (3)
Did not inhale through mouth	10 (0.5)	Did not inhale through mouth	7 (0.85)	Patient has expired inhaler	11 (1.5)
Did not remove cap	9 (0.43)	Patient has expired inhaler	4 (0.5)	After inhalation did not replace cap	9 (1.2)

TABLE III. Univariable associations between inhaler errors and uncontrolled asthma

Inhaler error	OR (95% CI) for uncontrolled asthma		
	Turbohaler-Symbicort (n = 2074)	Diskus-Seretide (n = 826)	MDI-Seretide (n = 760)
Did not remove cap/slide cover open*	4.17 (1.26-13.7)	1.34 (0.72-2.50)	1.47 (1.05-2.07)
Insufficient inspiratory effort†	1.34 (1.12-1.57)	1.74 (1.33-2.26)	1.25 (0.96-1.63)
Did not have head tilted such that chin is slightly upward	1.23 (1.03-1.45)	1.30 (0.99-1.69)	1.84 (1.39-2.44)
Did not breathe out to empty lungs before inhalation	1.27 (1.06-1.53)	1.48 (1.13-1.94)	2.13 (1.57-2.89)
No breath-hold (or holds breath for <3 s)	1.53 (1.26-1.85)	1.96 (1.46-2.63)	1.77 (1.34-2.35)
Did not seal lips around the mouthpiece‡	2.21 (1.29-3.79)	1.65 (0.90-3.03)	1.70 (1.10-2.64)
Patient has an expired inhaler	1.31 (0.61-2.79)	1.83 (0.33-10.07)	0.84 (0.25-2.77)
Patient has an empty inhaler	1.30 (0.79-2.12)	2.45 (0.99-6.02)	2.03 (0.89-4.66)
Did not actuate (MDI only) or did not inhale through mouth	1.53 (0.47-4.98)	2.57 (0.63-10.43)	1.65 (0.81-3.36)
After inhalation did not replace cap/cover	1.53 (0.93-2.51)	1.59 (0.63-3.99)	1.78 (0.52-6.09)
Incorrect second dose preparation, timing, or inhalation§	1.30 (1.03-1.62)	2.20 (1.25-3.86)	1.52 (1.15-2.02)
Exhaled into device before inhalation¶	1.33 (0.72-2.46)	0.97 (0.52-1.80)	2.54 (1.74-3.71)
DPIs only: Dose compromised after preparation because of shaking or tipping	2.08 (1.32-3.28)	1.22 (0.61-2.46)	—
DPIs only: Twist errors or compromised dose after preparation because of holding downward	1.11 (0.95-1.31)	0.91 (0.61-1.36)	—
MDI only: Actuation did not correspond with inhalation, actuation before inhalation	—	—	1.80 (1.32-2.46)
MDI only: Actuation did not correspond with inhalation, actuation after inhalation	—	—	1.05 (0.70-1.58)

Bold indicates statistical significance ($P < .05$).

*For MDI, error includes “did not shake device before actuation.”

†See Tables E1-E3 for more details.

‡For MDI, device was put into mouth but no seal was formed.

§For MDI, error includes lack of device knowledge.

¶For MDI, error includes “did not hold device upright.”

significantly associated with an increased likelihood of being in the uncontrolled asthma category: adjusted ORs (95% CI) were 1.30 (1.08-1.57) for Turbohaler and 1.56 (1.17-2.07) for Diskus. In the Turbohaler cohort only, “compromised dose because of shaking or tipping device” and “failure to remove cap” had strong associations with uncontrolled asthma, but were infrequent (3.4% and 0.4%, respectively). There was no association between the frequent error “did not breathe out to empty lungs before inhalation” and uncontrolled asthma.

Results from a sensitivity analysis to adjust for patient adherence can be seen in Figure E2 in this article’s Online Repository at www.jaci-inpractice.org. The ORs for “insufficient inspiratory effort” remained significantly associated with uncontrolled asthma after adjustment by Medication Adherence Rating Scale adherence score (OR, 1.30; CI, 1.08-1.57) for Turbohaler and 1.55 [1.15-2.08] for Diskus).

MDI cohort. For the MDI cohort, associations that remained significant after adjustment for other errors are presented in Figure 2. The most frequent error, “inspiratory effort not slow and deep,” was not associated with uncontrolled asthma when it was included in a multivariable model with other inhaler errors. Errors related to device knowledge and second dose preparation (made by 34.7% of patients) were significantly associated with uncontrolled asthma (OR, 1.48; 95% CI, 1.10-2.00), after adjustment by patient factors. Actuation before inhalation was common (made by 24.9% of patients) and was associated with uncontrolled asthma after adjustment by patient factors (OR, 1.55; 95% CI, 1.11-2.16). “Exhaling into the inhaler device or not holding device upright” had

a significant association with uncontrolled asthma (OR, 1.58; 95% CI, 1.01-2.47), but was less frequent (14.3%). All these errors remained significantly associated with uncontrolled asthma after further adjustment by patient adherence (see Figure E3 in this article’s Online Repository at www.jaci-inpractice.org).

Association with exacerbations

Univariable associations between individual errors and rate of exacerbations can be seen in Tables E5 to E7 in this article’s Online Repository at www.jaci-inpractice.org.

DPI cohorts. After adjustment by patient factors, the following errors were associated with an increased rate of exacerbations in the DPI cohorts: insufficient inspiratory effort (both devices), not sealing lips around the mouthpiece (Turbohaler only), dose compromised because of shaking or tipping device (Turbohaler only), and not removing cap from device (Turbohaler only). Aside from “not sealing lips around the mouthpiece,” these results reflect those from the primary analysis. Adjusted RRs (with 95% CI) for “insufficient inspiratory effort” were 1.29 (1.04-1.60) for patients using Turbohaler and 1.55 (1.17-2.07) for patients using Diskus. Associations for the other significant errors were stronger (RRs approaching 2.00 and above), but CIs were wider due to lower frequencies (Figure 3).

In the sensitivity analysis, “insufficient inspiratory effort” and “not sealing lips around mouthpiece” remained significantly associated with increased exacerbation rate in Turbohaler users (see Figure E4 in this article’s Online Repository at www.jaci-inpractice.org).

