Respiratory Medicine 185 (2021) 106507

Contents lists available at ScienceDirect

Respiratory Medicine

journal homepage: www.elsevier.com/locate/rmed

Original Research

Effectiveness of a pharmacist-led intervention on inhalation technique for asthma and COPD patients: The INSPIRA pilot cluster-randomized controlled trial

António Teixeira Rodrigues [a,*], Sónia Romano [a], Mariana Romão [a], Débora Figueira [a], Carolina Bulhosa [a], Anabela Madeira [b], Luis Rocha [c,d], José Alves [e]

[a] Centre for Health Evaluation & Research/Infosaude – National Association of Pharmacies (CEFAR/IS-ANF), Lisbon, Portugal
[b] Medicines Information Centre/Infosaude – National Association of Pharmacies (CEDIME/IS-ANF), Lisbon, Portugal
[c] Pulmonology Department, Portuguese Oncology Institute of Porto, Porto, Portugal
[d] Occupational Health Department, Portuguese Oncology Institute of Porto, Porto, Portugal
[e] Portuguese Lung Society, Porto, Portugal

ARTICLE INFO

Keywords:
Asthma
COPD
Inhalation technique
Education
Pharmaceutical care

ABSTRACT

Introduction: Asthma and COPD are leading causes of disability-adjusted life-years worldwide representing a huge burden on the health system and among patients. One of the reasons for the lack of disease control is poor inhalation technique, with impact on quality of life and symptom control.
Objective: To assess the effectiveness of a community pharmacist-led educational intervention on asthma and COPD patients' inhalation technique.
Methods: The INspira study is a 6-month pilot cluster randomized controlled trial, conducted in community pharmacies of Portugal, enrolling adults aged 18 years or older, with a self-reported diagnosis of asthma or COPD and on inhaled therapy. Pharmacies were randomly allocated to Intervention or Control group. Intervention focused mainly on inhalation technique education via demonstration and repetition. Primary outcome was the proportion of patients scoring 100% in at least one inhaler.
Results: From January to November 2019, 48 pharmacies recruited 201 asthma and COPD patients, of which 132 completed the 6-month follow-up. At the end of follow-up, the odds of intervention group patients score 100% compared to the control group were 5.63 (95% CI, [2.21; 14.35]) in all inhalers in use and 6.77 (95% CI, [2.52; 18.20]) considering at least one inhaler. Intervention group patients reported having a significantly lower number of scheduled appointments compared with the control group (OR = 0.17; 95% CI, [0.037; 0.79]; p = 0.0135). No other significant differences were found between groups.
Conclusion: This pilot study suggested that pharmacist interventions can improve patients' inhalation technique, with possible positive impact in healthcare resource use.

1. Introduction

Respiratory diseases are among the most common causes of death globally. Asthma and chronic obstructive pulmonary disease (COPD) are two chronic respiratory diseases top ranked as the most common causes of disability-adjusted life-years (DALY) [1]. The pharmacological approach to asthma and COPD includes mainly inhaled therapy, which is pivotal to the management of the symptoms and to prevent exacerbations. Despite the use of appropriate therapy, many patients experience a sub-optimal effect of their medication. Inadequate inhaler technique is one of the main reasons for poor disease control, with negative impact on health and economic outcomes [2–4]. Therefore, adherence to therapy and correct performance of inhaler technique are key factors to control the disease [5]. Various formulations and inhaler types are available in the market (e.g., dry powder inhalers (DPI), pressurized metered-dose inhalers (pMDI), soft mist inhalers (SMI)) with different sequential steps needed to achieve a correct and effective medicine deposition. Interventions as inhaler technique training showed to improve adherence, disease control and even allowed dose reduction in long term [6], contributing to gains in patients quality of life and

* Corresponding author. Rua Marechal Saldanha 1, 1249-069, Lisboa, Portugal.
E-mail address: antoniot.rodrigues@anf.pt (A.T. Rodrigues).

https://doi.org/10.1016/j.rmed.2021.106507
Received 26 March 2021; Received in revised form 31 May 2021; Accepted 5 June 2021
Available online 9 June 2021

reducing healthcare resource utilization [7]. Better outcomes can be achieved when there is regular reinforcement of correct technique [4,8], as passive interventions alone (e.g., using only a device-specific instruction pamphlet) are proven to be insufficient [9].

