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Inhalation technique and asthma outcomes with different corticosteroid-containing inhaler devices

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ABSTRACT

Objective: Inhaler devices must be used correctly to ensure the effectiveness of the asthma treatment. This study evaluated inhalation technique across different types of corticosteroid-containing inhaler devices as well as health outcomes in patients with asthma.

Methods: In a cross-sectional study, we evaluated inhaler technique by observing patients' handling of the inhaler devices and using checklists for four inhaler types, namely Diskus ($n=52$), pressure metered dose inhalers (pMDIs; $n=41$), Turbuhaler ($n=36$) and Twisthaler ($n=16$). We also collected data on patients' characteristics, asthma therapy, exacerbations, medication adherence (8-item Morisky Medication Adherence Scale), asthma control (Asthma Control Test) and quality of life (Saint George Respiratory Questionnaire).

Results: In total, we included 145 patients. The mean (SD) age of the patients was 54.5 (18.9) years and 57% were female. The majority of the patients (70%) made at least one error in their inhalation technique. Patients using Turbuhaler performed the highest number of elements correctly, followed by pMDIs, Twisthaler and Diskus. Patients with Diskus or Twisthaler had better adherence compared with patients using pMDIs or Turbuhaler. Patients using Twisthaler had better asthma outcomes than patients using the other device types.

Conclusions: Most patients with asthma made mistakes when handling their inhaler devices, especially those using Diskus. However, in addition to the device type being used, patients' characteristics, asthma therapy and medication adherence also played an important role in achieving good health outcomes.

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Background

Asthma is a common disease of the airways and lungs, and it places a substantial burden on patients as well as on the population health. According to World Health Organization (WHO) estimates, 235 million people worldwide have asthma [1]. The disorder causes respiratory symptoms which may limit activity, while exacerbations of asthma can be severe and in some cases fatal. According to the most recent WHO estimates, 383,000 deaths due to asthma occurred in 2015 [1]. The goal of asthma treatment is to achieve and maintain clinical control. The pharmacotherapy of asthma consists of controller and reliever medications. Controllers are for regular maintenance of asthma and control symptoms, reduce risks for exacerbations and reduce airway inflammation through a reduction in airway inflammation and bronchospasm. Inhaled corticosteroids are the most effective

controller medications currently available. Relievers are provided to all patients for as-needed use to reverse bronchoconstriction and quickly relieve asthma symptoms [2]. Asthma treatment for adults can be administered in different ways, including by inhalation or through oral or parenteral pathways, but the majority of medications are delivered by inhalation. Inhalation permits a high concentration of medication in the airways and causes fewer systemic adverse effects [2]. However, handling of an inhaler must be correct for effective delivery of the medication. The delivery to the site of the disease can be achieved with a number of different inhaler device types. Pressurized metered dose inhalers (pMDIs) and dry powder inhalers (DPIs) are the most commonly used devices for drug delivery in the treatment of asthma. Inhaler devices differ in their efficiency of drug delivery to the lower respiratory tract. The differences depend on the type of the device, formulation

of the medication, particle size and velocity of the aerosol cloud [2]. Formulation of the medication plays an important role in producing an effective inhalable medication. The medicine must be efficiently delivered into the lungs, to the appropriate site of action and remain in the lungs until the desired pharmacological effect occurs [3]. In asthmatics, the smaller particle aerosol ensures higher effectiveness than larger particle size aerosols in producing bronchodilation due to better penetration and retention in the lungs in the presence of airway narrowing [4]. The fine particles ($<5\ \mu\text{m}$) are those that actually reach the lungs and provide therapeutic benefit. The portion of the fine particle distribution may considerably vary among different inhaler devices. The study by Johnson et al. showed, that the dose of albuterol sulfate likely to reach the lungs was 2–3 times higher in one reliever medication compared to another [5]. In pMDIs, the use of spacer reduces the aerosol velocity and increases lung deposition of the fine particles [6].

For a majority of patients another important aspect is the complexity of device use [2]. Individual patient preference, convenience and ease of use may influence not only the efficiency of drug delivery but also patient adherence to treatment and long-term control [2]. The aim of this study was to evaluate inhalation technique across different types of corticosteroid-containing inhaler devices as well as health outcomes in patients with asthma.