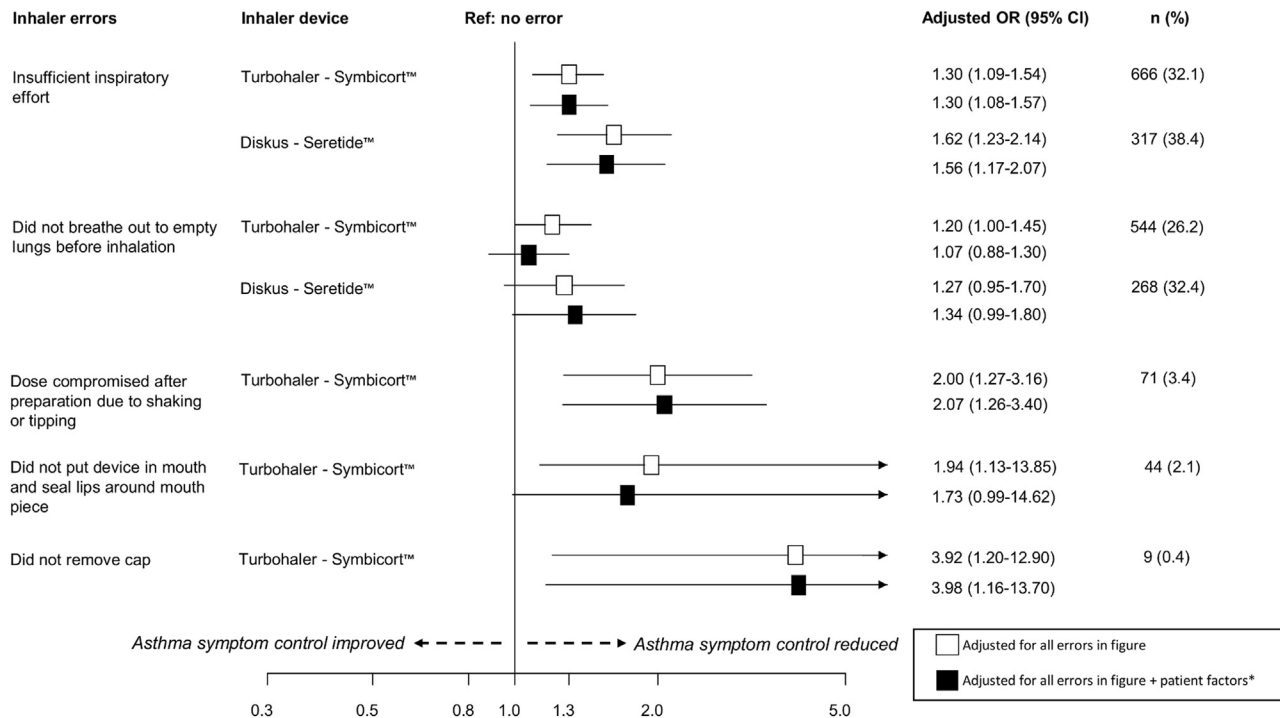


FIGURE 1. Association between inhaler errors (for DPIs) and uncontrolled asthma. *Note.* Errors omitted despite a significant univariable association were omitted because they were correlated with another error. *BMI*, Body mass index; *Ref*, reference group in logistic regression. *Patient factors used to adjust were age, sex, smoking status, BMI, rhinitis, and paracetamol use.

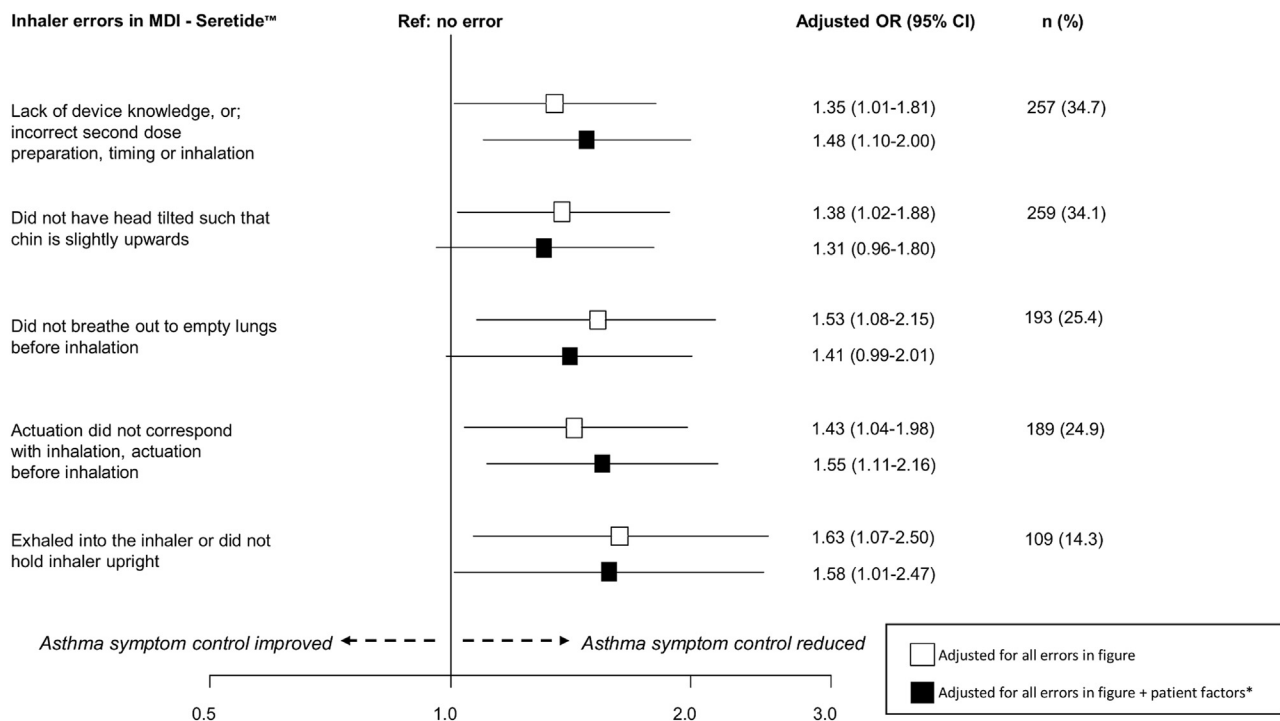


FIGURE 2. Association between inhaler errors (for MDI) and uncontrolled asthma. *BMI*, Body mass index; *Ref*, reference group in logistic regression. *Patient factors used to adjust were age, sex, smoking status, BMI, rhinitis, and paracetamol use.

