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Published in:
Journal of Asthma

DOI:
10.3109/02770903.2015.1099160

Publication date:
2016

Journal of Asthma

ISSN: 0277-0903 (Print) 1532-4303 (Online) Journal homepage: http://www.tandfonline.com/loi/ijas20

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To cite this article: Janine A. M. Westerik MD, Victoria Carter BSc, Henry Chrystyn MSc, PhD, Anne Burden MSc, Samantha L. Thompson PhD, Dermot Ryan MD, FRCGP, Kevin Gruffydd-Jones BM, BCh, FRCGP, John Haughney MD, FRCPE, FRCGP, Nicolas Roche MD, PhD, Federico Lavorini MD, PhD, Alberto Papi MD, Antonio Infantino MD, Miguel Roman-Rodriguez MD, Sinthia Bosnic-Anticevich B.Pharm(Hons), PhD, Karin Lisspers MD, PhD, Björn Ställberg MD, PhD, Svein Høegh Henrichsen MD, Thys van der Molen MD, PhD, Catherine Hutton BA & David B. Price MD, FRCGP (2016) Characteristics of patients making serious inhaler errors with a dry powder inhaler and association with asthma-related events in a primary care setting, Journal of Asthma, 53:3, 321-329, DOI: 10.3109/02770903.2015.1099160

To link to this article: http://dx.doi.org/10.3109/02770903.2015.1099160

Accepted author version posted online: 17 Nov 2015.
Published online: 26 Jan 2016.

http://tandfonline.com/ijas
ISSN: 0277-0903 (print), 1532-4303 (electronic)

Journal of ASTHMA

J Asthma, 2016; 53(3): 321–329
2016 Published with license by Taylor & Francis. DOI: 10.3109/02770903.2015.1099160

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EDUCATION

Characteristics of patients making serious inhaler errors with a dry powder inhaler and association with asthma-related events in a primary care setting

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Abstract

Objective: Correct inhaler technique is central to effective delivery of asthma therapy. The study aim was to identify factors associated with serious inhaler technique errors and their prevalence among primary care patients with asthma using the Diskus dry powder inhaler (DPI). *Methods*: This was a historical, multinational, cross-sectional study (2011–2013) using the iHARP database, an international initiative that includes patient- and healthcare provider-reported questionnaires from eight countries. Patients with asthma were observed for serious inhaler errors by trained healthcare providers as predefined by the iHARP steering committee. Multivariable logistic regression, stepwise reduced, was used to identify clinical characteristics and asthma-related outcomes associated with ≥1 serious errors. *Results*: Of 3681 patients with asthma, 623 (17%) were using a Diskus (mean [SD] age, 51 [14]; 61% women). A total of 341 (55%) patients made ≥1 serious errors. The most common errors were the failure to exhale before inhalation, insufficient breath-hold at the end of inhalation, and inhalation that was not forceful from the start. Factors significantly associated with ≥1 serious errors included asthma-related hospitalization the previous year (odds ratio [OR] 2.07; 95% confidence interval [CI], 1.26–3.40); obesity (OR 1.75; 1.17–2.63); poor asthma control the previous 4 weeks (OR 1.57; 1.04–2.36); female sex (OR 1.51; 1.08–2.10); and no inhaler technique review during the previous year (OR 1.45; 1.04–2.02). *Conclusions*: Patients with evidence of poor asthma control should be targeted for a review of their inhaler technique even when using a device thought to have a low error rate.

Keywords

Asthma therapy, cross-sectional, Diskus inhaler, inhalation devices, multinational

History

Received 4 July 2015
Revised 7 September 2015
Accepted 18 September 2015
Published online 18 January 2016

Introduction

The prevalence of uncontrolled asthma has remained at approximately 50% in recent European surveys despite the availability of effective therapies [1–3], with patient errors in using their inhaler devices likely playing a role [3,4]. Proper inhaler technique is an important component of effective asthma therapy: bronchodilators and inhaled corticosteroids (ICS) are delivered via a variety of inhaler devices, each with its specific dose preparation and handling technique, advantages and disadvantages [4–7].

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Data derived from randomized controlled trials (RCTs) indicate that clinical outcomes do not differ significantly among inhaler devices; however, these studies typically include only highly trained patients with correct inhalation technique [6–9]. Indeed, meta-analyses of observational studies and RCTs report that any inhaler device type is similarly effective as long as the patient is able to use it correctly and there is drug remaining in the device [7,10]. However, findings from observational studies indicate that patients with obstructive lung disease commonly misuse inhalers in clinical practice [11–16], and poor inhaler technique is associated with worse clinical outcomes [16–20].