In recent years, community pharmacists have shifted their role in the healthcare system from traditional medication dispensers to health care providers [10]. Pharmacists can have a valuable role in educational interventions as they are highly accessible and have regular contact with patients, which allows them to closely monitor medicines adherence and disease management [11,12]. This framework provides an opportunity to help health systems, challenged by the combined demand for primary care services and limited supply of general practitioners [13,14], to reduce unnecessary visits to family doctors and emergency departments.

As seen, there is extensive international literature demonstrating the effectiveness of pharmacist-led interventions in the community [15]. Moreover, both asthma and COPD prevalence are higher in Portugal than in other European countries [16]. Still, there is a lack of research on this topic in Portugal.

This pilot study aimed to provide data on the impact of a community pharmacist-led educational intervention on asthma and COPD patients' inhalation technique compared to usual care. Given its association with disease control, the study also aimed to assess the effect of the intervention on exacerbation rates, COPD-specific health status and general healthcare resource use.

2. Methods

2.1. Study design

The INspira trial is a 6-month pilot cluster randomized controlled trial (cRCT) – (intervention vs. control), of an inhalation technique education through pharmacist's demonstration and patient repetition, carried out between January and November 2019 in community pharmacies. The study protocol was approved by the Institute for Bioethics of the Catholic University of Portugal (IB-UCP) in December 2018, complying with the national ethical requirements and legal procedures. Study was registered on the ISRCTN registry (ISRCTN10844309). Patients provided informed consent to participate in the trial.

2.2. Pharmacy and participant enrollment

Pharmacies (the cluster units) from three different regions of mainland Portugal (districts of Faro, Lisboa and Setúbal), affiliated in the National Association of Pharmacies (27.6% of the total national affiliated pharmacies) and using the dispensing software – Sifarma® 2000, were invited to participate via email directed to the pharmacy owner. The community pharmacies which expressed a formal written consent to participate, were randomized to either the intervention or control arm. Pharmacies were randomized after recruitment conclusion, using an allocation ratio of 1:1. Randomization at the pharmacy level was used to prevent contamination between patients using the same pharmacy and avoid ethical issues from the pharmacist's perspective. Moreover, pharmacies from the same owner or in the same neighborhood could not be randomized into different groups.

Pharmacists in the intervention group (IG) received a classroom training session (≈4 h) addressing pathophysiology of asthma and COPD, pharmacological treatment (GINA and GOLD guidelines), the features of the main types of inhalers, the most common errors in the inhalation technique and intervention and study procedures. Physical training on the inhalation technique was performed using placebo devices. Attending the training session was mandatory for this group to perform the intervention.

Pharmacists in the control group (CG) received a web-based training session (≈2 h) focused only on the study procedures. The CG provided usual care for the 6 months following patient enrollment. Usual care consisted of patients receiving normal care with no additional protocolled intervention.

Eligible patients were adults aged 18 years or older using at least 1 of the targeted inhalers (both chronic or first user), and a self-reported diagnosis of asthma or COPD. The self-reported diagnosis was checked by the pharmacist, using a differential algorithm based on the age at the time of symptom onset; and subsequentially supported by a set of questions on: a) history of allergies; b) smoker status or continued exposition to biomass; c) type of symptoms response to short-action bronchodilator treatment; and d) therapeutic regimen.

Exclusion criteria were pregnancy, cognitive impairment as perceived by the pharmacist, motor limitations or other situation that jeopardized the performance of the inhalation technique, or any other condition that limited the understanding of study objectives or questionnaire completion.

During the recruitment period, whenever a targeted inhaler was dispensed on the participant pharmacies (intervention and control), an alert was automatically generated at the pharmacy software. Patients were screened for eligibility and invited to participate in the study. Because the intervention was educational, masking was not possible. Nevertheless, the trial was intentionally labeled as a "Study of inhaler use in asthma and COPD", so both pharmacists and patients could not perceive the study design. To conceal the allocation group, participants were informed that intervention was to be delivered in different time points between both study arms. Recruitment occurred between January and April 2019.

2.3. Intervention

Six out of the ten types of inhalers with the highest market shares in the country were included in the trial, taking into consideration the availability of placebo-inhaler devices - Breezhaler Ellipta; Spiromax; Turbohaler; pressurized Metered-Dose Inhalers (pMDI) and Respimat. The intervention consisted of a structured, pharmacist-led educational program, providing oral and written information to asthma and COPD patients about: a) inhalation technique (including physical demonstration) and b) disease characteristics, therapeutic regimen goals and adherence to prescribed therapy.

