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Determinants of poor inhaler technique and poor therapy adherence in obstructive lung diseases: a cross-sectional study in community pharmacies

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ABSTRACT

Background Correct inhaler use can be challenging in real life, with incorrect use resulting in poor symptom control. The aim of this study was to examine factors associated with poor inhaler technique and poor therapy adherence among patients with obstructive lung disease in community pharmacies.

Methods A cross-sectional study was conducted in patients with obstructive lung diseases in nine Belgian community pharmacies. Logistic regression analyses identified factors associated with poor inhaler technique and poor therapy adherence (assessed by the Test of Adherence to Inhalers and the modified Medication Possession Ratio).

Results Seventy obstructively impaired community patients (median age 64 y, 56% females) were included and the technique of 122 inhalers was assessed. Inhaler technique scored generally poor, with half of patients making critical errors in using at least one of their inhalers. In multivariable analysis, the use of multiple devices (adjusted OR, aOR 11.68; 95% CI 3.29 to 41.51) and a diagnosis of asthma-Chronic Obstructive Pulmonary Disease overlap (ACO; aOR 7.06; 95% CI 1.15 to 43.35), were associated with making critical errors in inhaler technique independent of quality of life. Non-adherence occurred in more than one-third of patients, and occurred in up to one half of the patients when also taking overuse into account. In multivariable analysis for therapy adherence, current smoking was associated with poor therapy adherence (aOR 0.15; 95% CI 0.02 to 0.96) independently of age and poor treatment knowledge. Therapy adherence was poor in patients with asthma compared with those with ACO. Current smokers and highly educated patients seemed to be at increased risk for inhaler overuse.

Conclusions Given the important role of a correct inhaler technique and therapy adherence in disease control, these findings emphasise the need for patient education and aiming uniformity in the inhaler device.

Trial registration number B670201835229.

Key messages

- ► Which factors determine poor inhaler technique and poor therapy adherence in patients with obstructive lung disease in Belgian community pharmacies?
- ► Our study showed that the use of multiple devices and a diagnosis of asthma-chronic obstructive pulmonary disease overlap are independently and significantly associated with a poor inhaler technique. Smoking and highly educated young patients seemed to be at increased risk for inhaler overuse.
- ► This community pharmacy-based study identified factors associated with critical errors in inhaler technique and poor therapy adherence, which may facilitate to detect patients most at risk for poor control of their respiratory disease.

exacerbations, inhaler therapy is the cornerstone treatment. A successful inhaler treatment relies on several factors but is mainly dependent on a good inhaler technique and therapy adherence.[2 3] A correct inhaler technique is crucial for optimal drug delivery to the lungs,[4] and to avoid local side effects, such as oropharyngeal candidiasis,[5] and dysphonia with the use of inhaled corticosteroids (ICS).[6]

Poor inhaler technique and poor adherence are major problems. WHO has estimated that only 50% of the chronic patients are adherent to long-term chronic therapies.[7] According to the systematic review published in 2016, only 31% of patients have been able to use an inhaler correctly, and the inhaler technique has not improved over the past 40 years.[8] After the launch of pressurised metered-dose inhalers (pMDI) in the 1960s, other devices have been developed such as dry powder inhalers (DPI) and Respimat Soft Mist inhalers (SMI). Despite innovations in devices and tools to support coordination, a

INTRODUCTION

Asthma and chronic obstructive pulmonary disease (COPD) are common diseases with increasing prevalence.[1] In order to relieve patients' symptoms and prevent

correct inhaler technique remains challenging in real life.[8]

The type of inhaler is an important determinant of incorrect inhaler technique.[9] Patient-related factors such as age,[10] COPD versus asthma diagnosis,[11] emotional status[9] and healthcare-related factors such as never receiving inhaler instructions (from a physician or pharmacist),[12 13] being treated in a group practice[9] and the prescription of multiple inhaler devices have been associated with incorrect inhaler technique.[12]

A broad range of factors may influence therapy adherence including patient's age, comorbidities, knowledge about the treatment and disease, cost, adverse effects of medication and poor physician-patient communication.[14] Consistent associations between therapy adherence and stronger inhaler-necessity beliefs and older age have been described before.[15] Differences in adherence level and pattern between asthma and COPD patients have been investigated.[16] However, little is known about the inhaler technique and adherence level among asthma-chronic obstructive pulmonary disease overlap (ACO) patients.

