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To cite this article: Sarah Ann Barbara, Vicky Kritikos, David B. Price & Sinthia Bosnic-Anticevich (2020): Identifying patients at risk of poor asthma outcomes associated with making inhaler technique errors, Journal of Asthma, DOI: [10.1080/02770903.2020.1742353](https://doi.org/10.1080/02770903.2020.1742353)

To link to this article: <https://doi.org/10.1080/02770903.2020.1742353>



Accepted author version posted online: 12 Mar 2020.
Published online: 31 Mar 2020.



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Identifying patients at risk of poor asthma outcomes associated with making inhaler technique errors

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ABSTRACT

Objectives: Correct inhaler technique is essential to optimal clinical outcomes in asthma patients. The study aim was to use real-life data from the iHARP database to determine patient factors associated with the performance of inhaler technique errors associated with poor asthma outcomes (as identified in the Critikal study) in patients with asthma prescribed the Turbuhaler (TH), Metered Dose Inhaler (MDI), and Accuhaler (AH) device.

Methods: This was a retrospective cross-sectional study using the iHARP database, a multi-national initiative including questionnaires and technique review. Identification of inhaler technique errors specifically associated with poor asthma outcomes was performed by reference to the Critikal study. Multivariable logistic regression was used to identify demographic and clinical factors associated with ≥ 1 of these errors.

Results: Factors significantly associated with ≥ 1 inhaler technique error and worsening asthma outcomes for the TH cohort include female gender, very poor to average self-assessment of inhaler technique; for the MDI cohort, female gender, secondary education, and current smoking status; and, in the AH cohort, lack of inhaler technique review by a trained healthcare professional in the previous twelve months and very poor to average self-assessment of inhaler technique.

Conclusions: Numerous specific patient demographic and clinical factors associated with the performance of these errors have been identified, differing according to device. Inhaler technique error associated with poor asthma outcomes is further widespread across devices. Knowledge of these factors and the frequency of their occurrence may assist in optimizing device selection and training.

ARTICLE HISTORY

Received 14 October 2019

Revised 3 March 2020

Accepted 9 March 2020

KEYWORDS

Asthma therapy; inhaler technique; turbuhaler; accuhaler; pressurized metered dose inhaler; database

Introduction

Asthma, an escalating health epidemic, is one of the leading contributors to the global burden of disease, placing significant costs on both the healthcare system and patient quality of life. Despite evidence that it can be effectively managed via appropriate inhaled pharmacotherapy, both hospitalizations and impacts on quality of life remain high.

Of concern is the burden of asthma associated with incorrect medication/inhaler use. Numerous studies have described the high prevalence of sub-optimal inhaler technique of asthma patients (1–4). Additional studies have further identified risk factors associated with the performance of inhaler technique errors (including female gender (5,6) older age (7–12), inferior education (13), lack of healthcare professional (HCP)-led inhaler technique education (5,8,10,14),

and diagnosis of chronic obstructive pulmonary disease (COPD) (15)).

However, a key limitation of these studies is that they have not focused on inhaler technique errors which are specifically linked to poor asthma outcomes, that is, uncontrolled asthma and/or increased exacerbations. Recently, ground-breaking research has identified that not all inhaler technique errors lead to clinically relevant effects, with only specific errors being directly related to poor asthma outcomes. This study, the CritiKal (16) study, specifically identified which errors are associated with these poor asthma outcomes in the turbuhaler (TH), metered dose inhaler (MDI), and accuhaler (AH) devices (listed in Table 1, below).

The importance of these errors, if those supported by evidence, cannot be underestimated, as, whilst it is important that patients are taught to perform all steps

Table 1. Inhaler technique errors associated with poor asthma outcomes.

Device	Error
TH	<i>Does not remove cap</i> <i>Shakes device during preparation</i> <i>Device not held upright after the base is twisted until inhalation (within 45 degrees)</i> <i>Shakes after dose preparation</i> <i>Does not breathe out slowly to empty lungs</i> <i>Fails to put in mouth and seal lips around mouthpiece</i> <i>Inhalation is not as fast as you can (defined as a very fast suck)</i> <i>Inhalation is not forceful from the start</i> <i>Inhalation is not as long as you can</i>
MDI	<i>Does not breathe out x</i> <i>Exhalation into the inhaler x</i> <i>Does not hold inhaler upright</i> <i>Does not have head tilted such that chin is slightly upwards x</i> <i>Actuation not corresponding to inhalation (actuation before inhalation)</i>
AH	<i>Does not breathe out slowly to empty lungs</i> <i>Inhalation is not as fast as you can (defined as a very fast suck)</i> <i>Inhalation is not forceful from the start</i> <i>Inhalation is not as long as you can</i>

Legend for Tables 1–4: TH: Turbuhaler.

MDI: Metered Dose Inhaler.

AH: Accuhaler.

associated with inhaler device use, the steps that truly need to be performed correctly are those that are associated with poor asthma outcomes. However, this information is not enough. In particular, it is essential to determine which patient cohorts are particularly at risk of making these specific errors, to enable the development of personalized interventions specifically targeted to patient's unique educational needs.

To better identify these patient cohorts, it is imperative that the factors associated with making these specific inhaler technique errors be identified. Therefore the aim of this research is to focus only on errors specifically associated with poor asthma outcomes, and to identify factors associated with making these errors.

Methods

Data source

The study was a retrospective cross-sectional study using data from the international Helping Asthma in Real life Patients (iHARP) database. iHARP data was collected prospectively between June 2011 and December 2014, from participating primary care practices in Australia, the United Kingdom, Italy, Spain, the Netherlands, France, Norway, and Sweden. Each practice received an identical face-to-face iHARP review using questionnaire and practitioner-led assessments to collect information about the patient's demographics, symptoms, lung function, and inhaler technique. A copy of the questionnaire is available from the following website: <http://iharp.org/questionnaire.aspx> (17).

Appropriate ethics approval for the iHARP service was obtained for each practice as per nation requirements. The Anonymous Data Ethics Protocols and Transparency (ADEPT) committee gave approval for the Woolcock Institute of Medical Research to use the iHARP database (ADEPT0617).