Patients in the IG received up to 4 face-to-face intervention sessions (baseline, 1, 3 and 6 months after recruitment). The 1-month visit was only performed in the IG and meant to reinforce the baseline educational intervention. The following package was followed:

a) inhalation technique

Firstly, patients were asked to demonstrate the inhalation technique with their own device, while the pharmacist assessed patient's technique (correct/incorrect steps) using a pre-defined checklist for each inhaler type; Secondly the pharmacist demonstrated the proper technique of the deemed incorrect steps, using a placebo device; Thirdly, a device-specific information leaflets regarding the technique were delivered to the patients with the steps incorrectly performed highlighted; Fourthly patients were asked to repeat the full technique. Patients could receive training on up to 4 different devices.

b) disease characteristics, therapeutic regimen goals and adherence to prescribed therapy

The pharmacist gave a short oral explanation about the disease (asthma or COPD), symptoms, maintenance therapy goals (e.g., avoid exacerbations or decline of the respiratory function, etc.), and the best practices to store and clean the inhaler devices. Additionally, verbally, the pharmacist highlighted the importance of patients taking medications as prescribed by their doctor, not stopping or decreasing the medications intake without previously discussing it.

For CG, baseline- and 3-month follow-up, served only as data collection visits. At 6 months, to allow these patients to benefit from the

educational intervention, the pharmacist-led inhalation technique intervention was also delivered to them. Firstly, the pharmacist recorded the usual study data and then proceeded to apply the intervention, starting by the assessment of the baseline inhaler technique. About 1-month before this time point, pharmacists in the CG received a classroom training program similar to the intervention arm, to qualify them to conduct the intervention at the 6-month follow-up.

As this was designed as a pragmatic trial, patients could skip any of the intermediate visits, i.e., the 1- or 3-month follow-up visits. To help pharmacies to follow-up patients through the project, a specific software add-on (INspira add-on) was activated in the dispensing software - Sifarma® of all participant pharmacies. The software add-on requirements were designed by the research team, and developed by the owner company of the Sifarma® dispensing software. About 10 days before the patients' next scheduled visit, the software triggered a pop-up alert in the pharmacy and an automatic text message to be sent to patients' telephone.

2.4. Outcomes

Outcomes data were collected at baseline (pre-intervention), 3 and 6-month follow-up visits for both groups. Performed inhalation technique, electronic data and questionnaires completed at the start of the study served as baseline data. Electronic data comprised anthropometric data, inhaled medicines, disease, and time since diagnosis. Questionnaires collected (i) sociodemographic data; and (ii) asthma or COPD-related self-reported data (comorbidities, concomitant medications, health resources use, control of the disease and COPD specific health status). The outcomes were measured at the patient level and the analysis considered pharmacies as patient clusters.

Intervention pharmacists assessed the inhalation technique at the start of the study and at 3- and 6-month follow-up visits, while control pharmacists assessed it only at 6-month follow-up. As groups were randomly assigned, it was assumed that both groups would score the same at baseline. Pharmacists scored the inhalation technique using specific checklists for each inhaler type, developed by the research team based on user guidelines and instruction package inserts from the manufacturers: eleventh-point checklist for Breezhaler (single-dose capsule DPI); eight-point checklist for Ellipta (multi-dose DPI), for Spiromax and for Turbohaler (multi-dose DPI); nine-point checklist for pMDIs and Respimat (SMI). One point was assigned for each correctly performed step. The sum of points was expressed as the percentage of total steps for each device.

The primary outcome was the proportion of patients (irrespective their diagnosis asthma or COPD) who achieved 100% of the technical score in all devices in use (conservative approach) or at least in one device in use (less conservative approach) in the 6-month assessment.

The secondary outcomes were:

Asthma severity – Assessed with the Asthma Control Test (ACT) [17]. The ACT is a validated questionnaire often used to evaluate asthma control in clinical practice and reflects the patient's status over the previous 4 weeks [17]. Includes four symptom/reliever questions plus a patient self-assessed level of control. The ACT scores ranges from 5 to 25: values between 5 and 15 indicate "very poorly controlled asthma"; those from 16 to 19 are "not well-controlled asthma" and values varying from 20 to 25 denote "well-controlled asthma" [18][17].

Dyspnea for COPD patients was determined by the modified Medical Research Council dyspnea (mMRC) scale [19] [20]. This tool comprises five statements describing the entire range of respiratory disability from none (score 0) to almost complete incapacity (score 4).

COPD-specific health status measured using the COPD Assessment Test (CAT) [21]. This tool measures the impact of the disease on patients' health status. Comprises eight items with a sematic six-point differential scale. Scores range from 0 to 40: 0–10, 11–20, 21–30 and 31–40 and represent a "low", "medium", "high" and "very high" impact of the disease on a person's health status, respectively [22].