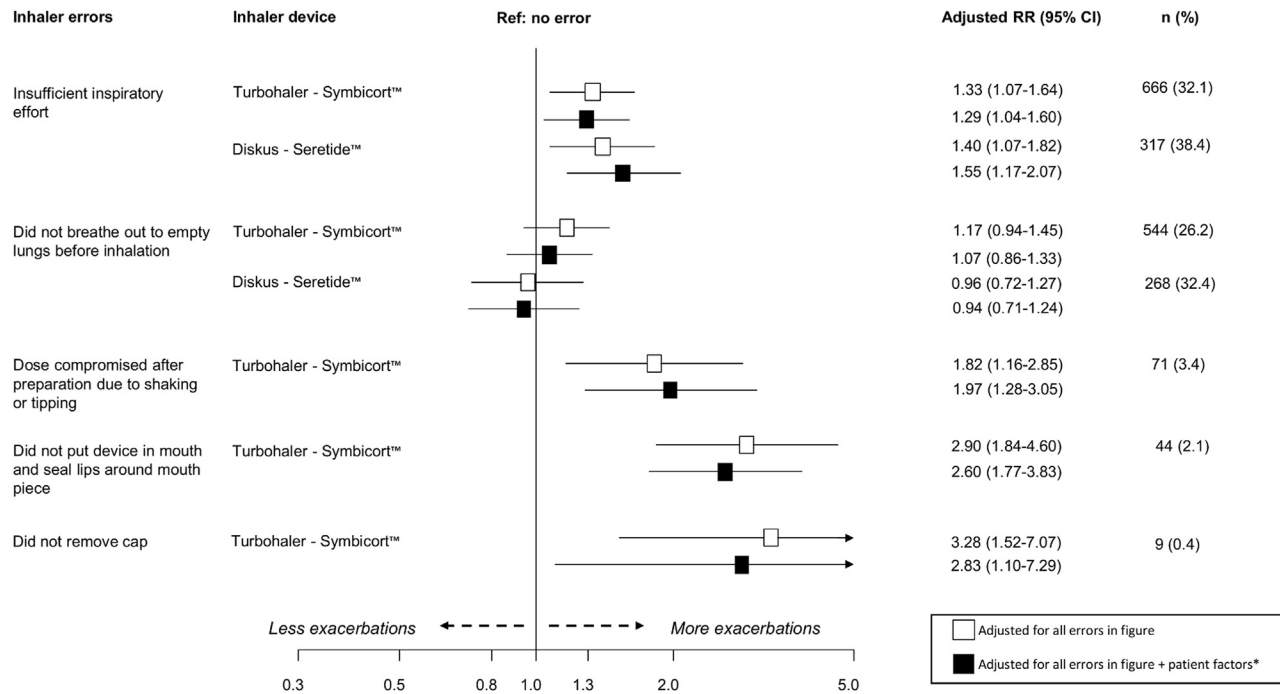


FIGURE 3. Association between inhaler errors (for DPIs) and rate of exacerbations. *BMI*, Body mass index; *Ref*, reference group in Poisson regression. *Patient factors used to adjust were age, sex, smoking status, BMI, rhinitis, and paracetamol use.

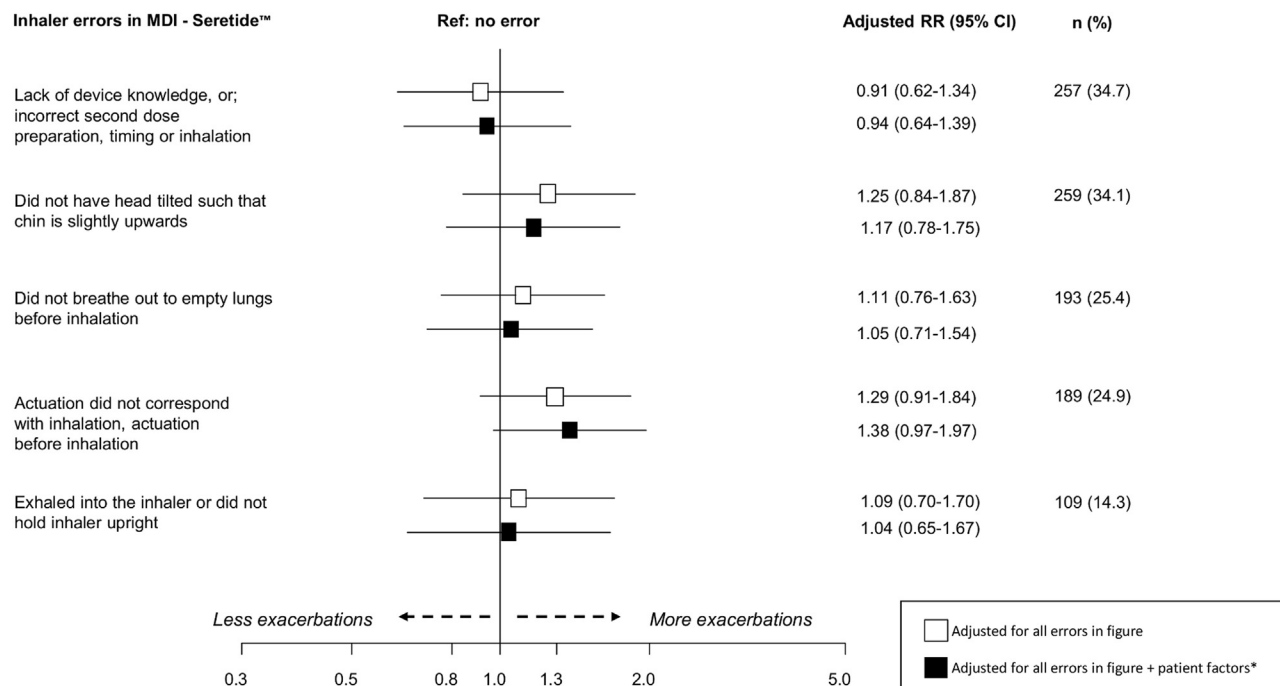


FIGURE 4. Association between inhaler errors (for MDI) and rate of exacerbations. *BMI*, Body mass index; *Ref*, reference group in Poisson regression. *Patient factors used to adjust were age, sex, smoking status, BMI, rhinitis, and paracetamol use.