Cohort definition

To be eligible for iHARP review, patients had to be diagnosed with asthma, prescribed fixed-dose combination inhaled corticosteroid and long-acting β_2 agonist (ICS/LABA) therapy, and have received at least two prescriptions for such therapy in the twelve months prior to the review via a TH, MDI, or AH.

Patients were excluded if they had received a diagnosis of chronic respiratory disease other than asthma, were at least 40 years of age with a history of smoking and no COPD exclusion, or been prescribed a separate ICS, long-term systemic treatment for asthma, or course of oral corticosteroids and/or antibiotics for a lower respiratory condition in the two weeks prior to review.

Our study cohort was restricted to the subset of patients from the database who were at least eighteen years of age and prescribed the TH, MDI, or AH devices. Patients were only using type of inhaler device. Analyses were carried out within device cohorts.

Study data

Patient demographic and clinical characteristics, including asthma control status and patient-self-assessment of inhaler technique [assessed 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,")] were obtained via questionnaires completed online or in hard-copy on the review day.

Asthma control was assessed using the four Global Initiative for Asthma (GINA) criteria at the time (18), which asked patients if the experienced during the week preceding the review: daytime symptoms (more than twice per week); any night waking due to asthma; need for reliever more than twice per week; and any limitation in daytime activity. Asthma control was defined as controlled (none of the above); partially controlled (1 or 2 of the above); or uncontrolled (3 or 4 of the above).

Self-reported adherence to maintenance therapy was assessed for patients from countries other than the Netherlands using the Medication Adherence Rating

Scale (MARS). For patients from the Netherlands, adherence to maintenance therapy was assessed with the question, “*Do you ever forget your prevention inhalation medication?*” Adherence was categorized as poor for responses of ‘very often,’ or ‘always,’ borderline for responses of ‘now and then’ or ‘regularly’ and good for responses of ‘never’ or ‘rarely.’

Other variables recorded during the iHARP interview explored in this study included age, gender, body mass index (BMI), and smoking status, which were shown in the CritiKal study (16) to be associated with significant differences in asthma control when varied. Educational status was further assessed, as recent research (19) had found an association between inferior educational levels and inhaler technique in patients with COPD, and we wanted to identify if this was also an issue in patients with asthma. Associations with patient-reported prior inhaler technique review by a HCP (20), and patient adherence (21) with poor inhaler technique have further been identified in the literature, and have thus been included as variables in this study. Finally, self-assessment of inhaler technique was further included as a variable, as prior research (22,23) has indicated there may be a discordance between patient perceptions of their accuracy in technique, and their actual accuracy. We therefore wanted to investigate if such a variable could possibly be associated with the performance of inhaler technique errors associated with poor asthma outcomes in practice.

Measurement of inhaler technique errors associated with poor asthma outcomes

Inhaler technique errors associated with poor asthma outcomes were defined as errors significantly associated with uncontrolled asthma and/or an increased rate of asthma exacerbations (ie having at least one exacerbation in the 12 months prior to review) (16). The list of such errors for all 3 inhaler devices is shown in Table 1. We only considered these errors, as these are the only ones shown in the literature to be associated with poor asthma outcomes (16). HCPs were trained to identify inhaler technique errors by watching standardized instructional videos. Observational evaluation of each participant was then conducted via reference to standardized, device-specific checklists developed by clinical experts in the iHARP steering committee. Whilst inhaler use was observed once or twice as per the number of doses required, the data used in this study is restricted to the errors only made on first inhalation through the device.

Statistical analyses

Statistical analyses were performed using SPSS Statistics version 24. Characteristics of patients who made no inhaler technique errors associated with poor asthma outcomes using each device were compared with those making one or more (≥ 1) inhaler technique errors associated with poor clinical outcomes. Continuous variables that were normally distributed were compared using the Student’s *t*-test and the Mann-Whitney *U*-test was used for continuous variables that were not normally distributed. Categorical variables were compared using the χ^2 test.

Characteristics associated with making errors associated with poor asthma outcomes were initially identified using univariate logistic regression models with a dichotomous indicator variable for errors associated with poor clinical outcomes made (yes/no) as the dependent variable, and the patient characteristics as independent variables.

Multivariate logistic regression analysis was then performed on the univariate predictors, with $p < 0.05$ used as the threshold for entry into the model. The goodness of fit of the logistic regression model was confirmed by the Hosmer-Lemeshow test. A significance level of $p < 0.05$ was used for all statistical procedures.

Results

Patients

After applying inclusion and exclusion criteria, the data from 4134 adult patients from the iHARP database with asthma were available for inclusion and analysis into this study. Three device cohorts were formed based on the three most common inhaler devices used by patients; with TH used by 2065 (46.2%) patients, MDI used by 1245 (27.9%) patients, and AH used by 824 (18.4%) patients. Using the GINA-defined criteria, 30.5% had controlled asthma, 43.9% had partly controlled asthma and 25.6% had uncontrolled asthma. There was no significant difference in these proportions across devices.

1) Turbuhaler cohort

a. Patient characteristics: There were 2065 (46.2%) patients, with patients present from the UK (1035 [50.1%]), France (7, [0.3%]), Holland (498, [24.1%]), Italy (104, [5.0%]), Norway (14, [0.7%]), Spain (273, [13.2%]), Sweden (55, [2.7%]), and Australia (79, [3.8%]). The final study cohort comprised 61% females, had a

Table 2a. Patient characteristics part 1 - TH.