Previous studies have mainly investigated the determinants of poor inhaler technique in outpatient clinics,[12 17] specialist respiratory service,[13] chest clinics[18] or in general practitioner practices.[9] The aim of this study was to examine factors associated with poor inhaler technique and poor therapy adherence in patients with obstructive lung disease in community pharmacies. Detection of these determinants could help community pharmacists to identify patients most at-risk for poor inhaler technique or poor adherence.

METHODS

Study design

We used baseline data from 70 patients with obstructive lung diseases enrolled in a pragmatic randomised controlled trial to improve inhaler technique using mHealth conducted in Belgian community pharmacies.[19]

Patients were enrolled from nine community pharmacies (rural and urban, located in East-Flanders, Belgium) on 15 days during the study period (March–December 2018). The participating pharmacies invited their regular patients with asthma and/or COPD to the study research date at their regular pharmacy.

Adult patients with self-reported chronic asthma or COPD who used an inhaler for their condition, and had their medication dispensing history recorded in the pharmacy software, were eligible for inclusion. Patients with insufficient comprehension of the Dutch language were excluded. If patients were not willing or not able to give an informed consent, or did not agree to participate in further follow-up, they were also excluded from participation.

Inhaler technique

Patients' inhaler technique was rated by the investigator, using a checklist per device. These checklists consisted of all the essential steps (10 steps for DPIs and SMIs, 11 steps for pMDIs, and 12 steps for pMDI with valved holding chamber (VHC) and Autohaler). The inhaler score was calculated as the proportion of the number of correct steps to the total number of steps. Critical errors were defined as errors that by itself will significantly impair the delivery of the drug to the lungs[20] (eg, not removing the cap of the device, not shaking a pMDI/Autohaler, not loading DPI/SMI/Autohaler correctly, or not inhaling vigorously and deeply through DPI). Shaking a pMDI was recommended to all patients to simplify patient education in real-life practice, even though shaking is unnecessary in case of a solution in hydrofluoroalkane devices.[4] Sensitivity analyses were performed with failure to shake a pMDI considered as a non-critical error when formulated as a solution.

Therapy adherence

Therapy adherence was measured by the Test of the Adherence to Inhalers (TAI) questionnaire. The TAI has been developed and validated by researchers from the Integrated Research Programmes on Asthma and COPD of the Spanish Society of Pulmonology and Thoracic Surgery. This questionnaire is designed in order to identify patients with low adherence, to determine the level of adherence and the pattern of non-adherence. The 12-item TAI consists of 10 questions to be filled in by the patient (10-item TAI), and 2 questions for the healthcare professional. Patients with a score of less than 50 on the 10-item TAI were classified as being non-adherent. The questions for healthcare professionals are scored with 1 or 2 points for poor or good knowledge of the regimen and/or whether or not making critical inhaler errors, respectively. Poor treatment knowledge was defined as poor regimen knowledge and/or poor inhalation technique resulting in a score of less than 4 on item 11 to 12 with those scoring 4 as reference category.[21 22]

To objectively evaluate inhaler overuse and reduce social-desirability bias, the modified medication possession ratio (mMPR) was calculated based on the pharmacy dispensing data of the past year. The mMPR was calculated by dividing the total days' supply of all prescriptions for ICS, long-acting β2-agonist (LABA) and/or long-acting muscarinic antagonist (LAMA) over a defined period by the sum of the days between first and last prescription, including the duration of the last prescription.[23] An mMPR based on the defined daily dose (DDD) (mMPRddd) was calculated and averaged over all different inhalers. An mMPRddd of 80%–120% was considered as adherent. An mMPR below 80% was considered as underuse and above 120% as overuse.