MDI cohort. After adjustment by patient factors, none of the MDI errors was significantly associated with exacerbation rate (Figure 4). There was no change when adjusting further by patient adherence (see Figure E5 in this article's Online Repository at www.jaci-inpractice.org).

DISCUSSION

Previous studies have shown that poor or improper inhaler technique in asthma is associated with reduced control^{10,11} and increased hospital visits.¹⁰ The CRITIKAL study is the first study to observe associations between specific inhaler errors and

poorer asthma outcomes, including increased likelihood of having uncontrolled symptoms and increased exacerbation rate. Errors were frequent (made by over 30% of patients in a number of cases), and were device-specific as well as generic across devices.

The findings of this study are consistent with evidence in the literature. A recent systematic review has shown that over the past 40 years the frequency and type of inhaler errors have not changed.²⁶ Generic errors, such as not exhaling, not holding the breath, insufficient speed of inhalation, dose preparation errors for DPIs, and coordination problems with MDIs, were the most common. The CRITIKAL study aimed to identify critical inhaler errors, with “critical” meaning those related to poor disease outcomes. The results provide useful indications of which errors could be classified as critical. Those identified in this study were consistent with errors identified in the recent systematic review.

One critical error in this study was insufficient inspiratory effort when using a DPI. All DPIs demonstrate flow-dependent dose emission and therefore the generic instruction when using these is to inhale as fast as possible.²⁷ *In vitro* dose emission²⁸ and gamma scintigraphy²⁹ have highlighted this phenomenon, but clinical evidence demonstrating the relevance of these laboratory and lung deposition studies is missing. The CRITIKAL study confirmed the importance of fast inhalation. Another generic inhalation error with DPIs, though not frequent, was failure to seal the lips around the mouthpiece, which was found to be associated with an increased rate of exacerbations when using the Turbohaler device.

In vitro data have shown the importance of dose preparation when using the Turbohaler.³⁰ Dose preparation errors in DPIs, such as not twisting the base of the Turbohaler, were frequent in this study, but were not associated with worse asthma outcomes. *In vitro* studies have also shown that exhaling into the mouthpiece of a DPI affects the quality of the dose that is emitted,^{30,31} but again, no association with worse outcomes was found in this study. This could be due to study limitations, discussed later in this section, or because these errors were correlated with other types of error that had a stronger impact.

Errors related to the second dose were critical for MDIs. This included exhaling into the inhaler before preparing the second dose, making a second inhalation from the first dose without preparing the second dose, and not waiting at least 30 seconds between inhaling the first and second doses (to permit refill of the chamber).

Not exhaling before an inhalation and not holding the breath are generic errors relevant to all devices. Studies have suggested that exhaling before an inhalation and breath-hold lead to greater lung deposition.³²⁻³⁴ Although associations were not significant in the multivariable models in this study, absence of both these actions was shown to have a significant univariable association with uncontrolled asthma. Not tilting the head slightly back is another generic inhalation manoeuvre—tilting is advised to ensure the medication particles remain entrained in the inhaled airstream. This error was associated with uncontrolled asthma in univariable analyses.

Slow inhalation is advised when using MDI devices (for better lung deposition) and has been linked to improvement in quality of life when patients have good coordination.³⁵ However, the results of this study did not show an impact on outcomes when inhalation was too fast. Rather, the critical MDI error found in

this study was poor coordination between the start of an inhalation and actuation of the dose (actuation coming before inhalation). This is in contrast with results seen in gamma scintigraphy studies, which suggested this was not important.³³ The CRITIKAL study results also highlighted “exhaling into the mouthpiece or not holding the inhaler upright” as a critical MDI error.

The CRITIKAL study is one of the largest studies to be carried out to investigate inhaler technique, and was carried out on a real-life, multinational study population. The results provide detailed evidence about inhaler technique, evidence that has previously been called for in the literature.^{36,37} The analysis allowed for potential confounding where possible, using patient factors known to influence asthma symptoms and response to medications.³⁸ The database contained other potential confounders, such as medication dose, which were also investigated for possible bias. Despite these measures, because of the design of this study—observational, rather than a randomized trial—there remains the possibility of confounding by unmeasured factors.

A limitation of any study that relies on potentially subjective observations is the possibility of interrater variability; that is, several observers may record the same information in different ways. The results of this study relied on the observations of inhaler errors by health care professionals who were purposefully trained. The study attempted to reduce interrater variability by training study personnel using the same materials (including video instruction), across the participating practices. However, it remains a possibility that variability in the assessment of the errors could have biased the results of the study. It may also have reduced the power of the study, which could explain inconsistencies between device cohorts.

The CRITIKAL study used inhaler technique information collected from 1 observation and made the assumption that observed errors reflected a pattern of misuse in that patient. It included only those patients with asthma who were receiving inhaled corticosteroids and long-acting beta agonist combined in a single device: but because this is the most commonly used treatment for asthma, it is likely that the findings are generalizable. This study did not examine any patterns with inhaled corticosteroid dose in particular; however, it is possible that in patients receiving high doses of inhaled corticosteroid, the impact of incorrect inhaler technique was underestimated. It has been shown that dose response levels off at approximately 500 µg, yet prescriptions above this dose are common.^{39,40} When a larger dose is inhaled, an effective amount may still reach its target even if inhaler errors are made. Thus, the effect of errors may potentially be greater than what was observed in the CRITIKAL study, when doses are in the recommended range.

Sensitivity analyses were carried out to account for possible confounding by adherence, which has been linked to inhaler errors and asthma outcomes.⁴¹ Several critical errors remained significantly associated with uncontrolled asthma. However, patient-reported adherence was not used in the main analysis because it has sometimes been shown to be an unreliable measure of adherence.^{25,42}

The results from this study provide evidence to support changes to routine patient management and structured review, with targeted training to reduce critical errors. Greater emphasis on inhaler training has been called for in the literature^{36,37}—for patients as well as for the health care professionals managing the patients.⁴³

CONCLUSIONS

Specific inhaler errors have been identified as critical errors, evidenced by frequency and association with poor asthma outcomes. Primary and secondary care management should target inhaler training to reduce critical errors.

We thank all the participants of the iHARP group who contributed data to this study and conducted field research.

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METHODS

Determining adherence

Medication Adherence Rating Scale (MARS) adherence was reported using the MARS score. This measures adherence on a 6-point scale (never, rarely, sometimes, regular, often, and always) in response to the following questions about their controller inhaler use:

- I use it only when I feel breathless.
- I avoid using it if I can.
- I forget to take it.
- I decide to miss a dose.
- I choose to take it once a day.