Characteristic	Total (n = 2065)	0 errors (n = 817)	≥ 1 errors (n = 1248)	p value
Age, mean (SD)	50 (15)	50 (15)	50 (14)	0.97
18-30 years, n (%)	270 (13)	106 (13)	164 (13)	0.013
31-50 years, n (%)	703 (34)	290 (36)	413 (33)	
51-70 years, n (%)	1016 (49)	379 (46)	637 (51)	
> 70 years, n (%)	76 (4)	42 (5)	34 (3)	
Sexn(%)				0.001
Female	1250 (61)	459 (56)	791 (63)	
Male	815 (39)	358 (44)	457 (37)	
Body mass index, n (%)	0.27			
Underweight	20 (1)	5 (1)	15 (1)	
Normal	622 (30)	251 (31)	371 (30)	
Overweight	751 (36)	442 (38)	309 (35)	
Obese	672 (33)	252 (15)	420 (34)	
Smoking status, n (%)	0.322			
Current smoker	281 (14)	102 (13)	179 (14)	
Ex-smoker	686 (33)	284 (35)	402 (32)	
Non-smoker	1098 (53)	431 (53)	667 (54)	
Education, known status, n (%)	1400 (68)	527 (38)	873 (62)	0.054
Post-graduate or professional degree	49 (4)	18 (3)	31 (4)	
University degree	466 (33)	187 (36)	279 (32)	
Secondary education	704 (50)	272 (52)	432 (50)	
Primary education	155 (11)	43 (8)	112 (13)	
None	26 (2)	7 (1)	19 (2)	
Patient-reported prior inhaler review by HCP	1019 (49)	431(35)	588 (38)	0.012
Patient self-assessment of inhaler technique, n(%), known	1728 (84)	645 (37)	1083 (63)	0.001
Very poor to poor	54 (3)	12 (2)	42 (4)	
Fair to average	286 (17)	85 (13)	201 (19)	
Good to excellent	1388 (80)	548 (85)	840 (78)	
Adherence to therapy, n(%)	2029 (98)	803 (65)	1226 (79)	0.021
Poor	491 (24)	171 (21)	320 (26)	
Borderline	84 (4)	29 (4)	55 (4)	
Good	1454 (72)	603 (75)	851 (69)	
Adherence to therapy in the Netherlands, n(%), known	498 (24)	248 (50)	250 (50)	0.643
Poor	42(8)	18 (7)	24 (10)	
Borderline	101 (20)	51 (20)	50 (20)	
Good	355 (71)	179 (72)	176 (70)	

mean (SD) age of 50 (15) years, and 281 (14%) were current smokers (Table 2a).

b. Patient characteristics associated with making TH technique errors associated with poor asthma outcomes: Sixty percent (60.4%) of patients made from 1 to 6 errors associated with poor clinical outcomes, most commonly one (605 [29.3%]), two (310 [15.0%]), and three (183 [8.9%]) errors; 150 patients (7.2%) made at least four errors. The most frequently made errors were not exhaling slowly to empty the lungs (26.3%), not holding the device upright (within 45°) after the base is twisted until inhalation (19.6%), and not inhaling forcefully from the start of inhalation (18.8%) (Figure 1).

Patients making at least one error associated with poor asthma outcomes were significantly more likely to be female, not have undertaken an inhaler review within the twelve months prior to the iHARP assessment, have 'poor-to-borderline' adherence to therapy as opposed to 'good' adherence, and self-assess their inhaler technique as 'very poor to average' as opposed to 'good-to-excellent.' Whilst age appeared to be a factor, subsequent univariate logistic regression did not

reveal any significant relationship between age and critical error performance. Body mass index, smoking status, and educational status were not significantly associated with making at least one error associated with poor asthma outcomes (Table 2a).

c. Risk factors for making inhaler technique errors associated with poor asthma outcomes: multivariable model. The univariable logistic regression results for the risk of making ≥ 1 error associated with poor asthma outcomes are reported in Table 2b. There were no correlations between the univariate predictors.

A multivariable logistic regression was performed to determine the effects of gender, inhaler technique review by a trained healthcare professional, MARS adherence, age, and self-assessment of inhaler technique on the risk of performing at least one error associated with poor asthma outcomes.

The multivariable logistic regression model contained 4 independent variables, and was statistically significant ($\chi^2 = 32.990$, $df = 5$, $p < 0.001$) (Table 2c).

Both gender and self-assessment of inhaler technique were significantly associated with the likelihood

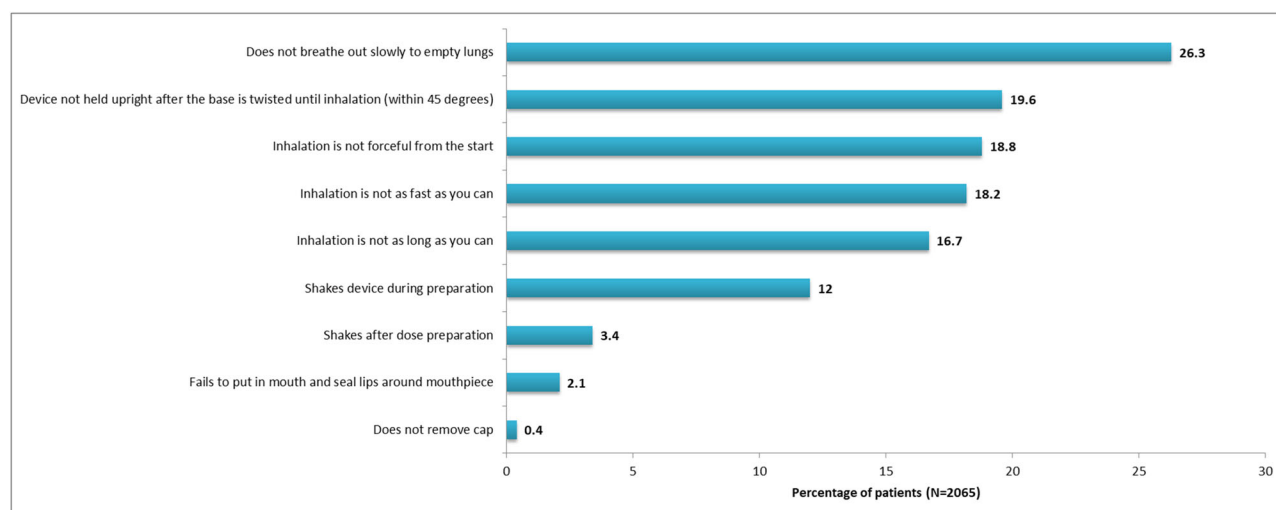


Figure 1. Incidence of TH errors associated with poor asthma outcomes.

Table 2b. Univariate and multivariate logistic regression - TH.