Covariables

The handgrip strength, as a proxy for respiratory muscle strength,[24] was measured using the hand dynamometer Hydraulic Jamar. The patient was asked to sit straight up with the elbow bent at 90° and to squeeze with maximal strength. The handgrip strength of each hand was

measured three times, and the mean value of the dominant hand was calculated. The handgrip strength % predicted was calculated as the mean dominant handgrip strength of the patient divided by the right mean grip strength reference values of similar age and sex.[25]

Generic health status was assessed using the valuation section of the EuroQol five-dimension questionnaire on a score between 0 (worst imaginable health status) and 100 (best health status) on overall quality of life (QoL).[26]

Patient characteristics such as height, weight, education level, smoking status, respiratory diagnosis and adverse drug events were collected through self-report. Body mass index (BMI, kg/m²) was calculated from weight and height. Education level was categorised into low education (primary education and lower secondary education) and high education level (upper secondary education and higher education).

If a patient used one or more inhalers of the same type (eg, two pMDIs), it was defined as using a single device. Patients using different types of inhalers (eg, a pMDI and a DPI) were defined as multiple inhalers.

Statistical analysis

In order to examine patients' characteristics, descriptive statistics were applied. Categorical variables were described as counts (n) with percentages. Continuous data were described as mean with SD when normally distributed and as median with IQR when not normally distributed.

Logistic regression analyses were undertaken to identify factors associated with critical inhaler errors and therapy non-adherence (TAI <50). Effect sizes were expressed in ORs with their 95% CIs. The variables studied for predicting critical errors were: age,[10] respiratory diagnosis,[11] the use of multiple devices,[12] QoL,[9] received inhaler instruction by pharmacist and/or physician before[12] and handgrip strength.[27] The variables studied for predicting non-adherence were: age, QoL, education level, poor treatment knowledge, the use of multiple devices, adverse events and smoking status.[15 28] A manual forward selection process was used to add factors with a p<0.15. Additional logistic regression analyses were performed for poor therapy adherence, objectively defined as an mMPR <80% or >120%. Model quality was assessed using the Hosmer and Lemeshow test, Nagelkerke R^2 and classification table. Data analyses were performed using IBM SPSS Statistics V.25. P values <0.05 were considered significant (two sided). Post hoc power analysis was performed to determine the achieved power to reach statistical significance, based on the total sample size, the effect estimates, the observed R-square and alpha of 0.05. Statistical power was calculated using G*Power V.3.1.9.2.

RESULTS

Patient characteristics

Of the 122 subjects eligible for the study, 52 patients declined to participate and more than half (n=70) agreed to participate. Sociodemographic and clinical characteristics of enrolled patients are presented in table 1. The median age was 64 years, mean BMI 26 kg/m² and 56% were female. In total, 31 patients had asthma (44%), 27 COPD (39%) and 12 ACO (17%). About half of the patients reported at least one exacerbation in the previous year, requiring a hospitalisation in one out of five (21%). Adverse drug events of inhaler therapy were reported in 43% (n=30). The most reported adverse drug events were a dry mouth (n=16) and a hoarse voice (n=13). Median number of chronic comedication was 2 for asthma patients and 5 for COPD or ACO patients (Kruskal-Wallis, p=0.020).

Inhaler technique

In total, 133 inhalers were used by 70 patients. Two-thirds of the patients used more than one inhaler. About half of the patients used a single device (n=38, 54%) and the most commonly used device was a DPI (table 1).

Only 21% of patients reported that both their pharmacist and physician had taught them the inhaler technique before the start of the study (n=15). While their physician or their pharmacist, had instructed them on the inhaler technique in almost three quarters of patients (n=50, 71%), still 7% reported not to have learnt the technique by any pharmacist or physician before the start of the study (n=5) (table 1).

In total, 122 inhalers were scored regarding patient's inhaler technique, including DPIs (n=72), pMDIs (n=33), SMIs (n=11), pMDI with VHC (n=5) and Autohaler (n=1). The most frequent inhaler errors with DPI and pMDI were mistakes in posture, no full expiration before inhalation and no inspiration breath-hold (table 2). Inhaler technique scored generally poor with half of patients making critical errors in using at least one of their inhalers (n=36, 51%). Only one patient (1.4%) performed a perfect inhaler technique. Among patients using a single device, the proportion of patients making critical errors was 23% (n=7/30) in DPI users compared with 43% (n=3/7) in pMDI users.