Adherence was categorized as poor (any of the questions answered with “often” or “always”), borderline (more than 1 question with “sometimes”), and good (none of above).

Power calculation

The power calculation was based on the logistic regression that would be performed in the primary analysis. The effect size to be detected was an OR of 0.8 (or 1.25 when reference group is reversed), and this assumed a proportion of 0.65 *controlled* patients with asthma in the category of interest and a proportion of 0.7 *controlled* patients with asthma in the reference category. The calculation assumed a correlation among covariates of $R^2 = 1$ and used a 2-tailed test with $\alpha = 0.025$. The calculation determined that 752 patients were required to achieve 80% power in an individual device cohort.

Potential confounders

The following variables were available in the iHARP database and were investigated as potential confounders in multivariable models:

- Age of patient at time of iHARP review
- Sex
- Body mass index

- Smoking status at time of iHARP review, and packs per year for current smokers and ex-smokers
- Socioeconomic status marker (highest education attained)
- Country where iHARP review took place
- Year of iHARP review
- Duration of asthma (years)
- Peak inspiratory flow: Assessed using a Vitelograph AIMS device for the global populations and a Vitelograph Spiromax for the UK and Australia populations
- Peak expiratory flow
- Unrelated comorbidities expressed using the Charlson comorbidity index
- Presence of comorbid diseases, including connective tissue disease, chronic pulmonary disease, congestive heart failure, myocardial infarction, tumors peripheral vascular disease, ulcer diagnosis, leukemia, dementia, liver disease, lymphoma, diabetes mellitus, hemiplegia, cerebrovascular disease, moderate or severe renal disease, AIDS
- Presence of patient-reported rhinitis and severity: Rhinitis symptoms were recorded in response to the question “Do you have any of these symptoms: itchy, runny, blocked nose or sneezing when you don’t have a cold?” Rhinitis was categorized as None (answered question with “No”), Mild Rhinitis (answered question with “Occasionally and little bother” or “Most days and a little bother”), Severe Rhinitis (answered question with “Occasionally and quite a bother” or “Most days and a lot of bother”)
- Presence of gastroesophageal reflux disease, self-reported
- Patient-reported side effects, including continual sore mouth/throat, oral thrush, bruising, hoarse voice, abnormal weight gain, and cough
- Adherence to therapy (MARS score, described above in [Methods](#) section)
- Paracetamol use, reported by the patients as regular, intermittent, or not used
- Currently prescribed combination therapy and dose

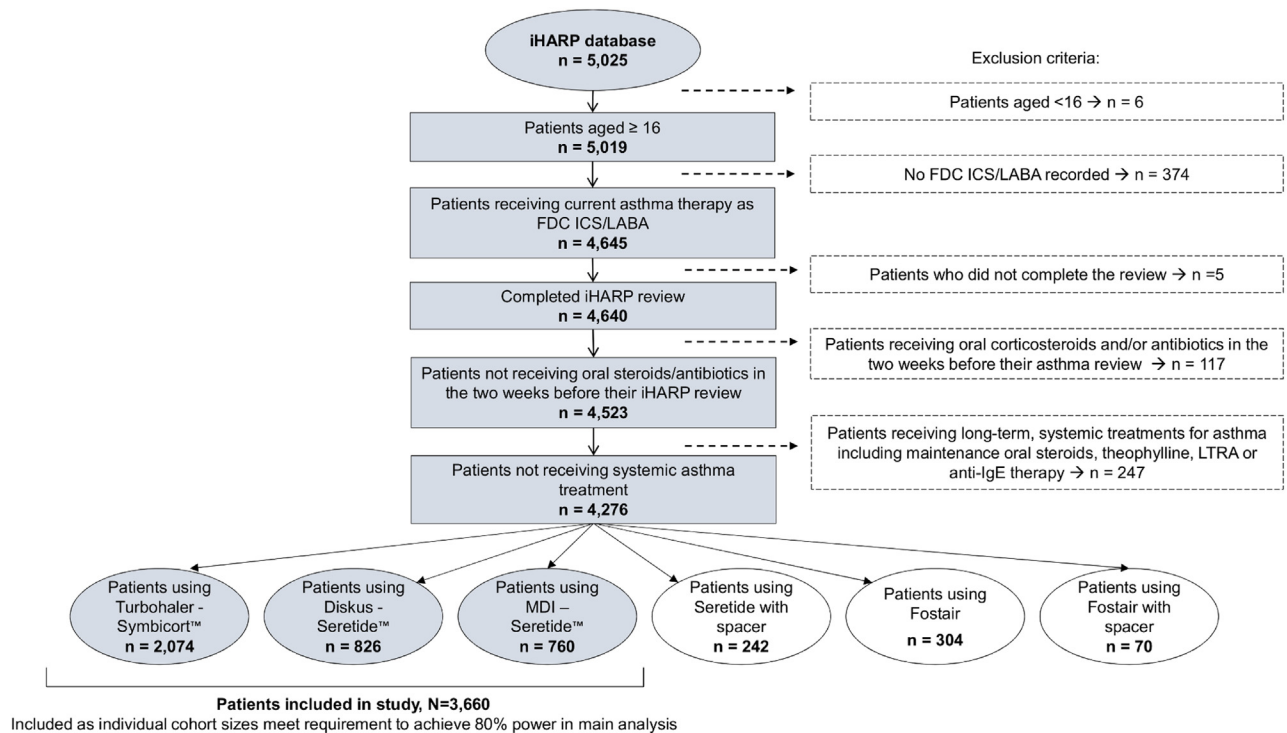


FIGURE E1. Flow diagram showing study cohorts derived from the iHARP database. *FDC ICS/LABA*, Fixed-dose combination with inhaled corticosteroids/long-acting beta agonist; *LTRA*, leukotriene receptor antagonist.