		TH								95% C.I. for Exp(B)	
Analysis	Predictors	Reference Category (0)	Category (1)	B	S.E.	Wald	df	Sig.	Exp(B)	Lower	Upper
Univariate	Gender	Male	Female	0.300	0.092	10.69	1	0.001	1.35	1.128	1.616
	Inhaler Technique Reviewed	Reviewed	Not reviewed	0.226	0.090	6.273	1	0.012	1.253	1.05	1.496
	MARS adherence	Good	Poor/Borderline	0.284	0.102	7.688	1	0.006	1.329	1.087	1.624
	Age - Group 1	> 51 years	18-30 years	-0.030	0.139	0.046	1	0.831	0.971	0.739	1.275
	Age - Group 2	> 51 years	31-50 years	-0.113	0.099	1.302	1	0.254	0.894	0.736	1.084
	Age- Group 3	> 51 years	18-50 years	-0.090	0.090	0.991	1	0.320	0.914	0.766	1.091
	Self-assessment of inhaler technique	Good to excellent	Very poor to average	0.491	0.132	13.836	1	0.000	1.634	1.262	2.117
Multivariate (no interaction)	Gender	Male	Female	0.383	0.102	14.083	1	<0.001	1.467	1.201	1.793
	Self-assessment of inhaler technique	Good to excellent	Very poor to average	0.474	0.133	12.649	1	<0.001	1.607	1.237	2.086
	MARS adherence	Poor/Borderline	Good	-0.121	0.109	1.237	1	0.266	0.886	0.716	1.096
	Inhaler Technique Reviewed	Not reviewed	Reviewed	-0.147	0.102	2.097	1	0.148	0.863	0.707	1.053

of making an error associated with poor asthma outcomes. In particular, females were almost 1.5 times more likely than males to make an error associated with poor asthma outcomes (OR = 1.467, 95% CI:1.201–1.793, $p < 0.001$), and those who self-assessed their inhaler technique to be “very-poor-to-average” were almost twice as likely to make an error associated with poor asthma outcomes to those who self-assessed their inhaler technique as “good-to-excellent”(OR = 1.607, 95% CI:1.237–2.086, $p < 0.001$). There were no interactions between the variables.

2) MDI Cohort

a. Patient characteristics: There were 1245 (27.9%) patients, with patients present from the UK (917 [73.1%]), Italy (149 [12.0%]), Spain (88 [7.1%]), Australia (57 [4.6%]), Holland (27 [2.2%]), Norway (5 [0.4%]), and France (2 [0.2%]). The final study cohort comprised 60% females, had a mean (SD) age of 50

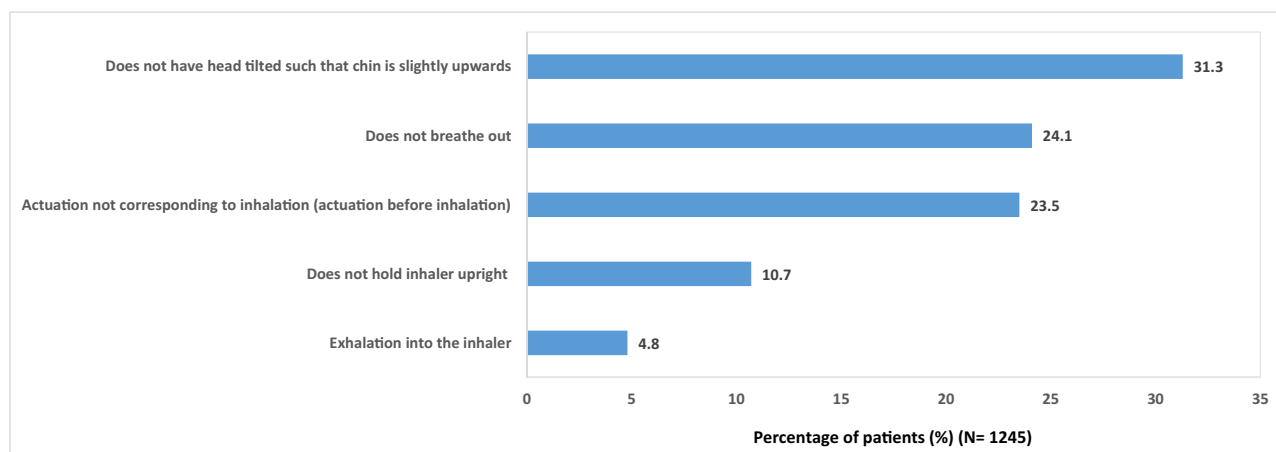
(14) years, and 167 (13) were current smokers (Table 3).

b. Patient characteristics associated with making MDI technique errors associated with poor asthma outcomes: Fifty seven percent (57.3%) of patients made from 1 to 5 errors associated with poor asthma outcomes, most commonly one (421 [33.8%]), two (176 [14.1%]), and three (63 [5.1%]) errors; 53 patients (4.3%) made at least four errors. The most frequently made errors were not tilting the head such that the chin is slightly upwards during inhalation (31.3%), not exhaling prior to inhalation (24.1%), and actuating the inhaler device prior to inhalation (23.5%) (Figure 2).

Patients making at least one error associated with poor asthma outcomes were significantly more likely to be female, have no greater than a secondary education, and rate their inhaler technique as ‘very poor to average’ (Table 3a). Whilst smoking status appeared

Table 3a. Patient characteristics, part 1 - MDI.