Healthcare resource use and exacerbations – Participants were asked to report the number of programmed medical doctor appointments regarding disease management, along with the occurrence of asthma/COPD exacerbations and type of health resources needed to address the event.

2.5. Sample size

Sample size was based on the hypothesis that the IG would achieve a proportion of subjects attaining a inhalation technique score of 100% at least as great as the one observed in a previous study conducted by the research center [23]. A baseline proportion of 30% (either condition) and an expected proportion of 60% at 6-month follow-up in the IG. Assuming an alpha of 5%, 80% power and an allocation ratio of 1:1, we estimated that the minimum total sample size to detect differences between intervention and control group is 96 subjects (48 subjects per group). Accounting for a drop-out rate of 30%, this yields a total of 138 subjects to be recruited in an individually randomized trial (69 for each of the two groups). However, considering that correlation of individual responses within pharmacies (clusters) could be present due to the cluster design, an intra-cluster correlation Coefficient (ICC) of 0.3, estimated from the previous study data [23], was considered. Assuming each pharmacy could recruit three patients of each condition, it was considered a design effect of 1.6, reaching a total number of 222 subjects and 74 pharmacies (37 per group) to be recruited. The sample size was calculated using the software G*Power version 3.1.9.2 developed by Heinrich-Heine-University in Germany.

2.6. Statistical analysis

Descriptive statistics were calculated by study arm and by diagnosis (asthma and COPD). Categorical data were summarized by absolute and relative counts, including counts of missing observations. Continuous outcomes were summarized by the number of non-missing values, mean and standard deviation (SD). Primary outcome results were estimated for the whole dataset, irrespectively of the patients' condition.

The IG was compared with the CG, performing an intention to treat analysis for all primary and secondary outcomes. Primary analysis only considered patients for which a 6-month technical score was available for the reported inhalers at baseline (those assessed in the IG and declared in the CG at baseline). For the patient reported outcomes the two groups were compared considering the baseline, 3-month and 6-month evaluation. Missing data were handled as missing at random (MAR).

A mixed-effect logistic regression was used to analyze the primary outcome, using pharmacy as random effects to account for the cluster randomization, and the treatment allocation as a fixed effect. This allowed to test for differences in the primary outcome between the intervention and the control groups.

For the secondary categorical outcomes, the model included a time $\times$ group interaction term as fixed effects and patient ID and pharmacy as random effects. As an alternative, in cases with contingency tables with low cell counts, a Fisher's exact test was performed with the Haldane-Anscombe correction. The continuous secondary outcomes were assessed by a mixed-effect linear regression, considering the same fixed and random effects.

Comparisons between patients who accepted to participate in the study and those who refused and, between those who were lost to follow up and those who completed the study, were performed using the chi-square or Fisher's exact test for categorical variables and *t*-test or nonparametric Wilcoxon–Mann–Whitney test for continuous variables. Comparisons comprised the following data: age, gender, time since diagnosis, body mass index (BMI), pathology (asthma or COPD), CAT, ACT and mMRC scores.

All analyses were performed using 95% confidence intervals and two-sided p-values < 0.05 were considered significant.

3. Results

3.1. Study participants and follow-up

From a total of 760 pharmacies assessed for eligibility, 655 were invited to participate. From those, about 14% (n = 92) expressed interest to participate in the study, exceeding the total number of pharmacies required (n = 74). A total of 45 pharmacies were randomized to intervention and 47 to control. About 73% (n = 67) of the these attended the training required to integrate the study, and 52.2% (n = 48) recruited at least one patient. Only pharmacies that recruited at least one patient were included in the analysis. Participant pharmacies recruited a total of 201 asthma or COPD patients, of which 132 (65.7%) completed the trial. On average, there were 4 patients per pharmacy, ranging from 1 to 11.

A total of 167 patients refused to participate in the study. Compared to study participants, the proportion of men among those who refused was higher ($p = 0.0036$) and had a similar age and diagnosis distribution ($p > 0.05$) (Supplementary Material 1). The main reasons for refusal were lack of time (n = 75; 44.9%) and not being used to participate in this kind of study (n = 36; 21.6%). Fig. 1 depicts the study flow of the clusters and the patients for the trial.