The correct use of an inhaler involves device-specific dose preparation steps followed by the inhalation pattern appropriate to the device. The ideal pattern with a dry powder inhaler (DPI) is a full exhalation (ideally to residual volume), then a rapid and forcible inhalation (also described as ''deep and hard as you can''), followed by a breath-hold for 10 s or as long as possible [5]. Unlike standard pressurized metered-dose inhalers (pMDIs), DPIs are breath-actuated so they obviate the need to co-ordinate actuation and inhalation [5]. It has been suggested that some patients experiencing an asthma exacerbation could be unable to generate the forcible inhalation required with DPIs [21]. However, the Diskus DPI (also known as the Accuhaler) is designed to facilitate ease of use, and there is some evidence to suggest that, of the DPIs, this device is associated with fewest inhaler technique errors [14,22–24]. In a randomized study of patients with obstructive lung disease who were hospitalized for an exacerbation, the highest number of optimum inhalation profiles were observed with the Diskus (100%), followed by a pMDI with a Volumatic spacer (87%), and the lowest number with MDIs alone (14%) [24].

The global Helping Asthma in Real People (HARP) project seeks to understand and address the reasons for uncontrolled asthma [25]. The HARP inhaler technique assessment initiative (iHARP) is an extension of HARP that incorporates an assessment of potential handling errors and an appraisal of patient inhalation profile against device-specific thresholds in addition to the standard review [26,27]. Inhaler use has been reviewed for 5000 patients since the launch of iHARP in June 2011. The aim of this study was to use iHARP data to identify factors associated with serious inhaler technique errors, as observed by healthcare providers (HCPs), and their prevalence among primary care patients with asthma using the Diskus dry powder inhaler.

Methods

Data source

This cross-sectional observational study used anonymized patient data from the iHARP database, an international database administered by the Respiratory Effectiveness Group [28] comprising anonymized data from practices receiving the iHARP asthma review service [26,27]. Data for the study were collected from June 2011 to November 2013; permission to use the data for research was obtained from primary care practices in Australia and seven European countries (the United Kingdom [UK], Italy, Spain, the Netherlands, France, Norway and Sweden). The data included patient demographic characteristics, respiratory reviews by trained HCPs and results of asthma questionnaires completed by patients on the day of the iHARP asthma review. For patients assessed within the UK, these data were linked to anonymized clinical, diagnostic and prescribing information from electronic medical records.

Each of the participating centers obtained appropriate ethics approval for the iHARP asthma review service based on their country-specific requirements. This study was registered with the European Network of Centers for Pharmacoepidemiology and Pharmacovigilance (as ENCePP/SDPP/8020) [29].

Cohort definition

The cohort drawn from the iHARP database for the current study was restricted to adult patients ($\geq$18 years old) who were receiving fixed-dose combination ICS/LABA therapy delivered by a Diskus device.

Patients eligible for iHARP respiratory review, an ongoing international initiative, are 16 years and older, have a current diagnosis of asthma and have received two or more prescriptions for fixed-dose combination ICS/long-acting beta-agonist (LABA) therapy in the year before the review [26,27]. Patients are excluded from iHARP if they have a diagnosis of chronic obstructive pulmonary disease (COPD) or any chronic respiratory disease other than asthma, or if they are prescribed separate ICS in addition to fixed-dose combination ICS/LABA, are receiving long-term systemic treatment for asthma (e.g. maintenance oral corticosteroids, theophylline, leukotriene receptor antagonists or anti-IgE therapy), or had received oral corticosteroids and/or antibiotics for a lower respiratory condition in the 2 weeks before respiratory review.

Study data and definitions

Demographic and clinical characteristics were obtained from the iHARP database (see Supplementary material for further details). All patients were asked whether their inhaler technique had been reviewed in the previous year by an HCP, and patients were asked to self-assess their inhaler technique using a Likert scale with scores ranging from 1 (''I think my inhaler technique is very poor'') to 6 (''I think my inhaler technique is excellent'').

Self-reported adherence to asthma therapy was assessed for patients from the UK, Italy, Spain, Australia, Sweden, France and Norway using the Medication Adherence Rating Scale (MARS) [30]. Adherence to asthma therapy for patients from the Netherlands was assessed using patients' answers to the question, ''Do you ever forget your prevention inhalation medication?'' Adherence was categorized as (1) poor for responses of ''very often'' or ''always''; (2) borderline for responses of ''now and then'' or ''regularly'' and (3) good for responses of ''never'' and ''rarely.''

The Global INitiative for Asthma (GINA) criteria [31] were used to assess asthma control during 1 week preceding the clinic visit; and the Asthma Therapy Assessment Questionnaire (ATAQ) [32] was used to assess asthma control during the preceding 4 weeks (see Supplementary material for details).

Table 1. Checklist of predefined serious errors for the Diskus device.

Does not slide cover as far as possible
Does not slide lever fully to open mouthpiece
Holds in a downward position after dose preparation (before an inhalation)
Shakes after dose preparation
Blowing into the device
Failure to exhale before inhalation
Failure to put in mouth and seal lips around mouthpiece
Failure to inhale through mouthpiece
Inhalation through the nose
Inhalation is not forceful from the start
No breath-hold for at least 3 s
Does not prepare second dose correctly
Does not correctly inhale second dose as above
Does not know when his or her device is empty

The numbers of patient-reported acute courses of oral corticosteroids, asthma-related hospitalizations and severe asthma exacerbations in the prior year were recorded during the iHARP review on the patient-completed questionnaire. Severe exacerbations were defined as patients having had either an asthma-related hospitalization or a course of oral corticosteroids (as defined above) in the prior year.