Characteristic	Total (n = 1245)	0 errors (n = 532)	≥ 1 errors (n = 713)	p value
Age, mean (SD)	50 (14)	51 (15)	51 (15)	0.301
18-30 years, n (%)	139 (11)	56 (11)	83 (12)	0.240
31-50 years, n (%)	456 (37)	212 (40)	244 (34)	
51-70 years, n (%)	609 (49)	248 (47)	361 (51)	
> 70 years, n (%)	41 (3)	16 (3)	25 (4)	
Sex, n (%)				0.003
Female	743 (60)	292 (55)	451 (63)	
Male	502 (40)	240 (45)	262 (37)	
Body mass index, n (%)		0.242		
Underweight	26 (2)	16 (3)	10 (1)	
Normal	363 (29)	155 (29)	208 (29)	
Overweight	429 (35)	185 (35)	244 (34)	
Obese	427 (34)	176 (33)	251 (35)	
Smoking status, n (%)	0.032			
Current smoker	167 (13)	56 (11)	111 (16)	
Ex-smoker	373 (30)	161 (30)	212 (30)	
Non-smoker	705 (57)	315 (59)	390 (55)	
Education, known status, n (%)	1023 (82)	436 (43)	587 (57)	0.009
Post-graduate or professional degree	59 (6)	30 (7)	29 (5)	
University degree	318 (31)	157 (36)	161 (27)	
Secondary education	517 (51)	201 (46)	316 (54)	
Primary education	109 (11)	43 (10)	66 (11)	
None	20 (2)	5 (1)	15 (3)	
Patient-reported prior inhaler review by HCP	639 (51)	277 (53)	362	0.596
Patient self-assessment of inhaler technique, n(%), known	1178 (95)	501 (43)	677 (57)	0.01
Very poor to poor	65 (5)	24 (5)	41 (6)	
Fair to average	232 (20)	80 (16)	152 (23)	
Good to excellent	881 (75)	397 (79)	484 (71)	
Adherence to therapy, n(%)	1196 (96)	509 (43)	687 (57)	0.881
Poor	448 (38)	188 (37)	260 (38)	
Borderline	64 (5)	26 (5)	38 (6)	
Good	684 (57)	295 (58)	389 (57)	
Adherence to therapy in the Netherlands, n(%), known	27 (2)	14 (52)	13 (48)	0.754
Poor	5 (19)	2 (14)	3 (23)	
Borderline	10 (37)	6 (43)	4 (31)	
Good	12 (44)	6 (43)	6 (46)	

**Figure 2.** Incidence of MDI errors associated with poor asthma outcomes.

to be a factor, subsequent univariate logistic regression did not reveal any significant relationship between smoking status and performance of inhaler technique errors associated with poor asthma outcomes (Table 3b). Age, body mass index, patient-reported prior inhaler technique review by a trained healthcare professional, and adherence to therapy were not identified associated with making such errors. (Table 3a).

c. Risk factors for making inhaler technique errors associated with poor asthma outcomes: multivariable model. The univariable logistic regression results for the risk of making ≥ 1 error associated with poor asthma outcomes are reported in Table 3b. There were no correlations between the univariate predictors.

A multivariable binomial logistic regression was performed to determine the effects of gender,

Table 3b. Univariate and multivariate logistic regression - MDI.

Analysis	Predictors	Reference Category (0)	Category (1)	B	S.E.	Wald	df	Sig.	Exp(B)	95% C.I. for Exp(B)	
										Lower	Upper
Univariate	Gender	Female	Male	−0.347	0.117	8.837	1	0.003	0.707	0.562	0.888
	Education	Postgrad/prof/uni degree	Secondary education	0.437	0.137	10.163	1	0.001	1.547	1.183	2.024
	Self-assessment of Inhaler Technique	Good to excellent	Very poor to average	0.420	0.139	9.108	1	0.003	1.522	1.159	2.000
	Smoking Status	Current Smoker	Non-smoker	−0.471	0.181	6.793	1	0.009	0.625	0.438	0.89
Multivariate	Gender	Male	Female	0.453	0.169	7.221	1	0.007	1.574	1.131	2.191
	Education	Secondary education	Postgrad/prof/uni degree	−0.355	0.168	4.453	1	0.035	0.701	0.504	0.975
	Self-assessment of Inhaler Technique	Very poor to average	Good to excellent	0.494	−0.283	0.2	1	0.157	0.753	0.509	1.115
	Smoking Status	Non-smoker	Current smoker	0.462	0.218	4.475	1	0.034	1.587	1.035	2.436

educational status, self-assessment of inhaler technique, and smoking status on the odds of performing at least one inhaler technique error associated with poor asthma outcomes.

The multivariable logistic regression model contained 4 independent variables, and was statistically significant ($\chi^2 = 20.153$, $df = 4$, $p < 0.001$) (Table 3b).

Gender, educational status, self-assessment of inhaler technique, and smoking status were significantly associated with an increased risk of making errors associated with poor asthma outcomes. The study identified that females were 1.6 times more likely to make an error associated with poor asthma outcomes, (OR = 1.574, 95% CI:1.131–2.191, $p < 0.05$), patients with a secondary education 1.4 times more likely to make an error associated with poor asthma outcomes compared to those with a university degree (OR = 1.427, 95% CI:1.026–1.984, $p < 0.001$), and current smokers almost 1.6 times more likely to make an error associated with poor asthma outcomes than nonsmokers (OR = 1.587, 95% CI:1.035–2.436, $p < 0.05$) (Table 3c). There were no interactions between the variables.

3) Ah cohort

a. Patient characteristics: There were 824 (18.4%) patients, with patients present from England (328 [39.8%]), Italy (148 [18.0%]), Spain (140 [17.0%]), Holland (127[15.4%]), Australia (46[5.6%]), France (11[1.3%]), Norway (17[2.1%]), and Sweden (7[0.8%]).

The final study cohort comprised 61% females and had a mean (SD) age of 51 (15) years. 105 (13) were current smokers (Table 4a).

b. Characteristics associated with making AH technique errors associated with poor asthma outcomes: Fifty one percent (51.6%) of patients made from 1 to 4 errors associated with poor asthma outcomes, most commonly one (216 [26.2%]), two (112 [13.6%]), and three (58 [7.0%]) errors; 39 patients (4.7%) made four errors. The most frequently

performed errors were not exhaling slowly to empty the lungs prior to inhalation (32.5%), not inhaling forcefully from the start (21.1%), and not inhaling as fast as one can (20.8%) (Figure 3).

Patients making ≥ 1 error associated with poor asthma outcomes were significantly more likely to have a secondary as opposed to tertiary education, have not had had their inhaler technique reviewed by a trained HCP in the previous 12 months, and self-assess their inhaler technique as being ‘very poor to average’ as opposed to ‘good to excellent’ (Table 4a).

Age, gender, body mass index, smoking status, MARS adherence were not significantly associated with making at least one error associated with poor asthma outcomes (Table 4a).

c. Risk factors for making AH technique errors associated with poor asthma outcomes: multivariable model.

