JOURNAL OF AEROSOL MEDICINE AND PULMONARY DRUG DELIVERY
Volume 31, Number 4, 2018
© Mary Ann Liebert, Inc.
Pp. 237–247
DOI: 10.1089/jamp.2017.1409

Preferences and Inhalation Techniques for Inhaler Devices Used by Patients with Chronic Obstructive Pulmonary Disease

Roxanne Bournival, PharmD,[1,2] Raphaël Coutu, PharmD,[1,2] Nicolas Goettel, PharmD,[1,2] Chun Dian Yang, PharmD,[1,2] Antoine Cantin-Lafleur, PharmD,[2,3] Catherine Lemieux, PharmD,[2,3] Anne-Marie Lévesque, PharmD,[2,3] Jean-François Patenaude-Monette, BPharm,[2,3] François-Olivier Roy, PharmD,[2,3] Lucie Blais, PhD,[2,4,5] Fanny Arbour, BPharm, MSc,[2,3] Anne Fillion, BPharm, MSc,[2,3] and Marie-France Beauchesne, PharmD,[1–3,5,6]; For the RESP Investigators*

Downloaded by Universita Degli Studi Di Torino from www.liebertpub.com at 07/26/23. For personal use only.

Abstract

Background: Inhaler technique and patient preferences are often overlooked when selecting maintenance treatments for patients with chronic obstructive pulmonary disease (COPD), but are important issues in ensuring drug efficacy and patient adherence. Few data on these issues are available for new inhalation devices.
Objectives: To evaluate the inhalation techniques for the HandiHaler®, Breezhaler®, Genuair®, and Respimat® inhalation devices, and patient preferences for the three latter inhalers that were recently developed.
Methods: A prospective two-center cross-sectional study of COPD patients was conducted. The patients were required to be current HandiHaler users who had not previously used the new inhalers (Breezhaler, Genuair, Respimat). The patients were given the new devices and asked to identify the one they preferred before and after using the inhaler. Each patient tried the HandiHaler and two devices out of the three new inhalers: one preferred by the patient and one imposed by the investigator. Their inhalation technique was evaluated using an assessment checklist. A logistic regression model was used to determine which device was used with the fewest errors.
Results: Of the 98 patients who completed the study, 57.1% (95% CI: 47.4–66.9) had an adequate HandiHaler technique. There was no difference between the proportions of patients with an adequate Breezhaler and Genuair inhalation technique (aOR 1.08, 95% CI: 0.51–2.30), but 62% fewer patients using Respimat had an adequate technique than those using Genuair (aOR for adequate technique 0.38, 95% CI: 0.18–0.82). There were no significant differences in the initial patient preferences for the three new inhalers, and no association between the patient's preference and an adequate inhaler technique.
Conclusion: Inhalation techniques were suboptimal and varied between inhalers. The arrival of new inhalers is an opportunity to reassess patient techniques and preferences. Further studies should also explore the association between the inhaler preferences and treatment adherence of patients.

Keywords: chronic obstructive pulmonary disease, COPD, inhalation device, inhalation technique, inhale, preference, satisfaction

[1]Department of Pharmacy, Centre Hospitalier Universitaire de Sherbrooke, Sherbrooke, Canada.
[2]Faculty of Pharmacy, Université de Montréal, Montréal, Canada.
[3]Department of Pharmacy, Hôpital du Sacré-Coeur de Montréal, Montréal, Canada.
[4]Research Center of Centre Intégré Universitaire de Santé et de Services Sociaux du Nord-de-l'Île-de-Montréal–Hôpital du Sacré-Cœur de Montréal, Montréal, Canada.
[5]Endowment Pharmaceutical Chair AstraZeneca in Respiratory Health, Québec, Canada.
[6]Research Center of Centre Intégré Universitaire de Santé et de Services Sociaux de l'Estrie–Centre Hospitalier Universitaire de Sherbrooke (CIUSSS de l'Estrie–Centre Hospitalier Universitaire de Sherbrooke), Sherbrooke, Canada.
*RESP Investigators in alphabetical order: Simon Bacon, Marie-France Beauchesne, Lucie Blais, Kim Lavoie, Catherine Lemiere, Gregory Moullec, Veronique Pepin, Adriana Spahija

Downloaded by Universita Degli Studi Di Torino from www.liebertpub.com at 07/26/23. For personal use only.

Introduction

Chronic obstructive pulmonary disease (COPD) is one of the leading causes of mortality and morbidity worldwide, and its prevalence has increased in recent decades.[1] Together with the cessation of smoking, pharmacological treatment with an inhaled medication to reduce symptoms and prevent exacerbation is a central part of disease management.[2]

As maintenance treatments for COPD, inhaled medications are preferred to oral medications because the drug is directly deposited in the lung, minimizing any systemic adverse effects. However, administering medication via inhalers is complex, usually requiring patient coordination and manual dexterity to perform the necessary steps for dose delivery. In recent years, several new inhaled drugs and new inhaler devices became available, extending the COPD treatment options. HandiHaler® is a single-dose dry powder inhaler (DPI) used to deliver tiotropium (Spiriva®), a long-acting muscarinic antagonist that is used in COPD maintenance treatments.[3] Breezhaler® (single-dose DPI), Genuair® (multidose DPI), and Respimat® (soft mist inhaler) are new inhaler devices that also deliver COPD maintenance drugs, either long-acting beta-agonists or muscarinic antagonists.[4–6]

The inhaler characteristics and the patient's ability to use the inhaler device correctly are often overlooked when selecting a new treatment, although they are important factors because correct inhaler use is related to the clinical efficacy of the drug.[7,8] When used correctly, all inhaler devices should be equally effective.[9] However, it has been shown that inhaler technique is generally poor. In fact, in a 2008 systematic literature review, the proportion of patients who had an incorrect inhaler technique with DPIs varied from 4% to 94%, depending on the device evaluated and the technique assessment method used,[7] but no studies have evaluated the new inhalation devices, such as Breezhaler, Genuair, and Respimat. Even though metered-dose inhalers (MDI) are not the focus of our study, it is reported that as many as 94% of MDI users had an incorrect inhaler technique.[10–12]

In addition to inhaler technique, adherence to inhaler therapy is also important for the control of COPD. Better treatment adherence and better outcomes have been observed in patients who are satisfied with their inhalers.[13,14] An association between patient's device preference and inhalation technique has also been suggested, but studies have reported conflicting results.[15,16] Therefore, patient preferences for inhalers and their inhalation techniques are important aspects of COPD management and should be evaluated for the new inhalers.