Study endpoint: serious inhaler technique errors

Serious inhaler technique errors identified by the HCPs were defined as errors potentially limiting drug uptake to the lungs, as enumerated by the iHARP steering committee before commencing the study. Table 1 depicts the checklist of predefined serious errors for the Diskus device.

The study HCPs – physicians in Italy, Norway and Spain, pharmacists in Australia, and nurses in the UK, the Netherlands, Sweden and France – were trained and tested to identify serious inhaler errors by watching a standardized instructional video. Eligible patients were invited to respiratory reviews at their primary care practices, during which the HCPs observed patients using their inhaler once, or twice if a second dose were required, and recorded serious errors against the checklist (Table 1).

Statistical analyses

Analyses were performed with SPSS Statistics versions 19 and 21 (IBM SPSS Statistics, Feltham, Middlesex, UK), SAS version 9.3 (SAS Institute, Marlow, Buckinghamshire, UK) and Microsoft Excel 2007 (Microsoft Corporation, Redmond, Washington). Statistically significant results were defined as a p value of ≤ 0.05.

Characteristics of patients who made no serious errors using a Diskus device were compared with those of patients making one or more (≥ 1) serious errors. Variables measured on the interval or ratio scale were compared using Student's t-test for normally distributed data and the Mann–Whitney U-test for skewed data. Categorical variables were compared using the χ^2 test.

Univariable logistic regression models, with a dichotomous indicator variable for serious errors made (yes/no) as the dependent variable and each patient characteristic as an explanatory (or predictor) variable, were first used to identify characteristics associated with making serious errors. Demographic and clinical characteristics associated with making ≥ 1 serious errors in the univariable model ($p < 0.05$) were then entered into a multivariable model, which was stepwise reduced to produce a final list of non-collinear independently associated variables. Significant interactions were defined as p value <0.10. A list of demographic and clinical characteristics included in the univariable model is in the Supplementary material.

Results

Patients

There were 3681 patients with asthma in the iHARP database who had a respiratory review between June 2011 and November 2013. Of these patients, 627 (17%) were using a Diskus inhaler. After excluding four (0.5%) patients aged <18 years, the final study cohort included 623 adult patients with asthma using Diskus who were from the UK (232 [37%]), Italy (149 [24%]), Spain (102 [16%]), the Netherlands (83 [13%]), Australia (37 [6%]), France (8 [1%]), Norway (5 [1%]) and Sweden (7 [1%]). The final study cohort comprised 61% women and had a mean (SD) age of 51 (14) years (Table 2). Approximately three quarters of patients had recorded lung function results; of these, 69% had a percent predicted forced expiratory volume in 1 s (FEV_1) or peak expiratory flow (PEF) that was >80% (Supplemental Table S1).

Serious errors and characteristics of patients making serious errors

Fifty-five percentage of patients made from 1 to 10 serious errors, most commonly one (157 [25%]), two (92 [15%]) or three errors (55 [9%]); 37 patients (6%) made four or more errors. The most frequent errors were the failure to exhale before inhalation, insufficient (or absent) breath-hold at the end of inhalation and inhalation that was not forceful from the start (Figure 1).

Patients making ≥ 1 serious errors were significantly more likely to be female, obese or lacking a university degree than those making no error (Table 2). Age, smoking status, the duration of asthma, the prevalence and severity of rhinitis and lung function test results were not significantly different between patients making 0 and ≥ 1 serious errors (Table 2, Supplemental Table S1). Patient-reported adherence to therapy did not differ between patients making 0 and ≥ 1 serious errors (Table 3).

Patients making ≥ 1 serious errors were significantly less likely to report that they had their inhaler technique reviewed by an HCP in the prior year or to report good to excellent inhaler technique proficiency (Table 3). In addition, those making ≥ 1 serious errors were significantly more likely to have poor asthma control in the previous 1–4 weeks, as assessed using the GINA criteria and/or ATAQ score (Table 3 and Supplemental Table S1).

Severe exacerbations and asthma-related hospitalizations during the previous year were significantly more frequent among patients making ≥ 1 serious inhaler errors than among those making no errors. The number of acute courses of oral corticosteroids was not significantly different between these

Table 2. Patient characteristics grouped by frequency of serious inhaler technique error (0 versus ≥1).