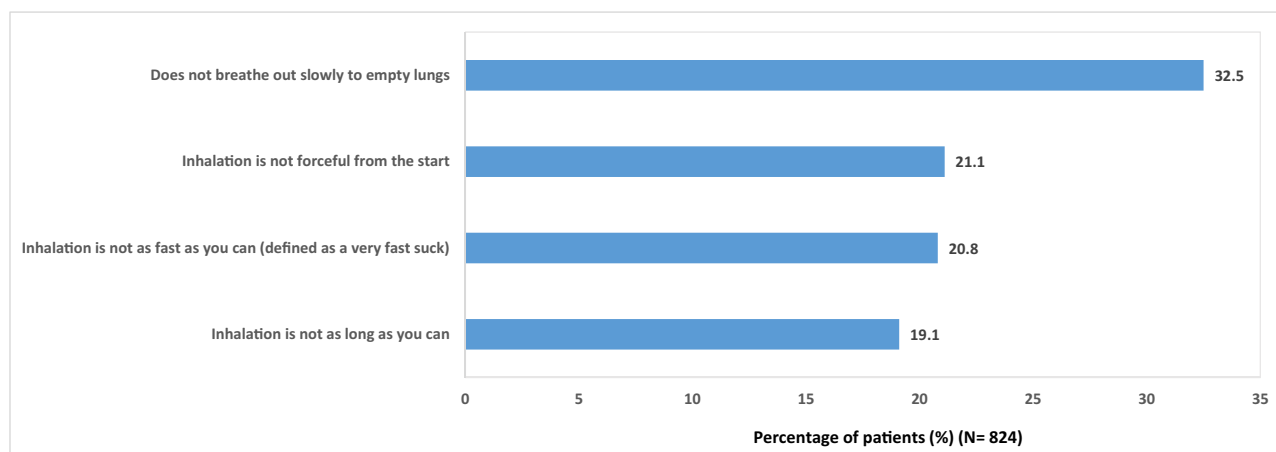
The univariable logistic regression results for the risk of making ≥ 1 inhaler technique error associated with poor asthma outcomes are reported in Table 4b. There were no correlations between the univariate predictors. The multivariable logistic regression model contained 2 independent variables and was statistically significant ($\chi^2 = 18.115$, $df = 12$, $p < 0.001$). Patients who made ≥ 1 error associated with poor asthma outcomes were almost twice as likely to not have had their inhaler technique reviewed in the previous 12 months (OR = 1.654, 95% CI:1.225–2.235, $p = 0.001$), and were 1.5 times as likely to have self-assessed their inhaler technique as being ‘very poor to average’ as opposed to ‘good to excellent’ (OR = 1.500, 95% CI:1.053–2.137, $p < 0.05$) (Table 4c). There were no interactions between the variables.

Discussion

This research, to our knowledge, is the first to identify patient factors associated with making inhaler technique errors specifically associated with poor asthma outcomes for people with asthma in primary care.

Table 4a. Patient characteristics part 1 - AH.

Characteristic	Total N (%) (n = 824)	0 errors (n = 399)	≥ 1 errors (n = 425)	p value
Age, mean (SD)	51 (15)	51 (14)	51 (15)	0.59
18-30 years, n (%)	91 (11)	46 (12)	45 (11)	0.24
31-50 years, n (%)	283 (34)	137 (34)	146 (34)	
51-70 years, n (%)	408 (50)	202 (51)	206 (48)	
> 70 years, n (%)	42 (5)	14 (4)	28 (7)	
Sex, n (%)				0.128
female,	495 (61)	229 (57)	266 (63)	
Male	329 (40)	170 (43)	159 (37)	
Body mass index, n (%)	0.944			
Underweight	9 (1)	5 (1)	4 (1)	
Normal	275 (33)	135 (34)	140 (33)	
Overweight	288 (35)	140 (35)	148 (35)	
Obese	252 (31)	119 (30)	133 (32)	
Smoking status, n (%)	0.554			
Current smoker	105 (13)	47 (12)	58 (14)	
Ex-smoker	260 (32)	132 (33)	128 (31)	
Non-smoker	459 (56)	220 (55)	239 (56)	
Education, known status, n (%)	641 (78%)	302 (47)	339 (53)	0.011
Post-graduate or professional degree	15 (2)	11 (4)	4 (1)	
University degree	187 (30)	99 (33)	88 (26)	
Secondary education	281 (44)	130 (43)	151 (45)	
Primary education	128 (20)	55 (18)	74 (22)	
None	30 (5)	8 (3)	22 (6)	
Patient-reported prior inhaler review by HCP	352 (43)	197 (49)	155 (37) (out of 423)	<0.001
Patient self-assessment of inhaler technique, n(%), known	716 (87)	346 (48)	370 (52)	0.026
Very poor to poor	27 (4)	12 (3)	15 (4)	
Fair to average	145 (20)	56 (16)	89 (24)	
Good to excellent	544 (76)	278 (80)	266 (72)	
Adherence to therapy, n(%)	790 (96)	388 (49)	402 (51)	0.072
Poor	263 (33)	114 (29)	149 (37)	
Borderline	51 (6)	26 (7)	25 (6)	
Good	476 (58)	248 (64)	228 (57)	
Adherence to therapy in the Netherlands, n(%), known	127 (15)	71 (56)	56 (44)	0.299
Poor	13 (10)	9 (13)	4 (7)	
Borderline	23 (18)	15 (21)	8 (14)	
Good	91 (71)	47 (66)	44 (79)	

**Figure 3.** Incidence of AH errors associated with poor asthma outcomes.

The risk factors for making inhaler technique errors which are associated with poor asthma outcomes were not identical across the different devices. For the TH, risk factors for performing ≥ 1 error associated with poor asthma outcomes were being female and being aware of sub-optimal inhaler technique (based on self-assessment of inhaler technique as “very-poor-to-average” relative to “good-to-excellent”). For the MDI, risk factors

for performing ≥ 1 error associated with poor asthma outcomes were being female, secondary as opposed to a postgrad/prof/or university education, and being a current smoker. For the AH, risk factors for performing ≥ 1 error associated with poor asthma outcomes were lack of inhaler technique review by a trained healthcare professional in the previous twelve months and being aware of sub-optimal inhaler technique (based on self-

Table 4b. Univariate and multivariate logistic regression - AH.