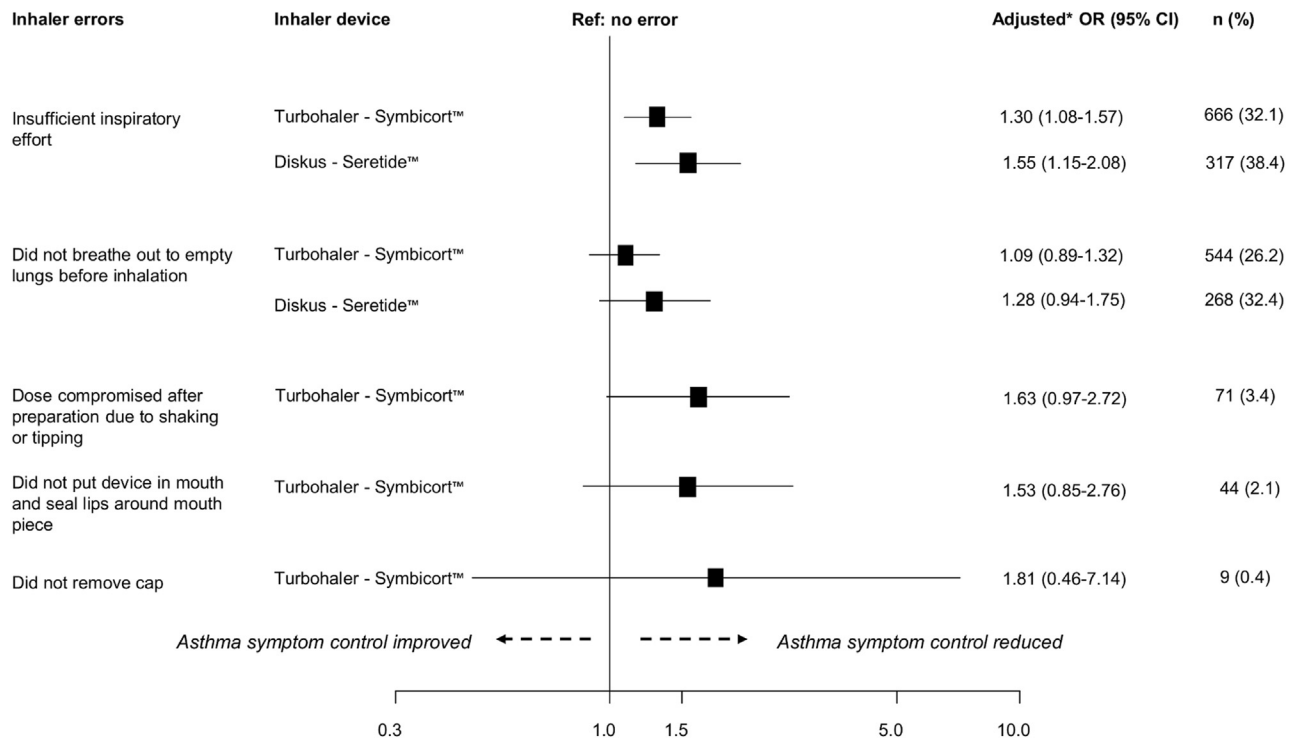
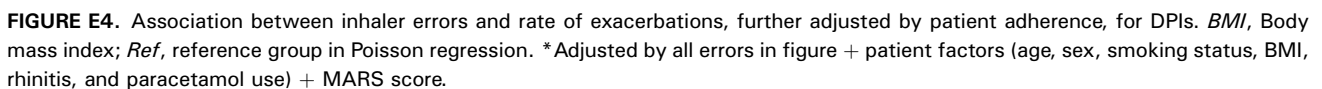
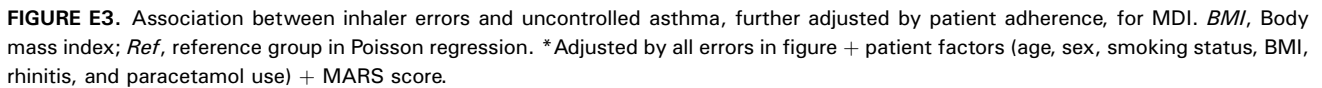


FIGURE E2. Association between inhaler errors and uncontrolled asthma, further adjusted by patient adherence, for DPIs. *BMI*, Body mass index; *Ref*, reference group in Poisson regression. *Adjusted by all errors in figure + patient factors (age, sex, smoking status, BMI, rhinitis, and paracetamol use) + MARS score.