The proportion of patients making critical errors was 29% in patients using a single device compared with 75% in patients using two different devices, and 100% in patients with three different devices. For statistical analyses, patients with two or three different devices were analysed together as patients using multiple devices. Table 3 shows the variables associated with poor inhaler technique. In univariable analyses, ACO (OR 5.45; 95% CI 1.22 to 24.43), the use of multiple devices (OR 8.77; 95% CI 2.94 to 26.14) and QoL (OR 0.96; 95% CI 0.93 to 1.00) were significantly associated with making critical errors in inhaler technique. We investigated in a sensitivity analysis whether the association was not driven by frequent use of comedication in ACO patients. However, the association between ACO and poor inhaler technique remained after adjusting for the number of chronic comedication (OR 5.62; 95% CI 1.22; 25.96). No associations were found between age, received inhaler

Table 1 Sociodemographic and clinical characteristics of the subjects

	Total (n=70)
Age in years, median (Q1-Q3)	64 (55–73)
Female, n (%)	39 (56)
BMI in kg/m², mean (SD)	26 (5)
Asthma, n (%)	31 (44)
COPD, n (%)	27 (39)
ACO, n (%)	12 (17)
Time since diagnosis in years, median (Q1–Q3)	13 (5–28)
Never smoker, n (%)	24 (34)
Past smoker, n (%)	32 (46)
Current smoker, n (%)	14 (20)
Pack-years among ever smokers, median (Q1–Q3)	30 (11–42)
Low education level, n (%)	28 (40)
High education level, n (%)	42 (60)
≥1 exacerbation in preceding year, n (%)	34 (49)
≥1 severe exacerbation in preceding year, n (%)	8 (11)
Handgrip strength dominant hand in kg, mean (SD)	30 (11)
Handgrip strength % predicted, mean (SD)	92 (24)
One inhaler, n (%)	24 (34)
Two inhalers, n (%)	31 (44)
Three inhalers, n (%)	13 (19)
Four inhalers, n (%)	2 (3)
DPI(s), n (%)	30 (43)
MDI(s), n (%)	8 (11)
SMI(s) (combinations), n (%)	11 (16)
DPI+MDI, n (%)	21 (30)
Single device, n (%)	38 (54)
SABA, n (%)	11 (16)
SABA/SAMA, n (%)	22 (31)
ICS, n (%)	2 (3)
LABA, n (%)	2 (3)
ICS/LABA, n (%)	36 (51)
LABA/LAMA, n (%)	7 (10)
ICS/LABA/LAMA, n (%)	23 (33)
Oral (leukotriene receptor antagonist or theophylline), n (%)	13 (19)
Quality of life, mean (SD)	69 (16)
Received inhaler instruction from both pharmacist and physician before, n (%)	15 (21)
Received inhaler instruction from pharmacist or physician before, n (%)	50 (71)
Received never inhaler instruction from pharmacist or physician, n (%)	5 (7)
Adverse drug events, n (%)	30 (43)

Continued

Table 1 Continued

	Total (n=70)
Poor treatment knowledge, n (%)	40 (57)
Number of chronic comedication and supplements, median (Q1–Q3)	4 (2–6)
Most frequently used chronic drugs, n (%)	
Beta-blocking agents (C07)	33 (47)
Drugs for acid-related disorders (A02)	25 (36)
Lipid-modifying agents (C10)	23 (33)
Antithrombotic agents (B01)	21 (30)
Psycholeptics (N05)	17 (24)
Agents acting on the renin–angiotensin system (C09)	15 (21)
Antidepressants (N06A)	13 (19)

No missing data.
ACO, asthma-COPD overlap; BMI, body mass index; COPD, chronic obstructive pulmonary disease; DPI, dry powder inhaler; ICS, inhaled corticosteroids; LABA, long-acting β_2-agonist; LAMA, long-acting muscarinic antagonist; MDI, metered-dose inhalers; SABA, short-acting β_2-agonist; SAMA, short-acting muscarinic antagonist; SMI, soft mist inhalers.

instruction or handgrip strength % predicted and poor inhaler technique as the outcome. However, handgrip strength % predicted was significantly associated with inhaling vigorously and deeply in DPI users (OR 1.09; 95% CI 1.02 to 1.17; p=0.015).