Methods

Study subjects

The study sample comprised patients who (I) had been prescribed medication containing inhaled corticosteroids (ICS) for regular use for at least 3 months without any changes in therapy; (II) stated they have asthma; (III) were aged 12 years or older; and (IV) were able to understand and communicate in the Slovenian language.

Study design

We performed a cross-sectional study in 16 community pharmacies across Slovenia in September 2014 and February 2015. Community pharmacists recruited eligible patients when their inhaler device was being dispensed. The subjects were consecutively enrolled if they had met the inclusion criteria. Data collection was carried out by the trained researchers in an area of the pharmacy that ensured an appropriate level of privacy. The information was obtained directly from the patients. However, the caregiver was present during the

interview and provided information if the patient was unable to. During the interview the researcher collected patient's demographic characteristics and complete information about asthma treatment in the past year. That was followed by assessment of inhalation technique and evaluation of asthma outcomes. Patients were included in the analysis based on the self-reported diagnosis of asthma, and patient-provided data were validated with information from the patient's GP.

Data collection

During the interview, the researcher obtained patient data, including age, sex, current smoking status, number of concomitant medications (for treatment of other diseases), educational level, living alone or sharing a household, possession of asthma self-management plan, asthma outcomes (exacerbations, asthma control, quality of life) and medication adherence. For evaluation of medication adherence, patients were asked to complete the 8-item Morisky Medication Adherence Scale (MMAS-8). MMAS-8 is a validated questionnaire, with scores ranging from 0 (non-adherence) to 8 (optimal adherence) [7–10]. Asthma control was evaluated by using the validated questionnaire Asthma Control Test (ACT) [11]. The assessment of asthma control was based on five items pertaining to the frequency of asthma symptoms and patient's self-evaluation of asthma control during the previous 4 weeks. Scores of ≥ 20 indicate controlled asthma and those of < 20 indicate uncontrolled asthma. Quality of life was evaluated by using Saint George Respiratory Questionnaire (SGRQ), which had been validated for use in patients with asthma [12]. It covers different aspects of patient health state and well-being related to respiratory disease. The sum of scores can range from 0 to 100, with a lower score indicating a better quality of life [12].

Exacerbation was defined as the occurrence of at least one event over a period of 1 year prior to the study indicating asthma exacerbation, namely emergency room visit due to asthma, hospitalization due to asthma, or treatment with oral corticosteroids.

Evaluation of inhalation technique

Trained researchers evaluated inhaler technique by observing each patient's handling of the corticosteroid-containing inhaler device and a checklist-based assessment. Checklists were developed by consensus after a systematic review of the literature and a review of summaries of product characteristics (SPCs) for all inhaler devices containing corticosteroids. We

developed different checklists to evaluate the following types of inhaler devices: Diskus, Turbuhaler, Twisthaler and pMDIs containing solutions or suspensions (without spacer). Complete checklists can be found in the [Supplementary material](#) Table S1. All key steps of inhalation technique were grouped into eight elements: (1) prepares the inhaler device, (2) breathes out fully, (3) does not blow into the inhaler device while exhaling, (4) puts the mouthpiece of the inhaler device into the mouth and closes lips around it, (5) inhales correctly, (6) holds breath for few seconds, (7) does not blow into the inhaler device while exhaling and (8) closes the inhaler device. This process allowed comparisons to be made between different types of inhaler devices (points 0–8). The elements that included multiple steps were only determined to be correct when all steps were performed correctly. The proportion of patients who performed each element correctly was then analyzed.

Statistical analysis

The difference in asthma control (median ACT score) and quality of life (median SGRQ total score) between patients who performed particular element of inhalation technique correct and those who performed it incorrect was evaluated using Mann-Whitney test. Additionally, the influence of device type on medication adherence was explored using the Kruskal-Wallis test.

In a *post hoc* analysis for Kruskal-Wallis test, the Twisthaler and the Diskus were grouped together and compared to the group with pMDIs and the Turbuhaler, using the Mann-Whitney test. In addition,

the difference between patients taking ICS and ICS/LABA in asthma control (ACT score) and quality of life (SGRQ Total score) was tested using the Mann-Whitney test.