Characteristic	Total *N* (%) (*n* = 623)	0 errors (*n* = 282)	≥1 errors (*n* = 341)	*p* value
Age, mean (SD)	51 (14)	50 (15)	51 (14)	0.84[a]
18–30 years, *n* (%)	66 (11)	36 (13)	30 (9)	
31–50 years, *n* (%)	219 (35)	94 (33)	125 (37)	
51–70 years, *n* (%)	313 (50)	140 (50)	173 (51)	
>70 years, *n* (%)	25 (4)	12 (4)	13 (4)	
Sex, female, *n* (%)	380 (61)	159 (56)	221 (65)	0.032[b]
male	243 (39)	123 (44)	120 (35)	
Body mass index[c], *n* (%)				
Underweight	8 (1)	4 (1)	4 (1)	0.036[b]
Normal	214 (34)	107 (38)	107 (31)	
Overweight	212 (34)	102 (36)	110 (32)	
Obese	189 (30)	69 (25)	120 (35)	
Smoking status, *n* (%)				
Current smoker	78 (13)	28 (10)	50 (15)	0.179[b]
Ex-smoker	189 (30)	91 (32)	98 (29)	
Non-smoker	356 (57)	163 (58)	193 (57)	
Education[d], known status, *n* (%)	(*n* = 499 [80])	(*n* = 216)	(*n* = 283)	
PG or professional degree	11 (2)	4 (2)	7 (3)	0.006[b]
University degree[e]	157 (31)	80 (37)	77 (27)	
Secondary education[e]	207 (41)	88 (41)	119 (42)	
Primary education[e]	100 (20)	39 (18)	61 (22)	
None	24 (5)	5 (2)	19 (7)	

Percentages are column percentages. BMI, body mass index; PG, postgraduate; SD, standard deviation.
[a]Mann–Whitney *U* test.
[b]χ^2 test.
[c]Underweight BMI < 18.5 kg/m^2; normal BMI = 18.5–24.99 kg/m^2; overweight BMI = 25–29.99 kg/m^2; obese BMI ≥ 30 kg/m^2.
[d]Errors by education reported as *n* (%) of known status.
[e]Completed or some education.

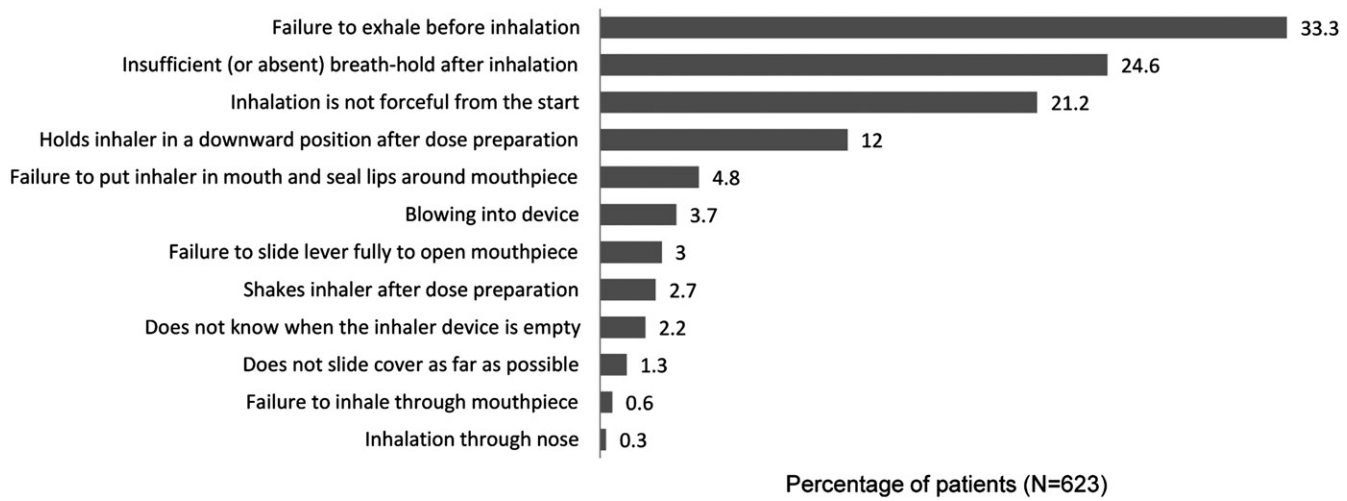

Figure 1. Percentage of patients making each type of serious inhaler error with the Diskus.

two patient groups overall (Table 3) or as a dichotomized variable (0 versus ≥1 oral corticosteroid course: $p = 0.070$ for the comparison between patients making 0 versus ≥ 1 serious error).

Risk factors for making serious inhaler technique errors: multivariable model

The univariable logistic regression results for the risk of a serious error are reported in the online Supplementary material (Supplemental Tables S2–S4).

In the multivariable logistic regression analysis, the most significant association with making ≥1 serious error was having experienced ≥1 asthma-related hospitalizations (inpatient or emergency department attendance) in the previous year (Table 4). Other factors significantly associated with making ≥1 serious errors included being female, being obese (versus underweight/normal weight), having no inhaler technique review in the prior year, and having poor asthma control in the prior 4 weeks (via ATAQ) versus having good/partial control.