The main objectives of this prospective two-center cross-sectional study were to evaluate the inhalation techniques of COPD patient with the HandiHaler device and compare the inhalation techniques with the new inhalers: Breezhaler, Genuair, and Respimat. In this study, we also explored the patient preferences for these new inhalers.

Methods

Study design

A prospective two-center cross-sectional study was conducted among patients with COPD selected from the *Registre de Données en Santé Pulmonaire* (RESP) database. RESP is a continually updated research database that includes patients with COPD and/or asthma who have agreed to be contacted for research projects. Recruitment for RESP took place between May and September of 2016 at two teaching hospitals in Quebec, Canada: the *Centre Hospitalier Universitaire de Sherbrooke* (CHUS) and the *Hôpital du Sacré-Coeur de Montréal* (HSCM).

Patients. The patients were required to meet the following inclusion criteria: age 18 years or older, pulmonologist-confirmed diagnosis of COPD documented in his/her medical records, current and autonomous use of the HandiHaler device, and ability to speak French or English. The exclusion criteria included past or current use of any of the new inhalation devices (Breezhaler, Genuair, or Respimat), treatment for an acute medical condition or hospitalization at the time of recruitment, or any other condition that could compromise their participation in the study.

Conduct of the study

A letter, including a description of the study and a consent form, was mailed to eligible patients selected from the RESP database. A week later, a pharmacy resident telephoned the patients to provide further information about the study, to confirm their eligibility, and to schedule an appointment with those who agreed to participate. The patients were then invited to a face-to-face interview at the hospital or at their home in the case of mobility or functional impairment. The participants received $50 compensation for their participation.

Demographic information was obtained from the RESP database and confirmed during the telephone interview. The patients were also questioned on the approximate duration of their HandiHaler use, their training on the HandiHaler technique in the preceding 3 months, current or previous use of other inhalers (patients were shown pictures of the Turbuhaler®, Diskus®, MDI, and MDI with spacer), self-reported manual dexterity impairment, and self-reported visual impairment.

The patient interviews were conducted by a pharmacy resident using a standardized approach. First, the HandiHaler technique was evaluated with an inhalation technique assessment checklist. The three new placebo inhalation devices (Breezhaler, Genuair, and Respimat), information sheets for the devices, and muted demonstration videos produced by the Canadian Pulmonary Association for each new device were then presented to each patient in a random order. The patient was invited to view the demonstration video for each inhaler, to read the information sheets describing the inhalation steps for each inhaler, and to manipulate the inhalers without practicing the inhalation technique.

After showing the videos, the pharmacy resident explained the specific characteristics of the devices that were not shown clearly in the videos: the soft mist projected by Respimat, the color change in the dose-confirmation window of Genuair, and the capsule blisters of Breezhaler. The pharmacy resident also pointed out the dose counters of Respimat and Genuair. Respimat was already assembled (cartridge inserted) when given to the patient, as recommended in local practices. The patient was then asked to choose the device he/she preferred (hereafter called the ''initially preferred device'') based on his/her first impressions and to describe the reasons behind his/her choice (hereinafter referred to as ''question 1'').

Downloaded by Universita Degli Studi Di Torino from www.liebertpub.com at 07/26/23. For personal use only.

Next, a second inhaler, different from the patient's preferred device (either Breezhaler, Genuair, or Respimat) was randomly assigned to the patient (hereafter called the ''imposed device''). The patients were then asked to use the initially preferred and imposed devices in a randomized order.

Before using the inhalers, the patients viewed the same video demonstrations specific to the devices to be used, now unmuted, to learn the correct use of each device. Up to three attempts with each device were allowed before the inhalation technique was evaluated. During the interview, the pharmacy resident did not answer questions; feedback was only given at the end of the visit.

After their inhalation techniques were evaluated, the patients were asked once again to identify their favorite device from the two devices tested (''initially preferred device'' vs ''imposed device'') and to explain why they preferred it (hereinafter referred to ''question 2''). Finally, the patients were asked to choose their favorite device from the two devices tested and the HandiHaler (hereinafter referred to as ''question 3'').

Outcomes and questionnaire development

The primary outcome was the proportion of patients with an adequate inhalation technique with the HandiHaler, according to the inhalation technique assessment checklist. The secondary outcomes included the inhalation techniques with and patient preferences for the new inhalers (Breezhaler, Genuair, and Respimat).

At the time of the study, there was no standardized tool for evaluating patient techniques with different inhalation devices. Consequently, a checklist was developed for the purpose of this study. This checklist was based on the *Réseau Québécois de l'Asthme et de la MPOC*[1] (RQAM) inhalation technique observation grid and individual product monographs[4–6,17] (Appendix A in Supplementary Data; Supplementary Data are available online at www.liebertpub.com/jamp).

The RQAM grid is a practical tool used by respiratory educators to evaluate a patient's inhalation technique. The RQAM checklists were adapted by modifying, adding, or deleting steps to generate a list of steps considered essential for adequate dose delivery with each device (Appendix A in Supplementary Data). Each checklist developed contained 5–10 steps that were considered major errors if not performed correctly, and 4–5 steps that were considered minor errors if not performed correctly. ''Major errors'' were errors that would compromise the delivery of an effective dose. ''Minor errors'' were deviations from the recommended technique that were not considered to significantly compromise drug delivery.

Each step could be associated with a minor error, a major error, or both (Appendix A in Supplementary Data). An inadequate technique was defined as the presence of at least one major error or two minor errors during the use of the device. The inhaler technique assessment checklists developed were reviewed by two pharmacists certified in asthma education and two respiratory therapists.

[1]The RQAM is presently known as the Réseau Québécois d'Éducation en Santé Respiratoire (RQESR).

Statistical analysis

To estimate the proportion of patients who adequately used their Handihaler, with a precision of 10% and a confidence level (CI) of 95%, a sample size of 73 patients was required, assuming that 25% of the COPD patients who attended pulmonology clinics used their HandiHaler adequately. An interim analysis undertaken when 50 patients had completed the study revealed that $\sim$60% of patients had an adequate technique with HandiHaler. Therefore, to maintain the same precision and confidence level, the sample size was revised and increased to 93 patients.

The patients' characteristics were described with proportions for categorical variables and with means with standard deviations (SD) for continuous variables. The proportion and 95% CI of patients with an adequate HandiHaler technique were estimated. The proportion and 95% CI of patients preferring each device when initially presented to them (i.e., initially preferred device) was also estimated. A χ^2 test was used to assess whether one of the devices was initially preferred to the others. As a descriptive analysis, we also estimated the proportion of patients who preferred each device after they tried them based on question 2 (initially preferred device and imposed device) and question 3 (initially preferred device, imposed device, and HandiHaler).