Respiratory diagnosis, multiple devices and QoL were entered into the multivariable model, explaining 44% of the variance of poor inhaler technique (table 3) with a 98% power to detect a significant difference for multiple devices. In the sensitivity analysis being less strict on critical errors based on the actual formulation, multiple devices, ACO, QoL and handgrip strength were also the strongest predictors of poor inhaler technique with only multiple devices being statistically significant (p=0.045).

Therapy non-adherence
According to the 10-item TAI score, 61% of patients were completely adherent (n=43). Of the 27 non-adherents, 56% patients (n=15) forgot to take their medication (=sporadic non-adherence), 11% patients (n=3) refused to take their medication (=deliberate non-adherence) and 33% (n=9) showed both of these patterns of non-adherence. According to the 12-item TAI score, 57% of the patients (n=40) had a poor knowledge of the regimen and/or inhaler technique (=unconscious behaviour).

Table 4 shows the variables associated with therapy non-adherence. The univariable factors significantly associated with therapy non-adherence were age and smoking status. Younger patients were more likely to be non-adherent (OR 0.96; 95% CI 0.93 to 0.99). Smoking seemed to result in a lower risk for poor therapy adherence, but the association lost significance for past smoking in multivariable analysis. Age, poor treatment

Table 2 Number (%) of patients performing correct steps per type of inhaler

	DPI (n=72)	pMDI (n=33)	SMI (n=11)	pMDI +VHC (n=5)	AH (n=1)
Make sure the mouth is empty	72 (100)	33 (100)	11 (100)	5 (100)	1 (100)
Remove the cap of the device*	72 (100)	32 (97)	10 (91)	5 (100)	1 (100)
Shake the device*		13 (39)		1 (20)	1 (100)
Prepare the device correctly*	62 (86)		4 (36)		1 (100)
Place the VHC correctly onto the device				4 (80)	
Keep the device upright		31 (94)		4 (80)	1 (100)
Exhale deeply next to the device	20 (28)	5 (15)	3 (27)	1 (20)	0 (0)
Stand or sit upright and bend the head slightly backwards	13 (18)	2 (6)	3 (27)	3 (60)	0 (0)
Seal the mouthpiece of the device with the lips	72 (100)	26 (79)	10 (91)	4 (100)	1 (100)
Make sure to not block the air holes of the device	71 (99)		11 (100)		1 (100)
Activate the device and manage a good hand-breath coordination		19 (58)	8 (73)		
Inhale vigorously and deeply*	65 (90)				
Inhale slowly and deeply		7 (21)	4 (36)		0 (0)
Activate the device and inhale deeply within 5 s. after activation				5 (100)	
Hold breath for 10 s	22 (31)	6 (18)	4 (36)	1 (20)	0 (0)
Inhale and exhale five times in the VHC				3 (60)	
Rinse the mouth and spit out (if corticosteroids)	35 (67)	3 (43)		2 (40)	1 (100)

*Critical steps.

AH, autohaler; DPI, dry powder inhaler; pMDI, pressurised metered-dose inhalers; SMI, soft mist inhalers; VHC, valved holding chamber.

knowledge and smoking status were entered into the multivariable model, explaining 21% of the variance of non-adherence (table 4). The estimated odds for non-adherence decreased by 85% for current smokers compared with never smokers, independently of age and poor treatment knowledge.