There was a significant interaction between body mass index (BMI) and inhaler technique review. Among overweight patients, those who had no inhaler technique review in the previous year were more likely to make a serious error compared with patients who had their inhaler technique

Table 3. Clinical characteristics grouped by serious inhaler error category (0 versus ≥ 1).

Clinical characteristic	Total N (%) ($n = 623$)	0 error (– = 282)	≥1 errors ($n = 341$)	p value
Patient-reported prior inhaler review by HCP[b], *n* (%)	297 (48)	150 (53)	147 (43)	0.012
Patient self-assessment of inhaler technique, *n* (%), known	($n = 588$ [94])	270 (96)	318 (93)	
Very poor to poor	24 (4)	11 (4)	13 (4)	0.024
Fair to average	122 (21)	43 (16)	79 (25)	
Good to excellent	442 (75)	216 (80)	226 (71)	
ATAQ asthma control, *n* (%), known	($n = 622$ [100])	282 (100)	340 (99.7)	
Poor control	137 (22)	47 (17)	90 (27)	0.012
Partial control	469 (75)	228 (81)	241 (71)	
Good control	16 (3)	7 (3)	9 (3)	
Adherence to therapy[c], *n* (%)				
Poor	202 (37)	84 (34)	118 (40)	0.087
Borderline	18 (3)	5 (2)	13 (4)	
Good	320 (59)	156 (64)	164 (56)	
Adherence to therapy in the Netherlands[d], *n (%), known*	($n = 59$ [71])	26 (70.3)	33 (72)	
Poor	2 (3)	2 (7.7)	0 (0)	0.12
Borderline	0	0 (0)	0 (0)	
Good	57 (97)	24 (92.3)	33 (100)	
Acute courses of oral corticosteroids[b], *n* (%)				
0	380 (61)	183 (65)	197 (58)	0.13
1	139 (22)	58 (21)	81 (24)	
2	59 (10	27 (10)	32 (9)	
≥3	45 (7)	14 (5)	31 (9)	
Severe exacerbations[b,e], *n* (%), known	($n = 622$ [100])	282 (100)	340 (99.7)	
0	355 (57)	176 (62)	179 (53)	0.044
1	132 (21)	55 (20)	77 (23)	
≥2	135 (22)	51 (18)	84 (25)	
Hospitalizations[b], *n* (%)				
0	531 (85)	255 (90)	276 (81)	0.008
1	42 (7)	10 (4)	32 (9)	
2	21 (3)	8 (3)	13 (4)	
≥3	28 (5)	9 (3)	19 (6)	

Abbreviations: ATAQ, Asthma Therapy Assessment Questionnaire; FEV_1, forced expiratory volume in 1 second; HCP, health care practitioner; PEF, peak expiratory flow.
[a]χ^2 test.
[b]In the year before an iHARP respiratory consultation.
[c]Number (%) calculated as percentage of patients from the UK, Italy, Spain, Australia, Sweden, France and Norway ($n = 245$ for 0 serious errors and $n = 295$ for ≥1 serious error).
[d]Number (%) calculated as percentage of known patients from the Netherlands ($n = 37$ for 0 serious errors and $n = 46$ for ≥1 serious error).
[e]Number (%) calculated as percentage of known.

Table 4. Demographic and clinical factors associated with making ≥1 serious error versus 0 (multivariable results).

	Reference category	Category	Odds ratio (95% CI)	p value	Overall p value
Sex	Male	Female	1.51 (1.08–2.10)		0.017
BMI	Underweight/Normal weight	Overweight	1.18 (0.80–1.74)	0.401	0.024
		Obese	1.75 (1.17–2.63)	0.007	
Inhaler review	Yes	No	1.45 (1.04–2.02)		0.027
ATAQ	Good control/Partial control	Poor control	1.57 (1.04–2.36)		0.031
Inpatient admission or ED attendance	0	≥1	2.07 (1.26–3.40)		0.004

Abbreviations: ATAQ, Asthma Therapy Assessment Questionnaire; BMI, body mass index; ED, emergency department.

reviewed (Table 5). Among patients who had no inhaler technique review in the previous year, overweight and obese patients were more likely to make a serious error compared with underweight/normal weight patients. (The proportions of patients reporting a previous inhaler technique review were 41% of those underweight/normal weight, 52% of those overweight and 50% of those obese; χ^2 test $p = 0.059$).

Discussion

We found that errors in Diskus inhaler technique are common among patients with asthma, with over half of patients in this study making ≥1 serious errors. The incidence of serious errors was significantly higher among female patients, obese patients and those who had not had their inhaler technique reviewed within the previous year, who were of lower educational level and who assessed their own technique as poor. We found that asthma-related hospitalizations and severe exacerbations during the previous year, and poor asthma control during the previous 4 weeks as measured on the ATAQ, were more common among patients who made ≥1 serious errors. In the multivariable model, risk factors identified for making ≥1 serious errors were having

Table 5. Odds ratios of recording a serious error (vs. not) for categorical variables – multivariable analyses (including interaction).