The proportions of patients with an adequate technique for each new device were compared with a generalized estimating equation (GEE) model, with a logistic link including all potential confounders. The following variables that may have influenced inhaler technique were included in the model: age, sex, the order of demonstration of the new devices (initially preferred device first or imposed device first), preference for new device (initially preferred vs. imposed), HandiHaler technique (adequate vs. inadequate), training received with the HandiHaler device in the preceding 3 months (dichotomized), duration of HandiHaler use (continuous), use of other inhalers, such as the Turbuhaler, Diskus, or MDI with and without spacer (dichotomized for each device), dexterity impairment, visual impairment, forced expiratory volume in one second, and last level of education completed (primary and below, secondary, or postsecondary).

These were selected during initial study design and included variables shown to influence inhaler technique according to literature review.[8,10,11,13–16,18–20] This model also allowed the variance to be adjusted for multiple observations per patient because the inhalation technique was tested for two new devices for each patient (initially preferred device and imposed device). Missing data were imputed using the most frequently occurring value. When there were too many missing data for a variable, the variable was excluded from the model. The odds ratio (OR) for an adequate technique and the 95% CI comparing the three new devices were estimated. All statistical analyses were performed with SAS version 9.3 (SAS Institute, Inc., Cary, NC).

Ethics approval

This study was approved by the Ethics Review Board of HSCM and CHUS. Written and informed consent was obtained from all the participants. Patients registered in the RESP database had already provided their consent to be contacted for subsequent research projects.

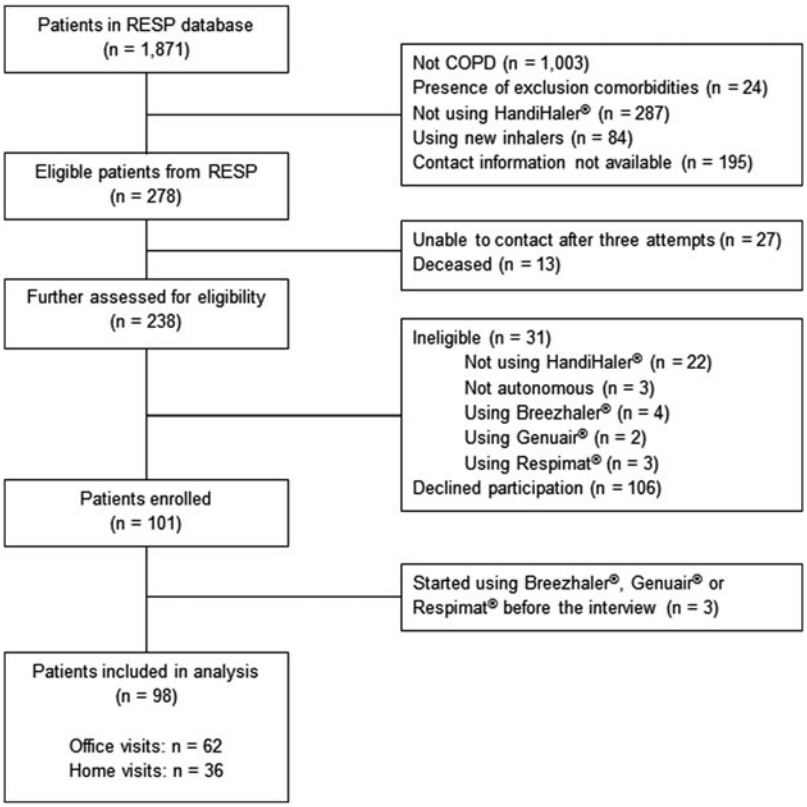

FIG. 1. Patient selection.

Downloaded by Universita Degli Studi Di Torino from www.liebertpub.com at 07/26/23. For personal use only.

Results

Patient characteristics

A patient selection flow chart and the reasons for exclusion are presented in Figure 1. A total of 278 COPD patients from the RESP database met our initial inclusion criteria. Of these, 238 patients were contacted and 31 were found to be ineligible after the telephone interview. Among the 207 eligible patients, 101 (48.8%) consented to participate and completed the study between May and September of 2016. Three patients had started to use a new inhalation device between recruitment and the interview, and were therefore excluded from the analyses.

The patients' characteristics ($n=98$) are shown in Table 1. The patients had a mean age of 69.8 years, and half were male (51.0%). The proportion of patients with concomitant asthma was 67.3%. The patients had used HandiHaler for 6.0 years on average, and the inhaler most frequently used other than HandiHaler was an MDI (89.8%). Few patients (12.2%) had received training on the use of HandiHaler during the preceding 3 months. Among the patients for whom pulmonary function tests, performed in the 2 years before enrollment in RESP, were available, most were GOLD stage II or higher.

The majority of patients (54.1%) had completed high school. There were no major differences in the patient characteristics between the new devices tested. It is worth noting that the groups shown in Table 1 are not mutually exclusive because each patient tested two new devices. The characteristics of the patients who declined participation are shown in Appendix B (Supplementary Data). There were no major differences between the characteristics of the study participants and those who declined participation, except that the proportion of GOLD stage II was larger among the participants.

A total of 196 observations of the techniques used with the new inhalers were evaluated: 59 patients tested the Breezhaler device, 70 patients tested the Genuair device, and 67 patients tested the Respimat device (Table 1 and Appendix C in Supplementary Data). The order of device testing was divided reasonably evenly between the patients: preferred device first for 51 patients (52.0%), and imposed device first for 47 patients (48.0%).

Inhalation techniques

Table 2 reports the most frequent errors made with each device tested. Among the 98 patients, 57.1% (95% CI: 47.4–66.9) showed an adequate HandiHaler inhalation technique, and 34.7% of the patients made no errors (including minor errors). The two most frequently missed steps with the HandiHaler were ''breathe out away from the device'' (37% made minor errors, 7% major errors), and ''remove device from mouth and hold your breath for 5–10 seconds'' (41% made minor errors, 12% major errors).