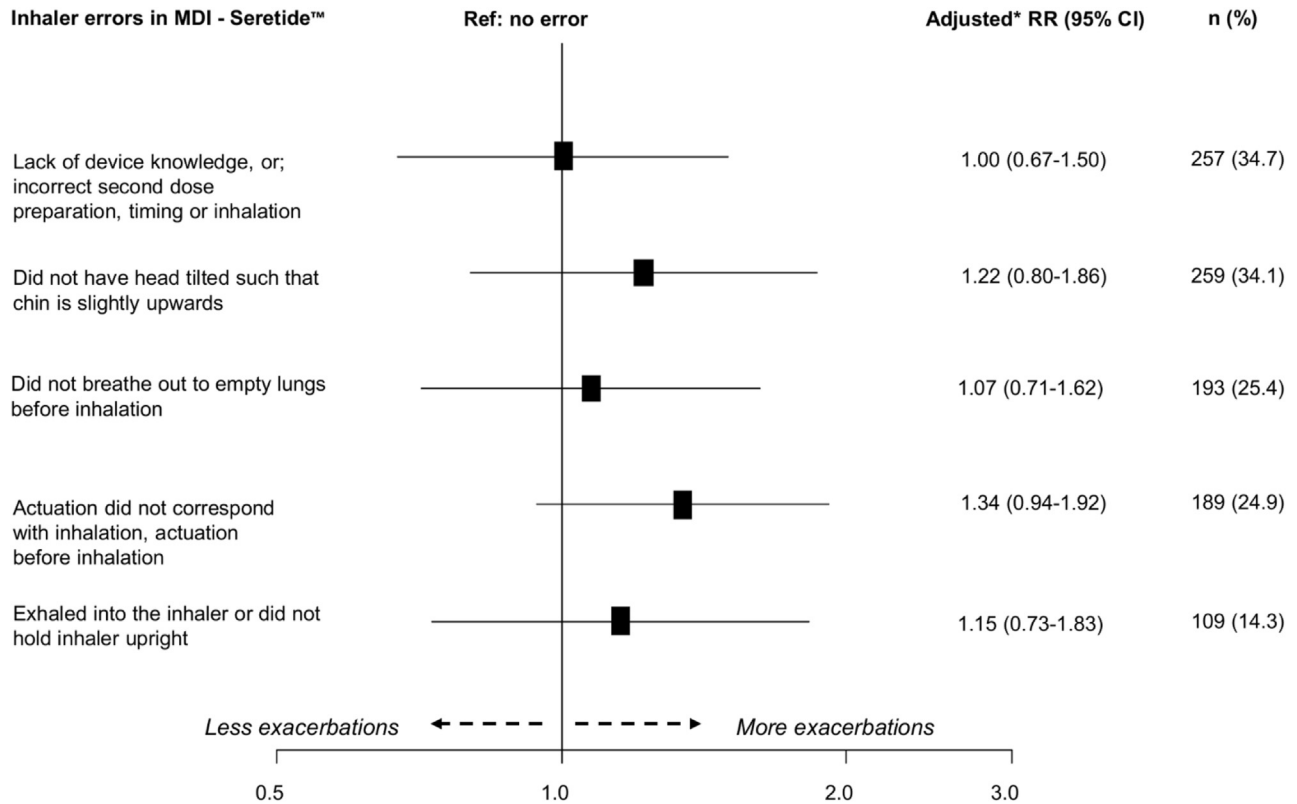


FIGURE E5. Association between inhaler errors and rate of exacerbations, further adjusted by patient adherence, for MDI. *BMI*, Body mass index; *Ref*, reference group in Poisson regression. *Adjusted by all errors in figure + patient factors (age, sex, smoking status, BMI, rhinitis, and paracetamol use) + MARS score.

TABLE E1. Grouped errors, derived from original errors observed when using Turbohaler- Symbicort

Grouped errors for final study	Individual errors observed during iHARP review
Insufficient inspiratory effort	Inhalation is not as fast as you can (defined as a very fast suck)
	Inhalation is not forceful from the start
	Inhalation is not as long as you can, at least >3 s
Twist errors (Device not held upright, base not twisted until it clicks or turn back to original position)	Doesn't hold device upright (mouthpiece skyward $\pm 45^\circ$) during dose preparation
	Dose preparation: Does not twist the base until it clicks
	Dose preparation: Does not turn it back to the original position
Did not have head tilted such that chin is slightly upward	Does not have head tilted such that chin is slightly upward
Did not breathe out to empty lungs before inhalation	Does not breathe out slowly to empty lungs to residual volume
No breath-hold following inhalation (or holds breath for <3 s)	No breath-hold for at least 3 s
Incorrect second dose preparation, timing, or inhalation	Exhales into inhaler before preparing a new dose
	Makes a second inhalation without preparing a second dose
	Makes a second inhalation from the first dose in place of their prescribed 2 doses
	If need second dose: takes second dose within 30 s
	Doesn't repeat the second inhalation, if need
Dose compromised after preparation because of shaking or tipping	Dose preparation: Shakes during preparation
	Device not held upright (mouthpiece skyward) after the base is twisted until inhalation (within 45 degrees)
	Shakes after dose preparation
Patient has empty inhaler	Patients can't tell when their device is empty
After inhalation did not replace cover	After (second) inhalation does not replace cap
Did not put device in mouth and seal lips around mouthpiece	Fails to put in mouth and seal lips around mouthpiece
Exhaled into the inhaler before inhalation	Exhale into the device (also called, blowing into the device before inhalation)
Patient has expired inhaler	Patient has an expired device
Did not inhale through mouth	Failure to inhale through mouthpiece
	Inhalation through the nose
Did not remove cap	Dose preparation: Does not remove cap

TABLE E2. Grouped errors, derived from original errors observed when using Diskus-Seretide

Grouped errors for final study	Individual errors observed during iHARP review
Insufficient inspiratory effort	Inhalation is not as fast as you can (defined as a very fast suck)
	Inhalation is not forceful from the start
	Inhalation is not as long as you can (>3 s)
Did not have head tilted such that chin is slightly upward	Failure to tilt head with chin slightly upward
Did not breathe out to empty lungs before inhalation	Does not breathe out slowly to empty lungs to residual volume
No breath-hold (or holds breath for <3 s)	No breath-hold (or for <3 s)
Compromised dose after preparation because of holding downward	Holds in a downward position after dose preparation (before an inhalation)
Incorrect second dose preparation, timing, or inhalation	Exhales into inhaler before preparing a new dose
	Makes a second inhalation without preparing a second dose
	Makes a second inhalation from the first dose in place of their prescribed 2 doses
	If need second dose: takes second dose within 30 s
	Not repeating the second inhalation
Did not put inhaler in mouth and seal lips around mouthpiece	Fails to put in mouth and seal lips around mouthpiece
Exhaled into device before inhalation	Exhale into the device
Did not slide cover fully open	Does not slide cover as far as possible
	Does not slide lever fully to open mouthpiece
Dose compromised after preparation because of shaking or tipping	Shakes after dose preparation
After inhalation did not replace cover	After (second) inhalation: Does not slide cover back
Patient had an empty inhaler	Patients don't know when their device is empty
Did not inhale through mouth	Failure to inhale through mouthpiece
	Inhalation through the nose
Patient has expired inhaler	Patient has an expired device

TABLE E3. Grouped errors, derived from original errors observed when using MDI-Seretide

Grouped errors for final study	Individual errors observed during iHARP review
Inspiratory effort, not slow and deep	Inhalation is not slow and deep, defined as lasting at least 3 s
Did not have head tilted such that chin is slightly upward	Does not have head tilted such that chin is slightly upward
Lack of device knowledge, or incorrect second dose preparation, timing, or inhalation	Exhales into inhaler before preparing a new dose
	Makes a second inhalation without preparing a second dose
	Makes a second inhalation from the first dose in place of their prescribed 2 doses
	Second dose within 30 s
	No repeat second inhalation
	If on Fostair ask if they know how long they can use their inhaler after receiving it from the pharmacy—should be less than 20 wk/5 mo
	Does not mention priming when asked: What do you do when you haven't used your inhaler for: Evohaler 1 wk?; or Fostair 2 wk?
	Does not mention priming when asked: What do you do when you use your inhaler for the first time?
No breath-hold (or holds breath for <3 s)	No breath-hold for at least 3 s
Did not breathe out to empty lungs before inhalation	Does not breathe out
Actuation did not correspond with inhalation, actuation before inhalation	Actuation not corresponding with inhalation; actuation before inhalation
Did not remove cap or shake device before actuation	Does not remove cap
	Does not shake before actuation
Exhaled into the inhaler or did not hold inhaler upright	Exhalation into the inhaler
	Does not hold inhaler upright
Actuation did not correspond with inhalation, actuation after inhalation	Actuation not corresponding with inhalation; actuation is too late
Did not seal lips around the mouthpiece	Puts inhaler in mouth but does not seal lips
Did not actuate or did not inhale through mouth	Failure to actuate
	Failure to inhale
	Inhalation through the nose
Patient has an empty inhaler	When asked patient does not know how to tell that their device is empty
Patient has an expired inhaler	Patient has an expired device
After inhalation did not replace cap	After (second) inhalation doesn't replace cap