	Reference category	Category	Odds ratio (95% CI)	*p* value	
Sex		Male	Female	1.50 (1.07, 2.11)	0.018
BMI by Inhaler check	Inhaler check = YES	Underweight/Normal weight	Overweight	0.75 (0.43, 1.32)	0.090
			Obese	1.26 (0.70, 2.27)	
	Inhaler check = NO		Overweight	1.77 (1.03, 3.03)	
			Obese	2.26 (1.28, 3.99)	
Inhaler check by BMI	Underweight/Normal	Inhaler check = Yes	No	0.91 (0.53, 1.57)	0.090
	Overweight		No	2.14 (1.22, 3.76)	
	Obese		No	1.63 (0.88, 3.01)	
ATAQ	Good control/Partial control	Poor control	1.60 (1.06, 2.41)	0.026	
Inpatient admission or ED attendance	0	1+	2.00 (1.22, 3.29)	0.006	

Abbreviations: ATAQ, Asthma Therapy Assessment Questionnaire; BMI, body mass index; ED, emergency department.

experienced ≥1 asthma-related hospitalizations during the previous year, being obese, being female, having poor asthma control during the previous 4 weeks (as measured by the ATAQ), and no patient-reported review of inhaler technique by an HCP during the previous year.

Results of this study support the consensus that incorrect inhaler technique is a common issue rather than an exception among patients with asthma [4,8,9]. The two errors most frequently reported in our study (failure to exhale before inhalation and insufficient [or absent] breath-hold at the end of inhalation) are in agreement with previously published reports of the most frequently observed errors with the Diskus being ''no exhalation before inhalation'' and ''no breath-holding after inhalation'' [13,15,23,33]. The third most common error in our study (inhalation that was not forceful from the start) has also been reported [13,15,33,34]. Specific dose preparation errors with the Diskus (does not slide cover as far as possible and does not slide lever fully to open mouthpiece) were found to be low (4.3% total), consistent with previous reports in which 7.3% of patients incorrectly loaded the dose [16] and 2.5% did not slide the lever as far as possible [23]. Other errors reported as common with the Diskus in previous observational studies include incorrect dose metering [15], failure to prime the device correctly [33,34] and exhaling into the device [13,23].

Our findings suggest that some patient characteristics may potentially predict incorrect inhalation technique, specifically female sex and obesity. One alternative explanation for these findings could be that suboptimally controlled asthma is more common in obese patients [35], and the phenotype of obese non-eosinophilic asthma responds poorly to ICS [36,37]. Moreover, we cannot rule out the possibility of these being statistically significant findings that are of no clinical significance or relevance.

We found that patients with a lower level of education, as previously reported [13,16,38], were more likely to make a serious error, although education was not included in the multivariable model because it was confounded by the BMI and inhaler review status. An association between inhaler misuse and older age has been described previously [13,16,38,39]. We found no significant association with age, although only 4% of patients in the study were older than 70 years. The incidence of errors was also not significantly associated with lung function in this study, perhaps because of our broad study population that was not limited to patients with severe asthma [21,38]. Instead, we found that sex and BMI may be more important factors to consider when selecting inhaler device.

The association between incorrect inhaler technique and lack of prior inhaler technique instruction by HCPs has been described previously [13,16,33,38]. However, in practice it is relevant not only whether inhaler technique instruction is given but also the nature of that instruction, as not all methods of instruction are equally effective. Furthermore, the action of checking to see what the patient is actually doing incorrectly and the associated feedback/correction from the HCP may be critical and needs to be considered [40]. Inhaler training has been shown to significantly improve the proportion of patients with proper inhaler technique and to produce improved asthma control scores [17,41–43]. That said, many HCPs are not skilled in using inhalation devices and could also benefit from training [44]; consequently, patients may not receive appropriate (if any) inhaler instruction.

We also found that a patient self-assessment of inhaler technique as being poor was associated with increased likelihood of inhaler errors, suggesting that a simple query to patients could be an easy, fast and inexpensive screening method to identify patients who would benefit from inhaler training. These data are actually inconsistent with other research showing that individuals who demonstrate errors may think they are using their devices correctly [9,45]. While it is easy to address inhaler technique for those who feel there is a problem, being able to identify those who have incorrect technique but do not realize it is more challenging. We need to look at other factors to detect those individuals, and the findings of this study have identified some of those factors.

Strengths of this study are its observational design and the inclusion of data from more than 600 patients undergoing inhaler technique review in a routine clinical setting in eight different countries. We intentionally applied minimal exclusion criteria in order to study a heterogeneous, representative population of patients with asthma to maximize generalizability of results to primary care practice; this was in contrast to enrolment in RCTs, which typically include only patients who demonstrate ideal inhaler technique in order to minimize potential bias. In addition, this study included patient-reported feedback, providing important insight into patient perspectives.