Among the 59 patients who tested the Breezhaler device, 66.1% had an adequate technique (Fig. 2). The most frequent errors were made in steps ''breathe out away from mouthpiece'' (14% made minor errors, 10% major errors) and ''inhale the medication rapidly and deeply'' (22% made major errors). Genuair was used adequately by 64.3% of the patients who tested the device. The most common errors were made in the steps ''breathe out away from the inhaler'' (17% made

Table 1. Patients' Baseline Characteristics According to the Devices Tested

	Breezhaler® (n = *59 observations)*	*Genuair®* (n = *70 observations)*	*Respimat®* (n = *67 observations)*	*Overall population*[a] (n = *98 patients)*
	n, (%) unless specified otherwise			
Age (years); mean ± SD	68.7 ± 8.1	70.6 ± 8.0	69.8 ± 8.3	69.8 ± 8.2
Male	28 (47.5)	36 (51.4)	36 (53.7)	50 (51.0)
Diagnosis				
COPD without concomitant asthma	21 (35.6)	22 (31.4)	21 (31.3)	32 (32.7)
COPD with concomitant asthma	38 (64.4)	48 (68.6)	46 (68.7)	66 (67.3)
Duration of HandiHaler® use (years); mean ± SD	5.9 ± 3.7	6.5 ± 3.8	5.7 ± 3.6	6.0 ± 3.7
Received teaching on HandiHaler® use within the previous 3 months	5 (8.5)	10 (14.3)	9 (13.4)	12 (12.2)
Previous use of inhalers				
Turbuhaler®	29 (49.2)	41 (58.6)	42 (62.7)	56 (57.1)
Diskus®	31 (52.5)	40 (57.1)	33 (49.3)	52 (53.1)
MDI	51 (86.4)	66 (94.3)	59 (88.1)	88 (89.8)
MDI with spacer	45 (76.3)	57 (81.4)	50 (74.6)	76 (77.6)
Impaired dexterity[b]	6 (10.2)	6 (8.6)	8 (11.9)	10 (10.2)
Visual impairment[b]	5 (8.5)	5 (7.1)	4 (6.0)	7 (7.1)
GOLD stage[c]				
GOLD 1	0 (0.0)	3 (4.3)	3 (4.5)	3 (3.1)
GOLD 2	22 (37.3)	24 (34.3)	24 (35.8)	35 (35.7)
GOLD 3	8 (13.6)	10 (14.3)	10 (14.9)	14 (14.3)
GOLD 4	7 (11.9)	5 (7.1)	6 (9.0)	9 (9.2)
Unavailable	22 (37.3)	28 (40.0)	24 (35.8)	37 (37.8)
Last level of education completed				
Primary or below	7 (11.9)	10 (14.3)	11 (16.4)	14 (14.3)
Secondary	34 (57.6)	35 (50.0)	37 (55.2)	53 (54.1)
College or university	17 (28.8)	22 (31.4)	17 (25.4)	28 (28.6)
Not available	1 (1.7)	3 (4.3)	2 (3.0)	3 (3.1)

[a]Total numbers of patients in the Breezhaler®, Genuair®, and Respimat® groups were twice the overall population because all patients tested two new devices.
[b]Dexterity impairment and visual impairment were self-reported.
[c]GOLD classification was determined using available pulmonary function tests performed up to 2 years before entry into the Registre de Données en Santé Respiratoire (RESP) database.
MDI, metered-dose inhaler; COPD, chronic obstructive pulmonary disease; GOLD, Global Initiative for Chronic Obstructive Lung Disease; SD, standard deviation.

Downloaded by Universita Degli Studi Di Torino from www.liebertpub.com at 07/26/23. For personal use only.

minor errors, 7% major error) and ''inhale rapidly and deeply'' (30% made major errors). Respimat was used correctly by 47.8% of the patients who tested the device. The most frequent errors with this device were made in the steps ''inhale slowly and deeply and press the dose release button while inhaling'' (21% made minor errors, 48% major errors) and ''breathe out before inhaling'' (18% made minor errors).

Device preferences

Before testing the inhalers (initially preferred device). After they were presented with the muted videos and information sheets about the three new devices, but before they actually used the inhalers (initially preferred device: question 1), 39.8% (95% CI: 30.1%–49.5%) of patients preferred Genuair, 36.7% (95% CI: 27.2%–46.3%) preferred Respimat, and 23.5% (95% CI: 15.1%–31.9%) preferred Breezhaler. These proportions were not found to be statistically significantly different ($p = 0.11$).

Before trying the new inhalers, the patients reported preferring Breezhaler for its apparent ease of use, its similarity to HandiHaler, its physical attributes (format and size), and the presence of a method of dose delivery confirmation (the audible vibration sound, the transparent capsules that allows one to check for remaining powder inside) (Appendix D in Supplementary Data). Patients who favored Genuair appreciated its apparent ease of use, the absence of capsules, and the presence of a method of dose delivery confirmation (the color control window and the audible ''click''). The most frequent reasons for preferring Respimat were its apparent ease of use, the soft mist it releases, the absence of capsules, and its physical attributes.

After testing the initially preferred and imposed inhalers. After testing two new inhalers, 70.4% still favored their initially preferred device, and 29.6% favored the device that had been imposed (question 2). When asked to select their favorite inhaler among the initially preferred device, the imposed device, and HandiHaler (question 3), 52.0% selected their initially preferred device, 18.4% selected the imposed device, and 29.6% selected HandiHaler, the device they routinely used.

Table 2. Most Frequent Errors in Using HandiHaler®, Breezhaler®, Genuair®, and Respimat®

	Minor error (%)	*Major error (%)*
Inhalation steps and errors with HandiHaler®		
Open the device	N/A	0%
Place capsule in the device	N/A	0%
Close the mouthpiece	N/A	0%
Press on the button once	8%	1%
Breathe out away from the device	37%	7%
Place mouthpiece in mouth and inhale slowly and deeply. Must hear the capsule vibrate	4%	2%
Remove the device from mouth and hold the breath for 5–10 seconds	41%	12%
Inhalation steps and errors with Breezhaler®		
Remove the cap	N/A	0%
Open inhaler	N/A	2%
Prepare capsule and insert in inhaler	N/A	2%
Close the inhaler	N/A	0%
Pierce the capsule	10%	3%
Release the buttons	N/A	3%
Breathe out away from the mouthpiece	14%	10%
Inhale the medication rapidly and deeply	0%	22%
Remove inhaler from mouth and hold the breath for 5–10 seconds	8%	3%
Open inhaler to see if there is powder left in capsule, inhale again without piercing the capsule.	15%	3%
Inhalation steps and errors with Genuair®		
Remove the cap	N/A	1%
Press button and release while holding inhaler horizontally, window should turn green	0%	8%
Breathe out away from inhaler	17%	7%
Inhale rapidly and deeply, should hear a click and the window should turn red	0%	30%
Remove inhaler from mouth and hold the breath for 5–10 seconds	11%	3%
Inhalation steps and errors with Respimat®		
Turn the base half a turn in the direction of the arrows until a ''click'' is heard	N/A	4%
Open cap completely	N/A	1%
Breathe out	18%	N/A
Close lips around mouthpiece without covering air vents	0%	4%
Inhale slowly and deeply, and press dose-release button once while inhaling	21%	48%
Hold breath for 5–10 seconds	6%	6%

N/A, not applicable to the device.