Table 3 Univariable and multivariable regression analysis of the determinants of poor inhaler technique

Variable	Patients making critical errors/total (%)	Univariable		Multivariable*	
		OR (95% CI)	P value	aOR (95% CI)	P value
Age (years)		1.01 (0.98 to 1.04)	0.640		
Respiratory diagnosis					
Asthma	11/31 (35)	Ref.		Ref.	
COPD	16/27 (59)	2.64 (0.91 to 7.66)	0.073	2.43 (0.66 to 8.99)	0.184
ACO	9/12 (75)	**5.45 (1.22 to 24.43)**	**0.027**	**7.06 (1.15 to 43.35)**	**0.035**
Multiple vs single device	25/32 (78) vs 11/38 (29)	**8.77 (2.94 to 26.14)**	**<0.001**	**11.68 (3.29 to 41.51)**	**<0.001**
Quality of life		**0.96 (0.93 to 1.00)**	**0.037**	0.96 (0.93 to 1.01)	0.087
Received inhaler instruction before from pharmacist/physician					
Never vs ever	3/5 (60) vs 33/65 (51)	1.45 (0.23 to 9.29)	0.692		
Handgrip strength % predicted		0.99 (0.97 to 1.01)	0.240		

Significant estimates (p<0.05) are indicated in bold.

*Nagelkerke R^2: 0.437; Hosmer and Lemeshow Goodness-of-fit test p-value: 0.575; correctly classified: 75.7%.

ACO, asthma-COPD overlap; aOR, adjusted OR; ; COPD, chronic obstructive pulmonary disease.

Table 4 Univariable and multivariable regression analysis of the determinants of non-adherence (TAI <50)

Variable	Non-adherent patients/total (%)	OR (95% CI)	P value	aOR (95% CI)	P value
Age (years)		**0.96 (0.93 to 0.99)**	**0.017**	0.98 (0.94 to 1.01)	0.228
Respiratory diagnosis					
Asthma	14/31 (45)	Ref.			
COPD	8/27 (30)	0.51 (0.17 to 1.52)	0.227		
ACO	5/12 (42)	0.87 (0.23 to 3.34)	0.836		
Multiple vs single device	13/32 (41) vs 14/38 (37)	1.17 (0.45 to 3.08)	0.746		
Quality of life		1.00 (0.96 to 1.03)	0.759		
High vs low education	17/42 (40) vs 10/28 (36)	1.22 (0.46 to 3.29)	0.689		
Poor treatment knowledge	17/40 (43) vs 10/30 (33)	1.48 (0.55 to 3.96)	0.436	2.89 (0.81 to 10.24)	0.100
Adverse drug events vs no	11/30 (37) vs 16/40 (40)	0.87 (0.33 to 2.30)	0.777		
Smoking status					
Never	14/24 (58)	Ref.		Ref.	
Past	10/32 (31)	**0.32 (0.11 to 0.98)**	**0.046**	0.32 (0.07 to 1.40)	0.130
Current	3/14 (21)	**0.19 (0.04 to 0.88)**	**0.034**	**0.15 (0.02 to 0.96)**	**0.045**

Significant estimates (p<0.05) are indicated in **bold**.
*Nagelkerke R^2: 0.210; Hosmer and Lemeshow goodness-of-fit test p value: 0.376; correctly classified: 71.4%.
ACO, asthma-COPD overlap; aOR, adjusted OR; ; COPD, chronic obstructive pulmonary disease; TAI, Test of the Adherence to Inhalers.

When also defining inhaler overuse as poor adherence, half of the patients were adherent having an mMPR between 80% and 120% (51%, n=36). Of the 34 non-adherent patients, 68% of the patients (n=23) demonstrated underuse and 32% (n=11) inhaler overuse. The drugs being overused were LABA/ICS (n=5), LABA (n=3), LAMA/LABA/ICS (n=2) and LABA/LAMA (n=1). Table 5 shows the variables associated with poor therapy adherence according to the mMPR. Only higher education level was significantly associated with poor adherence in univariable analyses. Respiratory diagnosis, education level, smoking status and multiple devices were entered into the multivariable model, explaining 39% of the variance of poor adherence (table 5). ACO (adjusted OR, aOR 0.13; 95% CI 0.02 to 0.97), higher education (aOR 14.81; 95% CI 3.21 to 68.43) and current smoking

Table 5 Univariable and multivariable regression analysis of the determinants of poor adherence (mMPR <80% or mMPR >120%)