The use of real-life datasets presents a set of limitations for which adjustments are not always possible, particularly the

issue of missing data, which in the required anonymized form was not feasible to retrieve. As the missing data in our study appeared randomly distributed (data not shown), we believe this limitation is unlikely to substantially bias the results. Another potential confounder is the possibility of inter-individual observation bias among the iHARP HCPs. While iHARP nurses and doctors receive the same training for observing and evaluating inhaler technique, different interpretations of observed technique are still possible, particularly with regard to the more subjective errors such as inhalation being ''not forceful''. Subsequent studies would benefit from incorporating objective appraisals of patient inhalation profiles using specific thresholds with devices such as the In-Check™ DIAL (Alliance Tech Medical, Granbury, TX), the Aerosol Inhalation Monitor® (Vitalograph), or any other system that measures inhalation profile [46]. Furthermore, medical staff were not blinded to the questionnaire results, which could potentially have influenced their observations. Data such as frequency of hospitalizations and exacerbations in the year preceding the patient review were obtained via a patient-completed questionnaire; hence, recall bias may be a further limitation of the study. Finally, the design of this study does not enable us to address the issue of cause and effect.

Using an international dataset enabled us to compare patient inhaler technique in several countries and to identify incorrect technique as a widespread problem. However, a limitation of this approach is possible confounding caused by inter-country differences in how disease outcomes are measured and recorded (e.g. the Netherlands does not use the MARS to measure adherence).

Nonetheless, although observational studies such as this may lack the internal validity achievable in RCTs, they provide a valuable insight into patient behavior and health outcomes in clinical practice. As such our findings should be considered in conjunction with those arising from other study designs including RCTs.

Our study focused on a single dry powder device, the Diskus inhaler, with which a rather low rate of errors has previously been reported [14,22–24]. Additional areas for further investigation include the characteristics of patients who made more than one serious error (quantity) and the impact of error type (quality) in order to clarify the importance and clinical relevance of each type of error. Further study is also needed to identify factors associated with making serious errors with other devices. The importance of choosing the right inhaler device for the individual patient is widely recognized [8,9,47,48], and selecting devices based on patient characteristics and preferences could be an important step for improving asthma control and along with assessing adherence should be the first step before increasing therapy. Patient preference for an inhaler device combined with ease of inhaler instructions is associated with an increased likelihood of correct use [14,34]. Personalized prescribing of inhaler devices could provide a safe and effective method of achieving better asthma control, fewer exacerbations, fewer hospital admissions and ultimately lower healthcare costs.

Conclusions

We found that inhaler technique errors are common among patients with asthma using the Diskus inhaler. The most frequent error in this study, the failure to exhale before inhalation, was observed in one third of patients. We found that errors were more common among female patients and obese patients. In addition to these two patient characteristics, factors significantly associated with making $\geq$1 serious errors were an asthma-related hospitalization or emergency department attendance the prior year, lack of an inhaler technique review within 1 year and poor asthma control over the previous 4 weeks. These findings highlight the importance of regular monitoring of inhaler technique and can aid in identifying patients who could benefit from a review of their Diskus inhaler technique. Patients with evidence of poor asthma control should be targeted for a review of their inhaler technique even when using a device thought to have a low error rate.

Acknowledgements

The iHARP database was funded by unrestricted grants from Mundipharma International Ltd and Research in Real-Life Ltd; these analyses were funded by an unrestricted grant from Teva Pharmaceuticals. Mundipharma and Teva played no role in study conduct or analysis and did not modify or approve the manuscript. The authors wish to direct a special appreciation to all the participants of the iHARP group who contributed data to this study and to Mundipharma, sponsors of the iHARP group. In addition, we thank Julie von Ziegenweidt for assistance with data extraction and Anna Gilchrist and Valerie L. Ashton, PhD, for editorial assistance. Elizabeth V. Hillyer, DVM, provided editorial and writing support, funded by Research in Real-Life, Ltd.

Declaration of interest

Janine A. M. Westerik declares that she has no conflicts of interest in relation to this article. Victoria Carter, Anne Burden, Samantha L. Thompson and Catherine Hutton were employees of Research in Real-Life (RiRL), which conducted this study and which has conducted paid research in respiratory disease on behalf of the following other organizations in the past 5 years: Aerocrine, AKL Ltd, Almirall, Astra Zeneca, Boehringer Ingelheim, Chiesi, GlaxoSmithKline, Meda, Mundipharma, Napp, Novartis, Orion, Sanofi, Takeda and Teva. Henry Chrystyn has no shares in any pharmaceutical companies. He has received sponsorship to carry out studies, together with Board Membership, consultant agreements and honoraria for presentation, from several pharmaceutical companies that market inhaled products. These include Almirall, AstraZeneca, Boehringer Ingelheim, Chiesi, GlaxoSmithKline, Innovata Biomed, Meda, Napp Pharmaceuticals, Mundipharma, NorPharma, Novartis, Orion, Sanofi, Teva, Truddell Medical International, UCB and Zentiva. Research sponsorship has also been received from grant awarding bodies (EPSRC and MRC). He owns 50% of Inhalation Consultancy Ltd. Dermot Ryan has provided consultancy to or lectured on behalf of AstraZeneca, GlaxoSmithKline, Novartis, Almirall, Teva, Meda, Uriach,