Downloaded by Universita Degli Studi Di Torino from www.liebertpub.com at 07/26/23. For personal use only.

Figure 3 illustrates the patients who retained their initially preferred device after each question. Of the 23 patients who initially preferred Breezhaler before trying the inhalers, 17 patients (73.9%) still favored it after trying it and an imposed inhaler, and 10 patients (43.5%) still preferred it to the imposed device and their usual device, HandiHaler, at the end of the interview. Of the 39 patients who initially preferred Genuair, 31 patients (79.5%) still preferred it after trying it and the imposed inhaler, and 21 patients (53.8%) still preferred it to the imposed device and HandiHaler. Of the 36 patients who initially preferred Respimat, 21 patients (58.3%) still preferred it after trying it and an imposed inhaler, and 20 patients (55.6%) still preferred it to the imposed device and HandiHaler.

The proportions of patients who preferred each device at the end of the interview are illustrated in Figure 4: 17.3% preferred Breezhaler, 30.6% preferred Genuair, 22.4% preferred Respimat, and 29.6% preferred HandiHaler. After trying the inhalers, the most frequent reasons for preferring Breezhaler were the presence of a method of dose delivery confirmation, its physical attributes, and its ease of use. The most frequent reasons for preferring Genuair were the absence of capsules, its ease of use, and the presence of a method of dose delivery confirmation. Patients who preferred Respimat appreciated its ease of use, the absence of capsules, and the soft mist released by the device. The most frequent reason for preferring HandiHaler was because it was familiar to the patient (Appendix D in Supplementary Data).

Table 3 reports the associations between the patient characteristics and the patients' inhaler technique derived with the GEE model. Genuair was selected as the reference

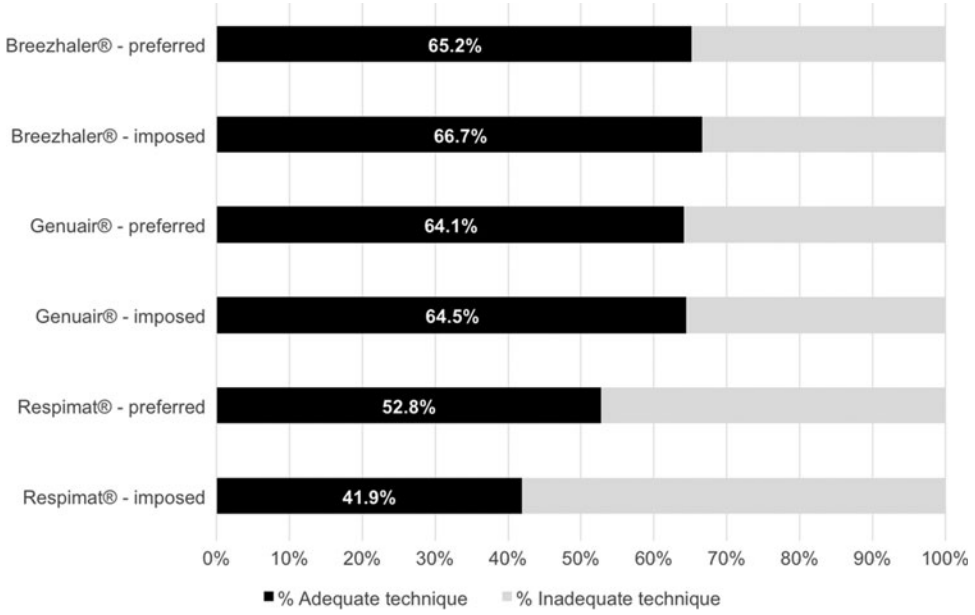

FIG. 2. Inhalation techniques with new inhalers.

Downloaded by Universita Degli Studi Di Torino from www.liebertpub.com at 07/26/23. For personal use only.

device in the model because it was the most frequently tested device and the most preferred. The crude ORs showed that the patients were less likely to have an adequate technique with Respimat than with Genuair (OR 0.49, 95% CI: 0.26–0.95), whereas we observed no significant differences between Breezhaler and Genuair. The addition of all potential confounders to the GEE model did not change the estimates much, with 62% fewer patients with Respimat than with Genuair who had an adequate technique and with no significant difference between Breezhaler and Genuair. Among all potential confounders included in the model, only age (OR 0.95, 95% CI 0.91–0.99) and an adequate HandiHaler technique (OR 3.11, 95% CI 1.55–6.21) were significantly associated with inhalation technique.

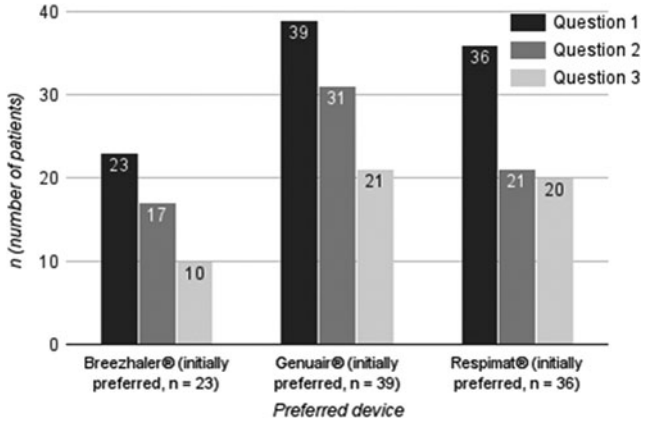

FIG. 3. Evolution of the initially preferred new device throughout the study.
Question 1: Initially preferred device: favorite device among Breezhaler®, Genuair®, and Respimat® after viewing muted videos and information sheets on the devices, but before using the devices.
Question 2: Initially preferred versus imposed device: favorite device between the initially preferred device and the imposed device, after using the devices.
Question 3: End of interview preference: favorite device among the initially preferred device, the imposed device, and HandiHaler®, after using the devices.