The association between the inhaler device type and the proportion of patients with exacerbation was tested using the chi-square test. Additionally, the association between inhaler device type and asthma control or quality of life was tested using one-way ANOVA. The Bonferroni *post hoc* test was used as a *post hoc* test for ANOVA due to equal variances. A *p* values below 0.05 were considered statistically significant.

Results

Study subjects

In total, we included 145 patients. Their characteristics are presented in [Table 1](#). The mean (SD) age of the patients was 54.9 (18.9) years and the majority were female (57.2%). Most patients took two medications for asthma treatment. The most commonly prescribed regimen was fixed combination ICS/LABA (once or twice daily) plus reliever medication (as needed). The most common corticosteroid-containing inhaler device type among included patients was Diskus ($N=52$), followed by pMDIs ($N=41$), Turbuhaler ($N=36$) and Twisthaler ($N=16$).

Inhalation technique

The majority of the patients (70%) made at least one error in their inhalation technique. The most common

Table 1. Study sample characteristics.

	Inhaler device type				
	All	Diskus	pMDI	Twisthaler	Turbuhaler
Characteristics	$N=145$	$N=52$	$N=41$	$N=16$	$N=36$
Age (mean)	55 yrs	53 yrs	54 yrs	54 yrs	58 yrs
Gender (% female)	57%	64%	54%	69%	47%
Current smoker	17%	25%	15%	19%	8%
Living alone	16%	12%	17%	0%	28%
Exacerbation in past year	22%	17%	24%	13%	31%
Possession of asthma action plan	14%	15%	7%	25%	14%
Education					
Primary school	47%	62%	49%	0%	44%
High school	45%	33%	46%	94%	39%
University	8%	6%	5%	6%	17%
Duration of Asthma Treatment					
Less than a year	14%	10%	20%	13%	14%
1–5 years	33%	26%	39%	50%	31%
6–10 years	17%	10%	12%	19%	31%
More than 10 years	36%	55%	29%	19%	25%
Controller Therapy					
ICS	39%	38%	46%	100%	6%
ICS/LABA	61%	62%	54%	0%	94%
No. of medicines for other concomitant diseases (mean)	2.5	2.6	2.4	1.7	2.6

Note. ICS: inhaled corticosteroid; ICS/LABA: fixed combination of inhaled corticosteroid and long acting beta agonist.

Table 2. Proportion of patients performing each element of inhaler technique correctly among different types of inhaler devices.

Elements	Inhaler device type				
	All	Diskus	pMDIs	Twisthaler	Turbuhaler
	<i>N</i> = 145	<i>N</i> = 52	<i>N</i> = 41	<i>N</i> = 16	<i>N</i> = 36
Prepares the inhaler device	56%	15%	93%	75%	64%
Breaths out fully	66%	60%	68%	56%	77%
Does not blow into the inhaler device while exhaling	78%	76%	88%	56%	81%
Puts the mouthpiece of the inhaler device into the mouth and closes lips around it	91%	96%	79%	100%	94%
Inhales correctly	73%	67%	59%	88%	89%
Holds breath for few seconds	84%	78%	88%	94%	86%
Does not blow into the inhaler device while exhaling	96%	92%	98%	100%	100%
Closes the inhaler device	92%	85%	95%	94%	97%
Mean number of correct elements (out of 8)	6.4	5.8	6.7	6.6	6.9

errors in general were incorrect preparation of the device, inadequate expiration before inhalation and improper inhalation (Table 2). The medians of ACT score (asthma control) and SGRQ score (quality of life) was not found to be statistically significantly different between patients who performed particular step correctly and those who did not (Mann-Whitney test; $p > 0.05$). Correctness of inhaler technique differed among inhaler devices (Table 2). On average, patients using a Turbuhaler performed the highest number of elements correctly (6.9), followed by pMDIs (6.7), Twisthaler (6.6) and Diskus (5.8). The difference between the Diskus and other device types was evident, particularly in the preparation of the device, which was performed correctly by only 15% of the patients with a Diskus. The most common mistake for patients with a Twisthaler was with exhalation before the start of inhalation, which was inadequate and/or breathing out into the inhaler device. Patients with pMDIs had the most problems performing correct inhalation element.