Stallergenes, Chiesi, Boehringer-Ingelheim, Orion. Kevin Gruffydd-Jones has spoken on behalf of and acted as a consultant for AstraZeneca, Boehringer Ingelheim, Chiesi, GlaxoSmithKline, Mundipharma/NAPP. John Haughney has received reimbursements for attending symposia, fees for speaking, organizing educational events, funds for research or fees for consulting from AstraZeneca, Boehringer Ingelheim, GlaxoSmithKline, Merck Sharp & Dohme, Mundipharma, Novartis and Teva. Nicolas Roche has received over the past 3 years (i) fees for speaking, organizing education, participation in advisory boards or consulting from Aerocrine, Almirall, AstraZeneca, Boehringer Ingelheim, Chiesi, Cipla, GlaxoSmithKline, MSD-Chibret, Mundipharma, Novartis, Pfizer, Stallergenes, Teva; (ii) research grants from Novartis, Boehringer Ingelheim and Pfizer. Federico Lavorini has received in the past 5 years honoraria for consultancy and presentations from the following pharmaceutical companies that market inhaled products: Almirall, AstraZeneca, Boehringer Ingelheim, Chiesi, GlaxoSmithKline, TEVA and Zentiva. Alberto Papi has received grants, personal fees and non-financial support from AstraZeneca, Chiesi Farmaceutici, GlaxoSmithKline, Boehringer Ingelheim, Merck Sharp & Dohme, Menarini, Novartis, Zambon, TEVA, Pfizer, Takeda and Mundipharma. Antonio Infantino has no conflicts of interest to declare in relation to this article. Miguel Román-Rodríguez has provided consultancy to or lectured on behalf of AstraZeneca, GlaxoSmithKline, Novartis, Almirall, Chiesi, Mundipharma, Boehringer-Ingelheim, Rovi and Teva. Sinthia Bosnic-Anticevich has received reimbursements for attending meetings, fees for speaking or consultancy from Mundipharma and Teva. Karin Lisspers has received payment for advisory board from Meda, Novartis, scientific committee from AstraZeneca, Novartis and for lectures from Meda, AstraZeneca, Novartis, GlaxoSmithKline, Nycomed and Boehringer Ingelheim. Björn Ställberg has received honoraria for educational activities and lectures from AstraZeneca, Boehringer Ingelheim, GlaxoSmithKline, Meda, MSD, Novartis and TEVA, and has served on advisory boards arranged by AstraZeneca, Novartis and Boehringer Ingelheim. Svein Høegh Henrichsen has no conflicts of interest to declare. Thys van der Molen has received grants for research, travel fees, reimbursement for presentations and advisory boards from AstraZeneca, GlaxoSmithKline, Almirall, Mundipharma, Boehringer Ingelheim, Chiesi, Teva and Novartis. David B. Price has Board Membership with Aerocrine, Almirall, Amgen, AstraZeneca, Boehringer Ingelheim, Chiesi, Meda, Mundipharma, Napp, Novartis and Teva. Consultancy: Almirall, Amgen, AstraZeneca, Boehringer Ingelheim, Chiesi, GlaxoSmithKline, Meda, Mundipharma, Napp, Novartis, Pfizer, Teva and Zentiva; Grants/Grants Pending with UK National Health Service, British Lung Foundation, Aerocrine, AstraZeneca, Boehringer Ingelheim, Chiesi, Eli Lilly, GlaxoSmithKline, Meda, Merck, Mundipharma, Novartis, Orion, Pfizer, Respiratory Effectiveness Group, Takeda, Teva and Zentiva; Payments for lectures/speaking: Almirall, AstraZeneca, Boehringer Ingelheim, Chiesi, Cipla, GlaxoSmithKline, Kyorin, Meda, Merck, Mundipharma, Novartis, Pfizer, SkyePharma, Takeda and Teva; Payment for manuscript preparation: Mundipharma and Teva; Patents (planned, pending or issued): AKL Ltd.; Payment for the development of educational materials: GlaxoSmithKline, Novartis; Stock/Stock options: Shares in AKL Ltd which produces phytopharmaceuticals and owns 80% of Research in Real Life Ltd and its subsidiary social enterprise Optimum Patient Care; received Payment for travel/accommodations/meeting expenses from Aerocrine, Boehringer Ingelheim, Mundipharma, Napp, Novartis and Teva; Funding for patient enrolment or completion of research: Almirral, Chiesi, Teva and Zentiva; Peer reviewer for grant committees: Medical Research Council (2014), Efficacy and Mechanism Evaluation programme (2012), HTA (2014); and Received unrestricted funding for investigator-initiated studies from Aerocrine, AKL Ltd, Almirall, Boehringer Ingelheim, Chiesi, Meda, Mundipharma, Napp, Novartis, Orion, Takeda, Teva and Zentiva.

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Supplementary material available online

Supplementary Tables S1–S4