Discussion

To our knowledge, this is the first study to compare inhalation techniques and patient preferences for new inhalers, including Respimat. We found no significant difference between the new inhalers in terms of patient preferences, but all the devices evaluated were generally associated with a suboptimal inhalation technique (only 47.8%–66.1% of patients had adequate techniques, depending on the device). Inhalation technique was numerically better with Breezhaler and Genuair than with Respimat. Patients tended to have a better technique with the preferred device than with the imposed device, but the difference was not statistically

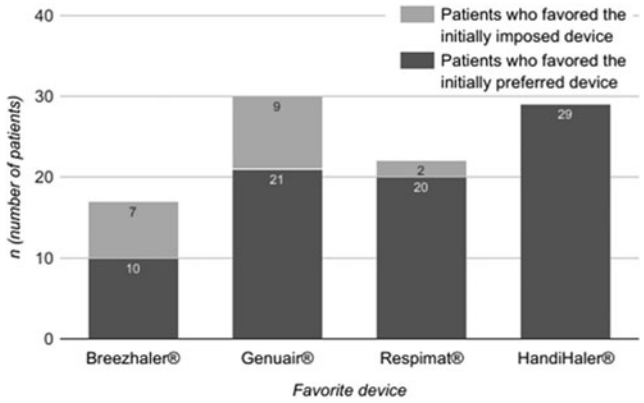

FIG. 4. Patients' favorite devices at the end of the interview (question 3).

Table 3. Association Between Patient Characteristics and Patient's Inhaler Technique

	Devices compared	*Crude OR (95% CI)*	*Adjusted OR (95% CI)*
Adequate inhaler technique	Breezhaler® vs. Genuair®	1.11 (0.58–2.16)	1.08 (0.51–2.30)
	Respimat® vs. Genuair®	0.49 (0.26–0.95)	0.38 (0.18–0.82)
Factors relating to adequate inhaler technique[a]	*Compared variables*	*Crude OR (95% CI)*	*Adjusted OR (95% CI)*
Increased age (years)		0.95 (0.92–0.99)	0.95 (0.91–0.99)
Sex	Male vs. female	1.17 (0.63–2.15)	1.01 (0.51–1.99)
Device preference	Preferred vs. imposed	1.09 (0.64–1.84)	1.17 (0.64–2.15)
HandiHaler® technique	Adequate vs. inadequate	2.32 (1.24–4.34)	3.11 (1.55–6.21)
Order of device technique observation	Preferred first vs. imposed first	0.89 (0.48–1.64)	0.65 (0.33–1.27)
Duration of HandiHaler® use (years)		1.00 (0.99–1.00)	1.00 (0.99–1.01)
Received teaching on HandiHaler® use in the last 3 months	Yes vs. no	1.44 (0.61–3.40)	1.86 (0.65–5.31)
Concomitant or previous use of			
Turbuhaler®	Yes vs. no	1.26 (0.68–2.36)	1.32 (0.65–2.68)
Diskus®	Yes vs. no	1.46 (0.79–2.69)	1.30 (0.63–2.69)
MDI	Yes vs. no	0.96 (0.42–2.23)	0.71 (0.29–1.75)
MDI with spacer	Yes vs. no	1.01 (0.47–2.14)	0.55 (0.22–1.36)
Impaired dexterity	Yes vs. no	0.83 (0.32–2.11)	0.73 (0.25–2.11)
Visual impairment	Yes vs. no	1.79 (0.46–6.98)	1.15 (0.22–5.86)
Last level of education completed[b]			
	Primary vs. postsecondary	1.25 (0.51–3.03)	1.26 (0.45–3.55)
	Secondary vs. postsecondary	1.25 (0.58–2.66)	1.13 (0.51–2.47)

[a]Forced expiratory volume in 1 second (FEV_1) was excluded from the model because of missing data.
[b]Last level of education: the value ''secondary'' was imputed for three patients with missing data.

Downloaded by Universita Degli Studi Di Torino from www.liebertpub.com at 07/26/23. For personal use only.

significant. We also observed that, despite being exposed to several new inhalers, almost a third of patients reported preferring their usual device, HandiHaler.

With their usual device, HandiHaler, the patients we evaluated had an inhalation technique judged as adequate in 57.1% of cases. This proportion is similar to that reported in the scientific literature, but is better than the proportion initially expected.[8,10,21] Differences in the proportions of patients with an adequate technique reported in the literature can be attributed to several factors, including the different study populations and the different technique assessment methods used. For example, in our study, the inhalation technique was considered adequate if no major errors or less than two minor errors were observed. If the threshold for an adequate technique is increased to no errors, the proportion of patients with an adequate technique drops to 34.7%, which is closer to the expected proportion.

These results must also be interpreted in light of the characteristics of the study population. The patients in our study were followed by pulmonologists and a multidisciplinary team (including pharmacists and respiratory therapists), who are best equipped to review and teach inhaler techniques. This may differ from other studies, which may have included more heterogeneous populations, and patients may have been followed by family physicians or other specialists.[22] If the study were conducted in a community setting, we would probably find a different proportion of adequate inhalation techniques. The patients were also selected from a pulmonary health research database, and those who agreed to participate in our study were probably more motivated than those who did not, and probably more conscious of their inhalation technique than those who refused to participate. The option of home visits also allowed the inclusion of patients with more advanced COPD and reduced mobility.

When we compared the inhalation techniques used with the new inhalers, no difference was detected between Breezhaler and Genuair. However, patients were less likely to have an adequate technique with Respimat than with the other devices evaluated. Because Respimat is not the device that requires the most steps for inhalation (eight steps vs. 13 steps with Breezhaler), it is unlikely that the number of steps required explains this tendency. An analysis of the most frequently reported errors with the device suggested that the step ''inhale slowly and deeply and press the dose release button while inhaling'' led to most errors, with up to 48% of patients committing a major error at this step. This is consistent with reports of other devices that require the user to synchronize inhalation and dose release, such as the MDI.[23–25]

It is noteworthy that few patients were observed to read the written instructions that were given to them about the devices, and the training videos seemed the most popular way for patients to learn about the new devices and how to use them. We believe that video demonstrations and written information alone are insufficient to ensure the acquisition of an adequate technique for Respimat, because synchronizing the device actuation and inhalation seems difficult to demonstrate adequately in videos and is not easy to learn without face to face training.[26]

In general and across the devices, the most frequently observed errors concerned the adequacy of inhalation and

Downloaded by Universita Degli Studi Di Torino from www.liebertpub.com at 07/26/23. For personal use only.

exhalation according to the device instructions. For example, Breezhaler and Genuair both require deep and rapid inhalation. The quality of inhalation with these devices was considered inadequate in 22% and 30% of patients, respectively, in our study.

Our results show a modest association between age and the new inhaler technique. As the patient's age increased, the likelihood of an adequate technique decreased, which may be explained by the cognitive impairment and comorbidity burden, which increase with age. These results are consistent with those in the literature,[8,15,18] and suggest that it is more challenging to learn to use a new device with increasing age. The HandiHaler technique was also considered a marker of the patient's baseline inhaler technique. After controlling for other confounders, an adequate HandiHaler technique was positively associated with the new inhaler technique. A patient who had an adequate HandiHaler technique was three times more likely to have an adequate inhalation technique with the new devices than a patient with an inadequate HandiHaler technique.