Variable	Non-adherent patients/total (%)	Univariable OR (95% CI)	P value	Multivariable* aOR (95% CI)	P value
Age (years)		0.99 (0.97 to 1.02)	0.685		
Respiratory diagnosis					
Asthma	17/31 (55)	Ref.		Ref.	
COPD	13/27 (48)	0.76 (0.27 to 2.15)	0.611	0.69 (0.15 to 3.05)	0.620
ACO	4/12 (33)	0.41 (0.10 to 1.66)	0.212	**0.13 (0.02 to 0.97)**	**0.047**
Multiple vs single device	13/32 (41) vs 21/38 (55)	0.55 (0.21 to 1.44)	0.224	0.39 (0.12 to 1.28)	0.122
Quality of life		1.03 (0.99 to 1.06)	0.129		
High vs low education	27/42 (64) vs 7/28 (25)	**5.40 (1.87 to 15.63)**	**0.002**	**14.81 (3.21 to 68.43)**	**0.001**
Poor treatment knowledge	18/40 (45) vs 16/30 (53)	0.72 (0.28 to 1.85)	0.491		
Adverse drug events vs no	14/30 (47) vs 20/40 (50)	0.88 (0.34 to 2.26)	0.782		
Smoking status					
Never	11/24 (46)	Ref.		Ref.	
Past	14/32 (44)	0.92 (0.32 to 2.66)	0.877	2.25 (0.47 to 10.73)	0.309
Current	9/14 (64)	2.13 (0.55 to 8.26)	0.275	**28.92 (2.65 to 315.91)**	**0.006**

Significant estimates (p<0.05) are indicated in bold.
*Nagelkerke R^2: 0.394; Hosmer and Lemeshow goodness-of-fit test p-value: 0.866; correctly classified: 72.9%.
ACO, asthma-COPD overlap; aOR, adjusted OR; ; COPD, chronic obstructive pulmonary disease; mMPR, modified medication possession ratio.

(aOR 28.92; 95% CI 2.65 to 315.91) were associated with poor adherence. Compared with patients with asthma, patients with ACO were more therapy adherent. Interestingly, this was driven by both less inhaler underuse (25% vs 39%) as inhaler overuse (8% vs 16%) among patients with ACO versus patients with asthma respectively. The proportion of poor adherence was 64% (16 underusers and 11 overusers) in higher educated patients compared with 25% (all seven underusers) in lower educated patients. More than half of the higher educated patients had a poor treatment knowledge (52%, n=22) compared with 64% (n=18) of the lower educated patients.

DISCUSSION

In our community pharmacy-based study, half of patients made critical errors in using at least one of their inhalers. Additionally, non-adherence occurred in more than one third of patients and occurred in up to one half of the patients, when also taking overuse into account. The use of multiple devices was the strongest determinant of a poor inhaler technique. Another factor significantly affecting poor inhaler technique was a diagnosis of ACO. The poor adherence in smoking and highly educated patients seemed to be driven by their increased risk for inhaler overuse.

The overall score on inhaler technique was low, with half of patients making critical errors and almost nobody showing a perfect inhaler technique. The systematic review of Sanchis *et al* already pointed to a very low overall prevalence of correct inhaler technique of 31% of the patients (28%–35%).[8] By the larger number of assessed steps in our checklist, we might have been even more strict in concluding a perfect inhaler technique.[29] The most common error for all devices was the posture, more specific forgetting to bend the head slightly backwards. This is an important (but non-critical) step that minimises impaction of the drug particles in the oropharynx, resulting in a higher dose deposited in the lungs.[30]

The strongest determinant of a poor inhaler technique was the use of multiple devices. This finding is in agreement with prior research.[29] The use of multiple devices confuses patients since different inhaler techniques are required.[31] However, a combination of a pMDI and a DPI is sometimes prescribed because short-acting bronchodilators are only reimbursed in pMDI in Belgium. Our results suggest a DPI to be the most user-friendly device as it has the lowest proportion of patients who made critical errors. This assumption has been confirmed by other studies.[32 33]