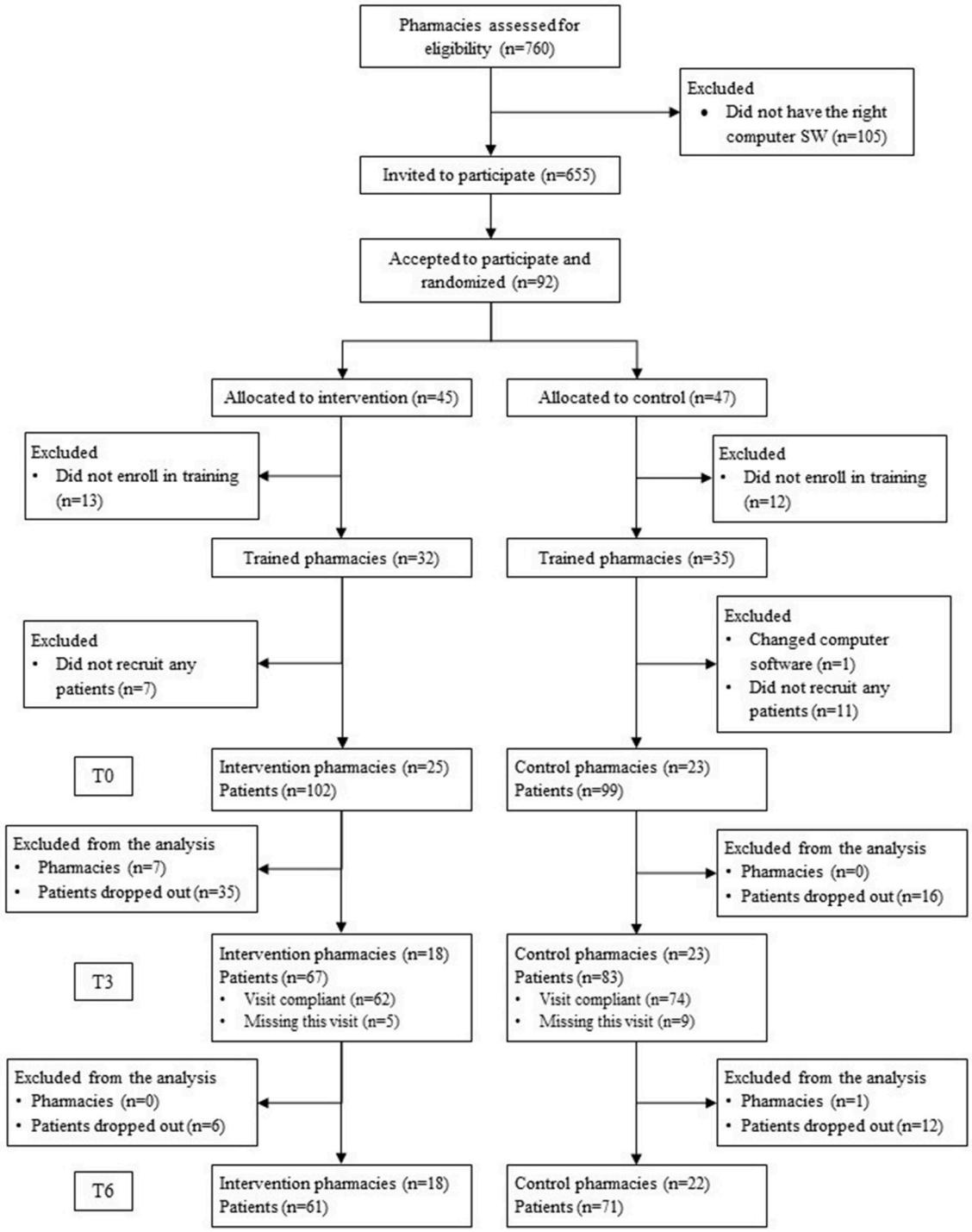

Fig. 1. Flowchart of pharmacies and patients through the study.

Main reasons for patients' drop-out were lost to follow-up (n = 30), change of residence (n = 9) and other as, for example, lack of interest in the trial and no time to participate. Regarding pharmacies, exclusion occurred by lack of study participants due to patients drop-out.

Participants in both IG and CG showed similar baseline sociodemographic and clinical characteristics (Table 1). Baseline characteristics by disease are depicted in supplementary material (Supplementary Material 2). No differences were found between the participants who dropped-out and those who completed the study (Supplementary Material 3).

3.2. Primary outcome

At baseline, only 20.62% of the IG patients registered a 100% score in all inhalers and 23.71% in at least one inhaler. At the end of follow-up, the proportion of patients with a maximum score was 65.57% in all inhalers and 70.49% in at least one inhaler, compared to 27.12% and 28.81% respectively, in the CG. The odds of achieving 100% score in all inhalers in the IG versus the CG was 5.63 (95% CI, [2.21; 14.35]). In a less conservative approach, the odds of intervention patients record a maximum score in at least one inhaler versus control was 6.77 (95% CI, [2.52; 18.20]). Similar results were retrieved in subgroup analysis by disease. Scores from both groups, time points and statistical analysis are detailed in Table 2.