There was no significant difference between the new inhalers in terms of the initial patient preferences, before they had tried the devices. Both before and after having tried the different inhalation devices, the most frequent reason the patients gave for preferring a specific device was its perceived ease of use. In the cases of Genuair and Respimat, this included the fact that these devices do not require medication capsules to be manually inserted before use. This is consistent with the literature.[15] Interestingly, after trying both the preferred and the imposed inhaler devices, a high proportion of patients ($\sim$70%) still favored their initially preferred device. This suggests that an initial device preference is a good indicator of final preference, so patients may not need to actually try a device to ensure their satisfaction with it.

Furthermore, patients who preferred Respimat after trying it were more likely to select it as their favorite device, even over their usual device, HandiHaler. Familiarity with a device was a frequent reason for device preference. Despite trying new devices, almost a third of patients reported that they favored their usual device to the new devices. It must be noted that our study was conducted in a single session. This short period of time might not reflect patient satisfaction in real life, after a longer period of use. Some aspects that should be considered in assessing patient preferences, such as the inherent drug properties (e.g., adverse effects, number of daily doses, etc.), cost, or cleaning requirements, were not evaluated.

The logistic regression used in this study did not reveal any significant association between the patient preferences and inhalation techniques. This is consistent with reports in the current literature.[13–15] Nevertheless, patient preference can have a positive effect on treatment adherence, which was not evaluated in this study.[16,19] Other potential confounders included in the regression model, such as sex, order of demonstration, duration of HandiHaler use, recent teaching on HandiHaler use, impaired dexterity, visual impairment, concomitant or previous use of other COPD inhalation devices, and highest level of education obtained, had no significant effect on the inhalation technique with the new inhalers. However, these results may be limited by a lack of statistical power.

One strength of this study is the fact that the HandiHaler technique was used to control for the patients' baseline ability. We also used a design that allowed testing two inhalers per patients, which avoided overloading each patient with new information. To our knowledge, this is the first study to evaluate the inhalation technique used with the Respimat device compared with the techniques used with other inhalers. Home visits allowed the inclusion of patients who would not necessarily have been included otherwise because of their limited mobility or because severe disease impeded their ability to travel. All the patients included also had a pulmonologist-confirmed diagnosis of COPD.

The results of our study should be interpreted in light of the following limitations. First, the demographic characteristics of the participants were not significantly different from those of the nonparticipants. However, the patients who agreed to participate might have been more motivated than normal, and may therefore have performed better than members of the general population of COPD patients.

Second, although we standardized the interview procedures to reduce inter-evaluator bias, the interpretation of inhaler errors might still differ from one interviewer to another. We chose to use videos, information sheets, and limited verbal instructions to standardize the procedures and to reproduce real-life scenarios in medical clinics. However, in real life, this is not the optimal way of teaching the technique for a device because videos also have limitations. As we observed, not all the patients read the information sheets carefully. In real life, patient techniques could be improved with practical training. Furthermore, because only one pharmacy resident at a time was available to conduct the interviews, the evaluators were not blinded to whether a device was imposed or preferred, which could introduce ascertainment bias.

Third, because we evaluated the inhalation techniques of current HandiHaler users, the proportion of patients with an adequate Breezhaler technique evaluated in our study might have been greater than the technique of those who had not previously used HandiHaler, because the two devices are similar. Moreover, because there was a high proportion of missing data for the classification of COPD severity, this variable was not included in the GEE model.

Fourth, no validated assessment tool is available for evaluating the inhalation technique. Therefore, we developed our own standardized (but not validated) assessment tool based on one used in practice. Because not all devices have the same number of steps, and those steps do not have the same impact on drug delivery, we considered using a dichotomous score to even out those differences. The choice of major or minor errors was based on clinical judgment. Because different assessment methods differ, it may be difficult to compare the results of our study with those of other studies.

Finally, as stated earlier, the patients selected for this study were followed at the pulmonology outpatient clinics in two teaching hospitals, which may have limited the extent to which the results can be generalized to the general COPD population. Moreover, few of included patients were classified as GOLD stage I because that population usually does not require specialized care.

Conclusion

In conclusion, this study shows that the inhalation technique used with HandiHaler and three new inhaler devices available for the treatment of COPD were generally

suboptimal. For the newer devices, patients had better inhalation technique with Genuair and Breezhaler than with Respimat. Specific problematic steps, on which the clinician should focus his/her teaching, were identified for each device. There was no significant preference for any of the new inhalers evaluated before the patients tried them, but we observed a trend toward Genuair and HandiHaler being the most preferred devices after they were tried. No significant association was detected between inhaler preference and inhalation technique. The arrival of new inhalers is an opportunity to reassess patient techniques and preferences. Further studies may also explore the association between patient preference and treatment adherence.

Authors' Contributions

All authors were responsible for the study conception and design.

L.B. obtained the funding.

R.B., R.C., N.G., C.D.Y., A.C.L., A.M.L., C.L., J.F.P.M., F.O.R., L.B., M.F.B., and F.A. were responsible for data extraction, data analysis, statistical analysis, and data interpretation.

R.B., R.C., N.G., and C.D.Y. wrote the article.

All the authors revised and approved the final version of the article.

Downloaded by Universita Degli Studi Di Torino from www.liebertpub.com at 07/26/23. For personal use only.

Acknowledgments

We thank Geneviève Garand and Annie Brodeur for revising the inhalation technique assessment checklist. We thank Geneviève Lalonde for her assistance during the recruitment of patients. We also thank Amélie Forget for her help in data extraction from the RESP database. We thank the Biostatistics Department of the Centre de Recherche du CHUS for assistance with the statistical analysis. We also thank many other collaborators for their valuable contributions. Inhaler placebos were provided by AstraZeneca Canada, Inc. (Genuair), Novartis Pharma Canada, Inc. (Breezhaler), and Boehringer Ingelheim Canada Ltd (HandiHaler, Respimat).

This work was supported by an unrestricted grant from AstraZeneca; this company was not involved in the study design, data collection or analysis, and interpretation of the results. The article was sent to AstraZeneca for courtesy review.

Authors' Disclosure Statement

The pharmacy residents have no conflicts of interest to declare (R.B., R.C., N.G., C.D.Y., A.C.L., A.M.L., C.L., J.F.P.M., and F.O.R.). M.F.B. has received honoraria as a speaker and research grants from AstraZeneca, Boehringer Ingelheim, and Novartis. L.B. has received research grants and contracts from AstraZeneca, GlaxoSmithKline, and Pfizer. F.A. has received honoraria as a speaker and has coordinated a project that received research grants from the pharmaceutical companies AstraZeneca, GlaxoSmithKline, and Nycomed Canada. A.F. has no conflict of interest to declare.