Analysis	Predictors	Reference Category (0)	Category (1)	B	S.E.	Wald	df	Sig.	Exp(B)	95% C.I. for Exp(B)	
										Lower	Upper
Univariate	Patient Reported Inhaler Review	Reviewed	Not reviewed	0.522	0.142	13.509	1	<0.001	1.686	1.276	2.228
	Self Assessment of Inhaler Technique	Good to excellent	Very poor to average	0.469	0.178	6.944	1	0.008	1.598	1.128	2.266
	Education (Group 1)	Post-graduate/prof/uni degreed	Secondary Education	0.328	0.185	3.147	1	0.076	1.389	0.966	1.996
	Education Level (Group 2)	Secondary	None/Primary	0.287	0.202	2.022	1	0.155	1.333	0.897	1.981
Multivariate (no interaction)	Patient Reported Inhaler Review	Reviewed	Not reviewed	0.503	0.153	10.774	1	0.001	1.654	1.225	2.235
	Self-Assessment of Inhaler Technique	Very poor to average	Good to excellent	-0.405	0.18	5.042	1	0.025	0.667	0.468	0.950

assessment of inhaler technique as “very poor to average” as opposed to “good for excellent”).

This study is important to this field of knowledge, research and practice as it, for the first time, focuses only on errors which have been proven to be associated with poor clinical outcomes in real life/daily practice (16), and focuses on determining predictors of errors associated with poor asthma outcomes. In the complex field of asthma management, this is particularly important as there are many facets to asthma management and the challenges associated with managing them all simultaneously can be overwhelming. This enables HCPs to target resources toward implementation of interventions specifically able to reduce the errors that really matter (those more likely to contribute to increased hospitalizations and healthcare expenditure). Identifying these factors can also enable a HCP to predict which patients are more likely to perform an error associated with poor asthma outcomes for at least three commonly prescribed devices. Ultimately, this new knowledge is able to assist HCPs to identify patients at risk of poor asthma outcomes, based on risk factors for poor medication use.

The study further identified that the performance of specific inhaler technique errors associated with poor asthma outcomes is common in practice, with over half of the cohort of patients using each device making at least one of these asthma-outcome-related errors. Overall, the most frequent errors associated with poor clinical outcomes for the dry powder inhalers (DPIs, being the TH and AH) were related to breathing maneuvers ienot exhaling prior to inhaling for the TH and AH, and positioning (not having the head tilted such that the chin is pointing slightly upwards) for the MDI device. In addition, whilst these were the most common errors associated with poor clinical outcomes, it is important to note that a majority of patients also made multiple errors associated with poor clinical outcomes.

These results correlate with prior studies indicating that incorrect technique when using inhaled medicines is very common among patients with asthma or COPD

(1,14,24), with some indicating that as few as 10% of patients use correct technique (4,5). Whilst varying from results from previous investigations identifying not holding the inhaler upright (9,25), not inhaling forcefully enough through the device (26) for DPIs, and continuing to inhale after device actuation (11) not coordinating actuation with inspiration (25), and incorrect preparation of the device (2,26) for the MDI to be more common errors, a number of factors could have contributed to these discrepancies. This includes limitation of analysis to errors associated with poor asthma outcomes only, and study design variations. This further highlights the advance made to this field of research with regards to identifying errors that truly matter with regards to clinical outcomes.

It was interesting to note that our study did not identify smoking status as a predictor for higher frequency of inhaler technique errors associated with poor clinical outcomes for any of the DPI devices. Smoking triples the risk of airflow obstruction in non-atopic asthmatics (27), potentially influencing the risk of not inhaling as fast as you can or as forcefully, inhaler technique errors determined to be associated with poor asthma outcomes in the TH and AH devices. However, as it is not known which phenotype of asthma our study cohort had, it is not known if this is potentially a predictor of making such errors. Future research could therefore aim to investigate this in patients with known non-atopic asthma.

In contrast to previous investigations, age was not associated with increased incidence of inhaler technique errors associated with poor asthma outcomes (5,7,8,10–13). However, this difference could be due to the influence of multiple factors potentially affecting inhaler technique also associated with age, such as declining muscle strength and inspiratory flow, which were potentially not accounted for in previous studies.

The results for gender correlated with results by Goodman et al. (6), and Capanoglu et al. (2) but contrasted with Van Beernendonk et al. (11) Hesselink et al. (25), Sadowski et al. (28) who did not identify any relationship between gender and device use. Chafin

et al. (29) further did not note a relationship between MDI device technique and gender when patients were inhaling at rates less than 18 L/min. However, it should be noted that they examined the MDI when used with a spacer, which assists in holding the medication particles for a longer period and such, facilitates the ease with which a slower, inspiratory breath can be taken. In our study, we did investigate any patients using a spacer or similar holding aid, and thus, gender still appears to be an issue in the real-world setting when only an MDI (without a spacer). It further contrasts with Westerik et al. (20), who identified a significant association between female gender and increased rates of serious errors in patients prescribed the AH; however, ours was the only study to explore *only* errors associated with poor asthma outcomes. In addition, we used an inter-continental database with a significantly greater sample size, improving accuracy.

Variations in the results regarding age in the MDI sample could further be due to explicit exclusion of patients with COPD in this study, a further factor associated with increased error rates in MDI users (15). In addition, it did not differentiate between patients with late- or early-onset asthma. This could affect the results by affecting their level of experience using their inhaler device and recency of training.

BMI was further identified not to be a risk factor for the performance of inhaler technique errors associated with poor asthma outcomes. This is important, as obesity doubles the odds of developing asthma (30), and with obesity becoming a growing health concern, it is essential that any further risks it may have on the management of asthma be identified and addressed as early as possible.

Lack of comprehensive training in device technique was further significant for the AH. Currently, there is explicit evidence that patients of any age are unlikely to use inhalers correctly unless they are given an effective educational intervention/instruction, including a physical demonstration, and have their inhaler technique checked regularly (1,3). The results of this study once again highlight the need for repeated intensive instruction in inhaler technique by trained healthcare professionals (at least in the previous 12 months), and the need to consider personalized prescribing. For example, a female patients may be more suited to the use of an AH device, whereas patients who are unable to attend regular review sessions on inhaler technique may be better suited to the use of a MDI or TH device. Personalized prescribing could therefore safely and effectively reduce exacerbations, hospitalizations admissions, and ultimately, healthcare costs.