Other significant determinants of a poor inhaler technique were a diagnosis of ACO and a lower QoL. In our study, COPD and ACO patients tend to make more critical errors than asthma patients. Our finding is in agreement with some studies showing that patients with asthma had a significantly better inhaler technique than patients with COPD,[11 13] while other studies have not observed this association,[9 12] or found an association that disappeared after adjustment for device type, age and level of instruction.[18] A possible explanation is that asthma patients feel more direct benefit or are more satisfied with their inhaler.[34] To our knowledge, the association with ACO has not yet been described. This finding could be explained by ACO patients being more likely to have comorbidities, which have been associated with poorer inhaler technique.[17 35] Furthermore, patients with a lower QoL tended to make more critical errors. This is in accordance with prior research that observed that patients with emotional problems were more likely to make inhalation mistakes.[9] The association between QoL and poor inhaler technique did not change after adjusting for the use of antidepressants. However, we had no information about depressive symptoms or personality type.

We could not replicate that grip strength was a significant determinant of inhaler technique.[27] However, only one patient on DPI and pMDI had a mean hand grip strength below 10 kg in our study, which is the minimum grip strength (as a proxy for inspiratory flow) for DPI.[36] Unlike previous research,[12 13] we could not find an association between patients who never received inhaler instructions from their pharmacist or physician and critical errors. This may be due to the fortunately low number of patients who have never been instructed before, and missing information on the number of previous instructions and how long ago these were. Nevertheless a continuous assessment of inhaler technique remains crucial since a poor technique causes poor disease control and patients may have forgotten the instructions at their first dispensing.

Poor adherence is influenced by various factors,[37] and younger age was the most important one in univariable analyses. This finding is in accordance with other research showing that older age relates to better adherence.[15] Overall, therapy adherence according to the TAI (61%) was slightly better than the estimated WHO adherence in chronic conditions (50%),[7] but could be overestimated, since patients may give socially desirable answers. Therefore, we also objectively evaluated adherence based on the pharmacy dispensing data. The TAI questionnaire is considered as a reliable tool to assess adherence to inhalers.[21] However, the TAI questionnaire only detects underuse but does not capture overuse of inhalers. This means that overusing patients could be classified as adherent patients according to the TAI. Therefore, the differences between the TAI and mMPR (based on the pharmacy medication history) were evaluated, which increased our insight into the association of smoking and higher education with inhaler adherence.

Although univariable analysis showed that smoking seemed to result in a lower risk for poor therapy adherence, the association with past smoking was not significant in the multivariable analysis. While this observation is contradictory to previous studies,[15] it might reflect a higher need for, or perceived benefit of, symptom relief among (ever) smokers in this cohort. As current smokers seemed more symptomatic and tend to overuse

medication, it resulted in a false conclusion that smoking lowers the risk for poor therapy adherence according to the TAI definition, which was countered in the mMPR analysis.

Moreover, a higher education level was the strongest determinant of non-adherence (mMPR <80% or mMPR >120%). This finding was contradictory to 4 out of 10 results included in a systematic review,[15] but similar to another study.[38] The authors attributed this to more trust in physicians' advice by less educated patients.[38] Unfortunately, we can add from our study that the proportion of patients among higher educated patients with a good treatment knowledge was still not higher than patients with a poor treatment knowledge. Moreover, the over-users were all higher educated patients.

A major strength of our study was the evaluation of a large number (n=122) of real-life inhaler technique demonstrations. Furthermore, adherence was assessed through a self-reported questionnaire and by pharmacy dispensing data. The mMPR was calculated on a standardised dosing and not individual regimens. For generalisability, the participants inclusion criteria were broad and also patients with ACO were included. However, the most vulnerable patients such as patients with cognitive deficits who do not come to the pharmacy themselves may be underrepresented. No spirometry results were available to confirm the diagnosis. However, this limitation supports the pragmatic framework. Another limitation of this study was the relatively small sample size of participating patients. This hampered the ability of the inclusion of more variables in the model to avoid overfitting.

In conclusion, our study shows that the use of multiple devices and a diagnosis of ACO are independently and significantly associated with a poor inhaler technique. Therapy adherence was poor in patients with asthma compared with those with asthma-COPD overlap, and smoking and highly educated patients seemed to be at increased risk for inhaler overuse. Given the important role of therapy adherence and a correct inhaler technique in disease control, these findings emphasise the need for patient education and aiming uniformity in the inhaler device.

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