Medication adherence

High medication adherence (MMAS score = 8) was found for 71.7%, 39.5%, 62.5% and 44.1% of patients with Diskus, pMDIs, Twisthaler and Turbuhaler, respectively. The distributions of MMAS scores among different inhaler device types are shown in Figure 1. Medication adherence was found to be significantly different among patients with different types of inhaler devices (Kruskal-Wallis test; $p = 0.032$). Patients with a Diskus or Twisthaler were found to have significantly better adherence compared with patients with pMDIs or Turbuhaler (Mann-Whitney Test; $p = 0.005$).

Health outcomes

The majority of patients (67%) were found to have controlled asthma. A statistically significant difference

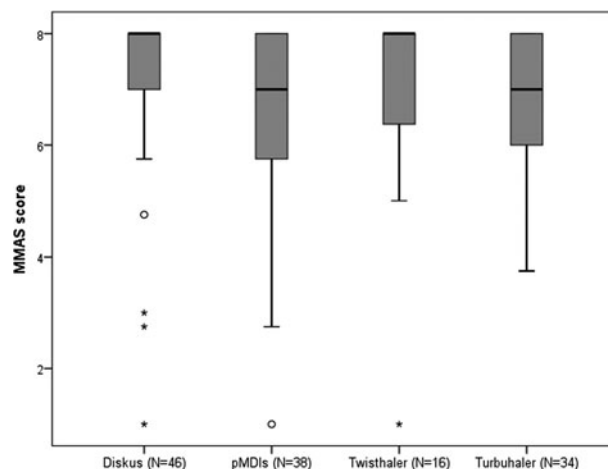


Figure 1. Box plot of MMAS score (medication adherence) among patients with different inhaler device types. The use of the ©MMAS is protected by US Copyright laws. Permission for use is required. A license agreement is available from Donald E. Morisky, MMAS Research, LLC 14725 NE, 20th St. Bellevue, WA 98007 or from dmorisky@gmail.com.

(Mann-Whitney Test; $p = 0.015$) was found in asthma control between patients receiving ICS only (median ACT score 22.5) and those with ICS and LABA (median ACT score 21.0). The proportion of patients who experienced asthma exacerbation ($n = 32$) requiring an ER visit, hospitalization or therapy with corticosteroids in the last year was higher among patients prescribed ICS/LABA compared to those without LABA (25.0% vs. 17.5%); however, the difference was not statistically significant (chi-square test; $p = 0.290$). A statistically significant difference was also found between patients receiving ICS only (median SGRQ Total score 20.1) and those with ICS/LABA (median SGRQ Total score 34.4) for quality of life (Mann-Whitney Test; $p = 0.006$).

Mean ACT score for patients with a Diskus, pMDIs, a Twisthaler and a Turbuhaler were 20.1, 20.5, 22.4 and 18.8, respectively. The proportion of patients with controlled asthma using Diskus, pMDIs, Twisthaler and Turbuhaler was 64.7%, 71.1%, 86.7%

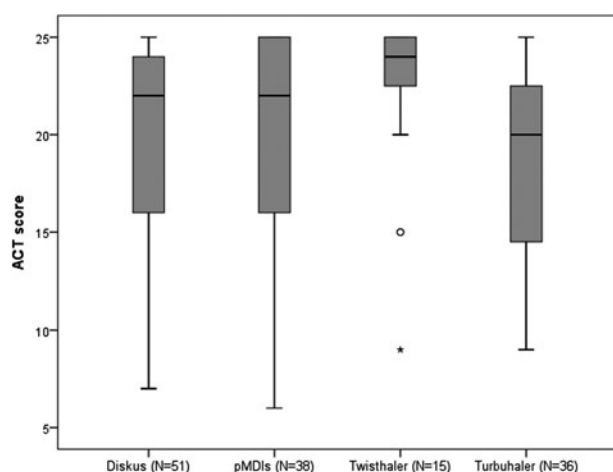


Figure 2. Box plot of ACT score (asthma control) among patients with different inhaler device types.