This study calls for a shift in the current paradigm as it relates to inhaler technique/use. Whilst historically, research and practice around inhaler technique has not been based on a specific understanding or knowledge about the inhaler technique errors that impact on asthma outcomes; we now have evidence that some (and not all) inhaler technique errors are directly associated with poor asthma outcomes. It is these specific evidence-based errors that therefore need to be 'named' and used in reference to all matters relating to inhaler technique in the future. Moving forward, there seems little value in obsessing over all errors but rather a precision approach which focuses on individuals and their ability to perform the 'critical' steps correctly is essential.

It further illuminates a demand to develop standardized terms to identify which errors are evidence-based in practice being linked to poor asthma outcomes. Whilst use of the words 'non-serious', 'potentially serious,' and 'serious' are often used in practice to describe the impact of an inhaler technique error on patient clinical asthma outcomes, there is no term present to describe an error shown by evidence to contribute to poor asthma outcomes. Development of a standardized internationally and inter-professionally recognized terminology can assist HCPs and patients to rapidly identify their risk of poor outcomes and discuss patient care and education in a manner explicitly understood by all parties.

This study is the first of its kind to identify the characteristics of the patients performing TH, MDI, and AH errors associated with poor asthma outcomes. Further investigations could assist in improving data by including objective inhaler technique with devices such as the InCheck™ Dial or the Aerosol Inhalation Monitor, accessing medical records from healthcare facilities rather than relying on patient recall, and further exploring the nature of certain patient characteristics (e.g. how often inhaler technique review had been performed in the previous 12 months, and which style of training).

Limitations of the study

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 anonymised form was not feasible to retrieve. In addition, variabilities in the abilities of the assessor to objectively evaluate particular inhaler technique errors may also have been evident, for example, with inhaler technique errors such as 'inhalation as fast as you can,' which may be interpreted differently between assessors.

A further limitation is that the study only explored patients who had been prescribed one type of inhaler

device. In the real-world setting, patients may be prescribed more than one type of inhaler device if they are on multiple respiratory medications. This could lead to confusion and difficulty remembering the steps for appropriate use of each device, which could potentially lead to a greater number of errors than what has been presented in the iHARP database. Investigation in a set of patients using multiple types of inhalers could assist in improving the external validity of the study.

Conclusion

This study indicates that inhaler technique errors associated with poor asthma outcomes differ according to particular patient characteristics. These patient characteristics should be used to predict those patients who are likely to experience poorer asthma outcomes, as a result of poor inhaler technique and should be used to guide more appropriate prescribing of inhaler devices.

Acknowledgements

The authors wish to acknowledge all the participants of the Observational and Pragmatic Research Institute for providing access to the iHARP data, and Mundipharma, for supporting the collection of data from the iHARP database via a research grant. No financial support from any entity was provided for this study.

Declaration of interest

In accordance with Taylor & Francis policy and my ethical obligation as a researcher, I am reporting the following conflicts of interest.

Grants from the Australian Research Council, Department of Health and Aging, University of Sydney, Commonwealth Govt of Australia (Guild Govt Agreement Scheme), Commonwealth Govt of Australia (Rural and Remote Pharmacy Workforce Development Program), NHMRC Co-operative Research Centre for Asthma, NHMRC Centre for Research Excellence in Severe Asthma, Asthma Foundation of NSW, Scherring Plough, TEVA Pharmaceuticals, AstraZeneca, Zentiva, Mundipharma International, MEDA Pharmaceuticals, Research in Real Life Pty (UK), University of Michigan, USA. Membership of Advisory Boards consultancies/Lecture honorarium: AZ, GSK, TEVA Pharmaceuticals, Mundipharma, Boehringer Ingelheim, Sanofi, Mylan.

Honoraria from AstraZeneca, GlaxoSmithKline and Pfizer, outside the submitted work.

Board membership with Aerocrine, Amgen, AstraZeneca, Boehringer Ingelheim, Chiesi, Mylan, Mundipharma, Napp, Novartis, Regeneron Pharmaceuticals, Sanofi Genzyme, Teva Pharmaceuticals; consultancy agreements with Almirall, Amgen, AstraZeneca, Boehringer Ingelheim, Chiesi, GlaxoSmithKline, Mylan, Mundipharma, Napp, Novartis, Pfizer, Teva Pharmaceuticals, Theravance; grants and

unrestricted funding for investigator-initiated studies (conducted through Observational and Pragmatic Research Institute Pte Ltd) from Aerocrine, AKL Research and Development Ltd, AstraZeneca, Boehringer Ingelheim, British Lung Foundation, Chiesi, Mylan, Mundipharma, Napp, Novartis, Pfizer, Regeneron Pharmaceuticals, Respiratory Effectiveness Group, Sanofi Genzyme, Teva Pharmaceuticals, Theravance, UK National Health Service, Zentiva (Sanofi Generics); payment for lectures/speaking engagements from Almirall, AstraZeneca, Boehringer Ingelheim, Chiesi, Cipla, GlaxoSmithKline, Kyorin, Mylan, Merck, Mundipharma, Novartis, Pfizer, Regeneron Pharmaceuticals, Sanofi Genzyme, Skyepharma, Teva Pharmaceuticals; payment for manuscript preparation from Mundipharma, Teva Pharmaceuticals; payment for the development of educational materials from Mundipharma, Novartis; payment for travel/accommodation/meeting expenses from Aerocrine, AstraZeneca, Boehringer Ingelheim, Mundipharma, Napp, Novartis, Teva Pharmaceuticals; funding for patient enrolment or completion of research from Chiesi, Novartis, Teva Pharmaceuticals, Zentiva (Sanofi Generics); stock/stock options from AKL Research and Development Ltd which produces phytopharmaceuticals; owns 74% of the social enterprise Optimum Patient Care Ltd (Australia and UK) and 74% of Observational and Pragmatic Research Institute Pte Ltd (Singapore); and is peer reviewer for grant committees of the Efficacy and Mechanism Evaluation programme, and Health Technology Assessment.

I have disclosed those interests fully to Taylor & Francis, and I have in place an approved plan for managing any potential conflicts arising from these involvements.

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