TABLE E4. Number of errors made by patients, by device type

Inhaler device type	Number of errors made by patients				Total
	No errors	1 or 2 errors	3 or 4 errors	5+ errors	
Turbohaler-Symbicort	404 (19.5)	1054 (50.8)	448 (21.6)	168 (8.1)	2074
Diskus-Seretide	245 (29.7)	365 (44.2)	167 (20.2)	49 (5.9)	826
MDI-Seretide	102 (13.4)	336 (44.2)	191 (25.1)	131 (17.2)	760

Chi-square test found a significant association between the number of errors and device type ($P < .001$).

TABLE E5. Inhaler errors, and their association with exacerbation rate, in patients using Turbohaler-Symbicort

Inhaler error	Frequency of error, n (%)	RR* (95% CI)
Twist errors (Device not held upright, base not twisted until it clicks or turn back to original position)	1012 (48.8)	0.78 (0.69-0.89)
Did not have head tilted such that chin is slightly upward	712 (34.3)	1.15 (1.00-1.31)
Insufficient inspiratory effort	666 (32.1)	1.41 (1.24-1.61)
Did not breathe out to empty lungs before inhalation	544 (26.2)	1.27 (1.10-1.46)
No breath-hold following inhalation (or holds breath for <3 s)	459 (22.1)	1.53 (1.33-1.77)
Incorrect second dose preparation, timing, or inhalation	327 (20.8)	0.99 (0.83-1.17)
Dose compromised after preparation because of shaking or tipping	71 (3.4)	1.95 (1.49-2.53)
Patient had an empty inhaler	57 (2.75)	1.08 (0.73-1.58)
After inhalation did not replace cover	55 (2.65)	1.46 (1.04-2.05)
Did not put device in mouth and seal lips around mouthpiece	44 (2.1)	3.41 (2.64-4.41)
Exhaled into the inhaler before inhalation	36 (1.74)	1.99 (1.39-2.84)
Patient has expired inhaler	24 (1.16)	1.04 (0.57-1.88)
Did not inhale through mouth	10 (0.5)	3.91 (2.42-6.32)
Did not remove cap	9 (0.43)	3.83 (2.30-6.37)

*RRs (from Poisson regression) compare exacerbation rates in patients who made the inhaler error, to patients who did not make the error. Estimates that are significant at the 5% level appear in bold.

TABLE E6. Inhaler errors, and their association with exacerbation rate, in patients using Diskus-Seretide

Inhaler error	Frequency of error, n (%)	RR* (95% CI)
Insufficient inhalation effort	317 (38.4)	1.38 (1.16-1.64)
Did not have head tilted such that chin is slightly upward	286 (34.6)	0.92 (0.77-1.11)
Did not breathe out to empty lungs before inhalation	268 (32.4)	1.07 (0.89-1.28)
No breath-hold following inhalation (or holds breath for <3 s)	204 (24.7)	1.29 (1.07-1.56)
Compromised dose after preparation because of holding downward	98 (11.9)	1.17 (0.91-1.51)
Incorrect second dose preparation, timing, or inhalation	44 (6.3)	1.58 (1.17-2.14)
Did not put inhaler in mouth and seal lips around mouthpiece	39 (4.7)	2.48 (1.88-3.27)
Exhaled into device before inhalation	38 (4.6)	1.52 (1.08-2.15)
Did not slide cover fully open	33 (4)	1.13 (0.74-1.72)
Dose compromised after preparation because of shaking or tipping	29 (3.5)	1.23 (0.81-1.89)
After inhalation did not replace cover	17 (2.1)	2.04 (1.32-3.15)
Patient had an empty inhaler	16 (1.9)	1.95 (1.23-3.09)
Did not inhale through mouth	7 (0.85)	3.29 (1.93-5.60)
Patient has expired inhaler	4 (0.5)	2.44 (1.09-5.45)

*RRs (Poisson regression) compare exacerbation rates between patients who made the inhaler error to patients who did not make the error. Estimates that are significant at the 5% level appear in bold.

TABLE E7. Inhaler errors, and their association with exacerbation rate, in patients using MDI-Seretide

Inhaler error	Frequency of error, n (%)	RR* (95% CI)
Inspiratory effort, not slow and deep	359 (47.2)	0.95 (0.76-1.18)
Did not have head tilted such that chin is slightly upward	259 (34.1)	1.34 (1.08-1.68)
Lack of device knowledge, or incorrect second dose preparation, timing, or inhalation	257 (34.7)	0.99 (0.78-1.24)
No breath-hold following inhalation (or holds breath for <3 s)	254 (33.4)	1.47 (1.18-1.84)
Did not breathe out to empty lungs before inhalation	193 (25.4)	1.28 (1.01-1.62)
Actuation did not correspond with inhalation, actuation before inhalation	189 (24.9)	1.43 (1.13-1.80)
Did not remove cap or shake device before actuation	144 (19)	0.92 (0.69-1.23)
Exhaled into the inhaler or did not hold inhaler upright	109 (14.3)	1.34 (1.01-1.78)
Actuation did not correspond with inhalation, actuation after inhalation	92 (12.1)	1.22 (0.90-1.66)
Did not seal lips around the mouthpiece	78 (10.3)	1.29 (0.93-1.78)
Did not actuate or did not inhale through mouth	30 (3.9)	1.50 (0.94-2.39)
Patient had an empty inhaler	23 (3)	1.12 (0.61-2.04)
Patient has expired inhaler	11 (1.5)	0.42 (0.1-1.68)
After inhalation did not replace cap	9 (1.2)	2.62 (1.40-4.92)

*RRs (Poisson regression) compare exacerbation rates between patients who made the inhaler error to patients who did not make the error. Estimates that are significant at the 5% level appear in bold.