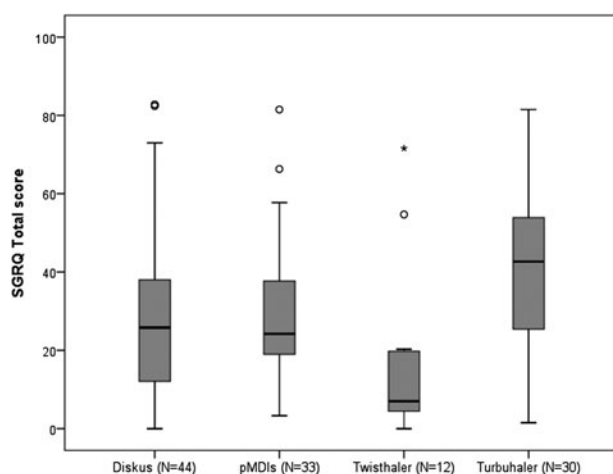


Figure 3. Box plot of SGRQ total score (quality of life) among patients with different inhaler device types.

and 58.3%, respectively. Patients prescribed a Twisthaler were found to have the best asthma control (Figure 2); however, the difference was not statistically significant (ANOVA; $p=0.118$). The proportion of patients with asthma exacerbation was the highest among those with a Turbuhaler (30.6%), followed by patients using pMDIs (24.4%), a Diskus (17.3%) and a Twisthaler (12.5%). Again, the difference was not statistically significant (chi-square test; $p=0.366$). Patients with a Twisthaler were also found to have the best quality of life (Figure 3). Mean (SD) SGRQ Total scores for patients with a Diskus, pMDIs, a Twisthaler and a Turbuhaler were 28.9 (23.0), 29.0 (17.7), 17.6 (22.6) and 41.8 (20.7), respectively. The difference between inhaler device types was found to be statistically significant (ANOVA; $p=0.005$). *Post hoc* testing showed the difference between the Turbuhaler and the Twisthaler (Bonferroni *post hoc* test; $p=0.006$).

However, Turbuhaler group comprised patients with more severe asthma than other types of devices. The majority of patients (94%) using a Turbuhaler had therapy with a combination of ICS and LABA, while all patients prescribed a Twisthaler had ICS therapy only.

Discussion

This study shows that incorrect use of inhaler devices in patients with asthma is common. The majority of patients (70%) made at least one error in performing their inhalation technique. This finding is consistent with findings of previous studies, which showed that 50–100% of patients make errors when using their inhaler devices [13–15].

The most common device-independent error was failure to breathe out prior inhalation. This error results in inadequate inhalation and leads to insufficient drug deposition in the lungs. On average more than a third of patients (34%) made this error. This finding is in line with results from a large observational study, which showed that the two most common device-independent errors were failure to breathe out before inhalation and not holding one's breath for a few seconds. These errors were observed in 40–47% of the patients [13, 16]. However, failure to hold breath was not a common error observed in our study; the majority of the patients (84%) performed that step correctly. Another common device-independent error was exhaling into the device, which was observed in 22% of patients. However, due to the differences in inhalation technique based on the device type, some errors were device-dependent. The most common device-dependent error was the incorrect preparation of the inhaler device, although there was great variability among different inhaler types (15–93%). The most important device-dependent error was incorrect inspiration, observed in 27% of patients.

Patients with particular inhaler device types were found to make errors with different frequencies. Patients using a Diskus most commonly made mistakes on various steps of inhalation. The main challenge for these patients was preparation of the inhaler; only 15% of the patients prepared the device entirely correctly. The main reason for incorrect preparation was failure to load the dose in a horizontal position. However, the impact of incorrect inhaler position on drug delivery is unknown. Approximately a third of patients did not inhale correctly, because their inspiration was either too slow or too shallow. Failure to achieve appropriate (i.e. forceful and rapid) inspiratory