Table 1
Baseline sociodemographic and clinical characteristics.

	Intervention group	Control group
	All (n = 102)	All (n = 99)
Age (years) [Mean (SD)]	62.82 (15.29)	61.48 (17.03)
Female [n, %]	68 (66.67%)	64 (64.65%)
Highest level of education [n, %]		
No education	1 (0.99%)	2 (2.02%)
Primary education (4th year)	32 (31.68%)	29 (29.29%)
Primary education (6th year)	13 (12.87%)	7 (7.07%)
Primary education (9th year)	12 (11.88%)	5 (5.05%)
Secondary education (12th year)	25 (24.75%)	27 (27.27%)
Higher education (university)	18 (17.82%)	29 (29.29%)
No of patients	101	99
Occupation [n, %]		
Employed	31 (30.39%)	36 (36.36%)
Unemployed	9 (8.82%)	8 (8.08%)
Pensioner	62 (60.78%)	54 (54.55%)
Other	0 (0%)	1 (1.01%)
No of patients	102	99
BMI* (Kg/m^2) **[Mean (SD)]**	27.42 (5.52)	26.91 (5.08)
No of patients	100	98
Smoking Status [n, %]		
Current smoker	21 (21.00%)	21 (21.43%)
Ex-smoker	35 (35.00%)	32 (32.65%)
Non-smoker	44 (44.00%)	45 (45.92%)
No of patients	100	98
Time since diagnosis (years) [Mean (SD)]	15.49 (16.59)	21.32 (19.08)
No of patients	96	96
Number of different types of inhalers Mean (SD)	1.26 (0.53)	1.19 (0.42)
Exact number [n, %]		
Number of different types of inhalers = 1	75 (78.13%)	80 (81.63%)
No of patients	96	98
Number of medications [Mean (SD)]	1.88 (1.12)	2.08 (1.22)
No of patients	102	99
Number of comorbidities [Mean (SD)]	2.18 (1.68)	2.01 (1.62)
No of patients	102	99

NOTE: The number of patients differs between variables because of missing answers.
Abbreviations are as follows: BMI: Body Mass Index; Number of medications: Asthma or COPD related medications (short-acting beta2-agonists (SABA), long-acting beta2-agonists (LABA), short-acting antimuscarinics (SAMA), long-acting antimuscarinics (LAMA), Inhaled corticosteroids (ICS), fixed-association LABA + LAMA, fixed-association ICS + LAMA, fixed-association SAMA + SABA, oral corticosteroids (OCS), monoclonal antibody, leukotriene receptor antagonists, methylxanthines, antihistamines, mucolytics, antitussives); Number of comorbidities: Asthma or COPD related comorbidities (hypertension, pulmonary hypertension, cardiac disease, osteoporosis, anemia, anxiety and/or depression, diabetes, sleep disorders, gastroesophageal reflux, sleep apnea).

3.3. Secondary outcomes

Approximately half of the asthmatic population reported a very poorly or not well-controlled asthma (ACT score <20) at baseline. At the end of the study, these proportion had decreased in both groups. No significant differences were found between mean ACT scores from intervention and control groups at 6 months (Mean Diff = 0.76; 95% CI, [-1.79; 3.32]; p = 0.956).

Regarding COPD patients, nearly 45% recorded a respiratory disability ≥2 in mMRC dyspnea scale at baseline. At the 6-month follow-up, that percentage diminished to 42.86% in the IG and to 35.71% in the CG. No significant differences were observed between groups (OR = 0.70; 95% CI, [0.03; 4.11]; p = 0.999). Likewise, no beneficial effect of the intervention was found in COPD-specific health status as seen in CAT scores (Mean Diff = −3.52; 95% CI, [-9.21; 2.18]; p = 0.481). Patient reported outcomes are summarized in Table 3.

Concerning healthcare resource use at baseline, about half of the study participants have had at least one scheduled doctor appointment in the 3 prior months. By the end of the study this proportion reduced in both intervention and control groups. Among the patients who completed the 6-month follow-up, there was a significantly lower number of IG patients reporting to have had a scheduled appointment compared with the CG (OR = 0.17; 95% CI, [0.037; 0.79]; p = 0.0135). Similar results were retrieved in subgroup analysis by disease.