References

1. Adeloye D, Chua S, Lee C, Basquill C, Papana A, Theodoratou E, Nair H, Gasevic D, Sridhar D, Campbell H, Chan KY, Sheikh A, Rudan I, and Global Health Epidemiology Reference G: Global and regional estimates of COPD prevalence: Systematic review and meta-analysis. J Glob Health. 2015;5:020415.
2. (GOLD) Global Initiative for Chronic Obstructive Lung Disease: Global Strategy for the Diagnosis, Management and Prevention of COPD. 2016; http://goldcopd.org/global-strategy-diagnosis-management-prevention-copd-2016. Accessed 5 October, 2016.
3. Aaron SD: Management and prevention of exacerbations of COPD. BMJ. 2014;349:g5237.
4. Novartis Pharmaceuticals Canada Inc: Seebri® Breezhaler® [Product monograph]. 2015. Accessed 11 October, 2016.
5. AstraZeneca Canada, Inc.: Tudorza® Genuair® [Product monograph]. 2017. Accessed October 11, 2016.
6. Boehringer Ingelheim: Spiriva® Respimat® [Product monograph]. 2015. Accessed 11 October, 2016.
7. Lavorini F, Magnan A, Dubus JC, Voshaar T, Corbetta L, Broeders M, Dekhuijzen R, Sanchis J, Viejo JL, Barnes P, Corrigan C, Levy M, and Crompton GK: Effect of incorrect use of dry powder inhalers on management of patients with asthma and COPD. Respir Med. 2008;102:593–604.
8. Melani AS, Bonavia M, Cilenti V, Cinti C, Lodi M, Martucci P, Serra M, Scichilone N, Sestini P, Aliani M, Neri M, and Gruppo Educazionale Associazione Italiana Pneumologi O: Inhaler mishandling remains common in real life and is associated with reduced disease control. Respir Med. 2011;105:930–938.
9. Dolovich MB, Ahrens RC, Hess DR, Anderson P, Dhand R, Rau JL, Smaldone GC, Guyatt G, American College of Chest P, American College of Asthma A, and Immunology: Device selection and outcomes of aerosol therapy: Evidence-based guidelines: American College of Chest Physicians/American College of Asthma, Allergy, and Immunology. Chest. 2005; 127:335–371.
10. Pothirat C, Chaiwong W, Phetsuk N, Pisalthanapuna S, Chetsadaphan N, and Choomuang W: Evaluating inhaler use technique in COPD patients. Int J Chron Obstruct Pulmon Dis. 2015;10:1291–1298.
11. Arora P, Kumar L, Vohra V, Sarin R, Jaiswal A, Puri MM, Rathee D, and Chakraborty P: Evaluating the technique of using inhalation device in COPD and bronchial asthma patients. Respir Med. 2014;108:992–998.
12. Molimard M, Raherison C, Lignot S, Depont F, Abouelfath A, and Moore N: Assessment of handling of inhaler devices in real life: An observational study in 3811 patients in primary care. J Aerosol Med. 2003;16:249–254.
13. Lavorini F, and Fontana GA: Inhaler technique and patient's preference for dry powder inhaler devices. Expert Opin Drug Deliv. 2014;11:1–3.
14. Chrystyn H, Small M, Milligan G, Higgins V, Gil EG, and Estruch J: Impact of patients' satisfaction with their inhalers on treatment compliance and health status in COPD. Respir Med. 2014;108:358–365.
15. Chorao P, Pereira AM, and Fonseca JA: Inhaler devices in asthma and COPD—an assessment of inhaler technique and patient preferences. Respir Med. 2014;108: 968–975.
16. Welch MJ, Nelson HS, Shapiro G, Bensch GW, Sokol WN, Smith JA, and Parasuraman BM: Comparison of patient preference and ease of teaching inhaler technique for Pulmicort Turbuhaler versus pressurized metered-dose inhalers. J Aerosol Med. 2004;17:129–139.

17. Comité scientifique du Réseau québecois de l'asthme et de la MPOC: Grilles d'observation des techniques d'inhalateurs [Checklists for observation of inhalation techniques]. 2015:1–3. http://www.rqesr.ca/fra/mdl-sec-doc.asp?f=grilles=inhalateurs_2017.pdf&1=fra&gi=4. Accessed October 5, 2016.
18. Wieshammer S, and Dreyhaupt J: Dry powder inhalers: Which factors determine the frequency of handling errors? Respiration. 2008;75:18–25.
19. Anderson P: Patient preference for and satisfaction with inhaler devices. Eur Respir Rev. 2005;14:109–116.
20. Hashmi A, Soomro JA, Memon A, and Soomro TK: Incorrect inhaler technique compromising quality of life of asthmatic patients. J Med. 2012;13:16–21.
21. Sriram KB, and Percival M: Suboptimal inhaler medication adherence and incorrect technique are common among chronic obstructive pulmonary disease patients. Chron Respir Dis. 2016;13:13–22.
22. Crane MA, Jenkins CR, Goeman DP, and Douglass JA: Inhaler device technique can be improved in older adults through tailored education: Findings from a randomised controlled trial. NPJ Prim Care Respir Med. 2014;24:14034.
23. Sanchis J, Gich I, Pedersen S, and Aerosol Drug Management Improvement T: Systematic review of errors in inhaler use: Has patient technique improved over time? Chest. 2016; 150:394–406.
24. Yawn BP, Colice GL, and Hodder R: Practical aspects of inhaler use in the management of chronic obstructive pulmonary disease in the primary care setting. Int J Chron Obstruct Pulmon Dis. 2012;7:495–502.
25. Vincken W, Dekhuijzen PR, Barnes P, and Group A: The ADMIT series - Issues in inhalation therapy. 4) How to choose inhaler devices for the treatment of COPD. Prim Care Respir J. 2010;19:10–20.
26. Axtell S, Haines S, and Fairclough J: Effectiveness of various methods of teaching proper inhaler technique: The importance of pharmacist counseling. J Pharm Pract. 2016; 30:195–201.

Received on June 12, 2017
in final form, October 13, 2017

Reviewed by:
Brad Drummond

Address correspondence to:
Lucie Blais, PhD
Faculté de Pharmacie
Université de Montréal
C.P. 6128, Succursale Centre-ville
Montréal
Québec H3C 3J7
Canada

E-mail: lucie.blais@umontreal.ca

Downloaded by Universita Degli Studi Di Torino from www.liebertpub.com at 07/26/23. For personal use only.