flow is the most important error in DPI inhalation technique since inspiration flow rate plays an important role in the extent of drug deposition. Nevertheless, inadequate airflow rate is not equally critical for all DPIs. Within a certain range, from 30 to 90 L/min, inhalation flow rate has a minimal impact on the dose emitted from the Diskus, while it has a significant effect on that released from the Turbuhaler [17]. A study by Palander et al. [18] showed that the Diskus delivered dose was 92% (SD 9%) to 93% (SD 8%) of the nominal dose at flow rates of 60–90 L/min, declining to 76% (SD 12%) at a flow rate of 30 L/min. However, the Turbuhaler dose accuracy was lower and dose consistency was more variable, particularly at the lowest flow rate of 30 L/min (72%, SD 22%); at the higher flow rate of 60 L/min, the delivered dose was 88% (SD 19%) of the labeled dose. Other common errors of Diskus users were failure to breathe out fully and blowing into the device, found in 40% and 24% of patients, respectively. The latter error was also made by 64% of patients with the Twisthaler. Moisture from the patient's breath or ambient air may represent a risk for the chemical stability of the product, but it also influences the dispersibility of the powder [19]. Multiple unit dose devices (e.g. Diskus) may offer a better protection against ingress of moisture compared to multi-dose devices (e.g. Turbuhaler). Additional advantage of multiple unit dose devices is more accurate metering of individual doses. On the other hand, multidose devices deliver drug to the lungs more effectively than multiple unit dose devices [20].

The greatest weakness in inhalation technique in patients who use pMDIs was found to be the inhalation step. Only 59% of those patients performed that step correctly. In the majority of patients, the breath was too short and quick. Additionally, poor synchronization of breathing in and hand actuation represented a common problem that can severely influence delivery of the drug into the lungs. In a study by Giraud et al., asthma was less stable in pMDI misusers than in good users and among misusers, asthma was less stable in poor coordinators [21]. Moreover, in a study by Newman et al., patients who coordinated inhalation and actuation were found to have a higher lung deposition (19%) compared to those who did not (7%) [22]. In patients with higher risk of improper inhalation or poor coordination, e.g. older patients or children, it is advisable to recommend the use of spacer. Its use reduces the aerosol velocity, which may increase lung deposition of the fine particles emitted from the pMDI. It also significantly filters out and thereby reduces oropharyngeal deposition of the larger

particles emitted from a pMDI, that potentially lead to local adverse drug reaction [6, 23].

Additionally, some patients (21%) using pMDIs did not effectively close the lips around inhaler device and part of the dose was lost as some mist escaped from their mouth.

Differences between inhaler devices were also found in the health outcomes. The highest proportion of patients with good asthma control was associated with Twisthaler use and the lowest proportion was in patients with a Turbuhaler. Diskus and pMDIs were found to be comparable regarding ACT score. An even more considerable difference than in asthma control was found in quality of life. Quality of life more thoroughly evaluates patient's health state, taking into account not only physical dimension of health like asthma control, but also psychological and social dimensions of health. Nevertheless, the same pattern was observed, with patients using a Twisthaler having the highest quality of life and patients with a Turbuhaler having the lowest. Again, patients with a Diskus and those with pMDIs were comparable in average SGRQ. Difference in quality of life was statistically significant; however, *post hoc* test only revealed a difference between Turbuhaler and Twisthaler.

These results may suggest that therapy with a Turbuhaler results in worse asthma control and quality of life compared to a Twisthaler. However, this difference can be attributed rather to the patient characteristics, their therapy, and their behavior in terms of medication adherence than to the device effectiveness or poor inhalation technique.

First, patients prescribed a Turbuhaler differed in many characteristics from other patients, which could lead to differences in health outcomes. The majority of patients (94%) using a Turbuhaler had therapy with a combination of ICS and LABA. According to Global Initiative for Asthma (GINA), this combination is prescribed in patients with more severe asthma that requires LABA to provide additional improvements in symptoms and lung function as well as to reduce risk of exacerbations [2]. However, all patients prescribed a Twisthaler had ICS therapy only. Moreover, a larger proportion of patients with serious exacerbations that required an ER visit or hospitalization was found among those prescribed a Turbuhaler compared to those with a Twisthaler. This finding indicates that the Turbuhaler group comprised patients with more severe asthma than other types of devices, especially the Twisthaler. Furthermore, patients with a Turbuhaler were on average 5 years older than the others. Age was found to be significantly correlated with quality of life

(Pearson $R^2=0.14$; $p < 0.001$). Older patients commonly have multiple chronic diseases which influence their quality of life. Even though we used a quality-of-life questionnaire specific for respiratory disease, a patient's general health state might partly contribute to the results on quality of life. Patients with a Turbuhaler on average had more medications for other concomitant diseases which may reflect a worse general health state compared to patients with a Twisthaler (2.6 vs. 1.7 medications).