At baseline, about 54% of the patients experienced at least one exacerbation episode during the last 3 months. Six months after, 25.42% of the respondents from the IG and 41.18% from the CG experienced exacerbations. No differences were found between groups at 6-month follow up (OR = 0.41; 95% CI, [0.10; 1.65]; p = 0.4410). Scheduled doctor appointments and exacerbation episodes are detailed in Table 4.

Table 2
Primary outcome.

	Intervention group	Control group	Statistical analysis
			Odds ratio [95% CI][a]
Patients Scoring 100% In all inhalers [n, %]			
Baseline	20 (20.83%)	–	–
No of patients with technique	96		
6 months	40 (65.57%)	16 (27.12%)	5.63 [2.21; 14.35]*
No of patients with technique	61	59	
At least in one inhaler [n, %]			
Baseline	23 (23.96%)	–	–
No of patients with technique	96		
6 months	43 (70.49%)	17 (28.81%)	6.77 [2.52; 18.20]*
No of patients with technique	61	59	

*statistically significant.
[a]Mixed-effect logistic regression, using pharmacy as random effects to account for the cluster randomization, and the treatment allocation as a fixed effect.[b] Mixed-effect linear regression, using pharmacy and patient ID as random effects to account for the cluster randomization, and the treatment allocation as a fixed effect.

Table 3
Asthma and COPD patients reported outcomes.

	Intervention group	Control group	Statistical analysis	
			Difference [95% CI][a]	Odds ratio [95% CI][b]
Asthma ACT score [n, %]				
Baseline [Mean (SD)]	18.65 (5.07)	19.82 (3.84)	–	–
Very poorly controlled	15 (27.27%)	8 (13.33%)	–	–
Not well-controlled	13 (23.64%)	20 (33.33%)	–	–
Well-controlled	27 (49.09%)	32 (53.33%)	–	–
No of patients	55	60		
6 months [Mean (SD)]	20.97 (3.75)	20.07 (3.8)	0.76 [-1.79; 3.32]	
Very poorly controlled	3 (9.68%)	5 (11.90%)	–	–
Not well-controlled	6 (19.35%)	9 (21.43%)	–	–
Well-controlled	22 (70.97%)	28 (66.67%)	–	–
No of patients	31	42		
COPD mMRC [n (%)]				
Baseline				
mMRC ≥ 2	22 (48.89%)	16 (42.11%)	–	–
No of patients	45	38		
6 months				
mMRC ≥ 2	12 (42.86%)	10 (35.71%)	–	0.70 [0.03; 14.11]
No of patients	28	28		
COPD CAT score [n (%)]				
Baseline [Mean (SD)]	16.04 (8.16)	18.58 (9.27)	–	–
Low impact	12 (26.67%)	9 (23.68%)	–	–
Medium impact	19 (42.22%)	13 (34.21%)	–	–
High Impact	12 (26.67%)	10 (26.32%)	–	–
Very high impact	2 (4.44%)	6 (15.79%)	–	–
No of patients	45	38		
6 months [Mean (SD)]	14.54 (9.34)	17.03 (8.58)	−3.52 [-9.21; 2.18]	
Low impact	10 (35.71%)	5 (17.24%)	–	–
Medium impact	11 (39.29%))	14 (48.28%)	–	–
High Impact	5 (17.86%)	7 (24.14%)	–	–
Very high impact	2 (7.14%)	3 (10.34%)	–	–
No of patients	28	29		

Abbreviations are as follows: ACT: Asthma Control Test - score range from 5 to 25 with lower values meaning less controlled asthma; mMRC: modified Medical Research Council dyspnea scale – range from 0 to 4 which means almost complete respiratory incapacity; CAT: COPD Assessment Test – range from 0 to 40, with higher values meaning worse health status.
[a] Mixed-effect linear regression, using pharmacy and patient ID as random effects to account for the cluster randomization, and the interaction between treatment allocation and time as a fixed effect. [b] Mixed-effect logistic regression, using pharmacy and patient ID as random effects to account for the cluster randomization, and the interaction between treatment allocation and time as a fixed effect.

Table 4
Healthcare resource use and history of exacerbation.