Second, incorrect inhalation technique can influence asthma outcomes. Studies have shown that incorrect use of inhaler devices may result in poor asthma control, increased emergency room visits, hospitalization and oral medication prescription as well as increased cost [24]. However, not all the steps of inhalation technique represent critical errors and do not have the same impact on drug deposition and consequently the effectiveness of medication. Consensus seems to be lacking on which errors in inhalation technique are critical since different steps were identified as critical across studies [13]. Critical errors mostly represented the steps regarding incorrect priming and loading the dose and failure to perform proper inhalation [25, 26]. Patients with a Diskus were found to make these errors most frequently. However, this study did not show the impact of a particular element on health outcomes, namely asthma control or quality of life.

Third, this study showed medication adherence to be worse in patients with a Turbuhaler and pMDIs compared to those with a Diskus or a Twisthaler. Poor medication adherence has been proven to be associated with reduced asthma control and worse quality of life [27, 28]. As adherence evaluated by MMAS-8 improves from low to medium or from medium to high, the odds of asthma control increase by 1.7 times [9]. Not only the inhalation technique, but also regular use of asthma medication may therefore substantially contribute to asthma outcomes.

The study also has some limitations. First, patient inclusion was based on self-reported asthma. However, 90% of the cases of self-reported asthma were confirmed by medical records. However, all the patients were included in the analysis. Among 10% of patients who were not confirmed to have asthma only, half (5%) had asthma and COPD, 3% had COPD and 2% other pulmonary obstructive diseases. Second, it is possible we have not been able to show the influence of inhalation technique on asthma outcomes due to the small sample size. Larger number of patients should have been enrolled. Third, patients with different inhaler

types have been prescribed different therapies (IGC only or IGC and LABA) and are therefore difficult to compare. Fourth, the inhalation technique in each patient was not evaluated by a single researcher; therefore, inter-rater variability may have influenced the results. Use of detailed checklists and training of evaluators before the study was conducted was carried out to decrease this variability. However, sensor-based technologies that use audio-based approaches assure more clinically accurate assessment of patient inhaler user technique than standard checklist methods. Audio-based monitoring provides quantitative measurements of the drug delivery of inhalers and improves the predictability of patient outcomes [29–32]. Fifth, we have decided to give all elements of inhalation technique equal weights. Some of the researchers identified critical errors and gave those elements greater weight or based their analysis solely on those elements. However, the review of the literature revealed great heterogeneity and apparently there is no consensus of what exact approach is the best. Sixth, environmental control, including secondhand smoke, or control of allergic rhinitis have not been taken into account, but may influence asthma patients' disease control.

Conclusions

The majority of patients make mistakes when handling their inhaler devices, especially those using a Diskus. The most common and critical errors for each device type should be kept in mind while educating patients about inhalation technique. However, in addition to the device type and its ease of use, patients' characteristics and medication adherence also play important roles in achieving good health outcomes in patients with asthma. Although disease severity and patient characteristics, namely age, sex or marital status cannot be influenced by health care providers, the medication adherence is an issue that can and should be addressed by doctors, pharmacists and other health care workers.

Acknowledgements

The use of the ©MMAS is protected by US Copyright laws. Permission for use is required. A license agreement is available from Donald E. Morisky, MMAS Research LLC 14725 NE 20th St. Bellevue WA 98007 or from dmorisky@gmail.com. The study was approved by the National Medical Ethics Committee of the Republic of Slovenia. No other approvals were required. Written informed consent to participate was obtained from all participants. For patients under 18 years old, written consent was also given by their parents.

Disclosure statement

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