	Intervention group	Control group	Statistical analysis OR [95% CI][a]
Scheduled doctor appointments			
Baseline			
Patients with event [n,%]	50 (49.02%)	55 (55.56%)	-
No of patients	102	99	
6 months			
Patients with event [n,%]	11 (18.64%)	35 (49.30%)	0.17 [0.037; 0.79] *
No of patients	59	71	
Exacerbations [in the last 3 months]			
Baseline			
Patients with event [n,%]	51 (50.50%)	57 (57.58%)	–
No of patients	101	99	
Leading to non-scheduled doctor appointments			
Patients with event [n,%]	26 (50.98%)	21 (36.84%)	–
Total events [n]	42	28	
Leading to ER visits			
Patients with event [n,%]	19 (37.25%)	13 (22.81%)	–
Total visits [n]	30	16	
6 months			
Patients with event [n,%]	15 (25.42%)	28 (41.18%)	0.41 [0.10; 1.65]
No of patients	59	68	
Leading to non-scheduled doctor appointments			
Patients with event [n,%]	3 (5.08%)	9 (13.24%)	–
Total events [n]	6	21	
Leading to ER visits			
Patients with event [n,%]	4 (6.78%)	8 (11.76%)	–
Total visits [n]	6	8	

*statistically significant; ER: emergency room.
[a]Mixed-effect logistic regression, using pharmacy and patient ID as random effects to account for the cluster randomization, and the interaction between treatment allocation and time as a fixed effect.

4. Discussion

The INspira pilot trial assessed the effectiveness of a community pharmacist-led educational intervention to improve the inhalation technique of asthma and COPD patients. Secondary outcomes (e.g. ACT, mMRC, exacerbations, medical appointments) were selected based on their association with the effectiveness of inhaled drug delivery and disease control [2,24]. At baseline, about 50% of the asthma patients reported a not well-controlled or very poorly controlled disease. As for COPD patients, about 45% presented some degree of respiratory disability (≥2 in mMRC dyspnea scale). These results are comparable to previously published studies [25–27] and confirm the existence of individuals with suboptimal disease control among such population. Study results also showed that patients frequently cannot correctly execute inhalation technique since less than one quarter of the study population have performed a perfect technique (100% score) at baseline. This finding has been repeatedly reported in the literature, with a threshold rounding 25% [2–4,11].

This 6-month pilot cRCT provides preliminary data suggesting that a structured pharmacist-led educational intervention can significantly improve patient's inhalation technique as it has been reported in other studies [27–30]. The intervention focused in delivering inhaler training using verbal and written counselling plus physical demonstration, a method proven to be the most effective [31]. At the end of the study, the odds of IG scoring 100% in the inhalation technique were at least 5 times higher than in the CG (5.63 considering a score of 100% in all inhalers and 6.77 considering a score of 100% in at least one). Similar results were retrieved considering subgroup analysis by respiratory illness [32]. Overall, it appears that multiple inhalers use can confuse patients [33].

Those with more than one inhaler seem to have more difficulties to master inhalation technique - the odds of scoring 100% reduced when all inhalers in use were added to the analysis. For future research this should be taken in attention as it may be a driver for lower medication adherence and poorer disease control [24].

In a study on COPD patients, Tommellein et al. [27] recorded an improvement in the inhalation technique and medication adherence, as well as a significantly lower proportion of hospitalizations because of increased disease control. Mehuys et al. [34] conducted a similar trial in patients with asthma and also showed that the education of asthma patients had a positive impact on health outcomes. At the end of their trial, ACT scores had increased significantly in the intervention arm for the subgroup of patients having insufficiently controlled asthma at baseline, which was associated to better inhalation technique and medicine adherence [34]. These outcomes provide an insight of the impact of this type of approach, and reinforce the importance of educational interventions to achieve better compliance and disease control [32]. Moreover, previous studies showed that patients who had already received educational interventions had better technique compared to the ones who did not [35,36]. However, the literature also shows a decrease in the quality of the inhalation technique over time [7], which reinforces the need for regular and periodic educational sessions or every time a patient changes its type of inhaler [4,7,8]. The INspira intervention significantly reduced the number of scheduled doctor appointments in the IG compared to the CG. Similar studies conducted in the community pharmacy setting also revealed a reduction in the number of hospitalizations [27,34,36], which leads to the consideration that pharmacist-led educational interventions of this kind may reduce the burden to health services and lead to significant savings for the health system. No other significant differences were observed in further secondary outcomes (ACT, mMRC, CAT and number of exacerbations), which is in agreement with findings from other studies conducted in various health care settings [27,34]. However, half of the patients in this study presented a poor disease control at baseline, enhancing the potential for improvement. A significant progress would be expected specially in asthma patients' technique as this is a reversible condition. Nevertheless, these results should be interpreted with caution, considering these were secondary outcomes, the total number of patients at 6-month follow-up and the short duration of the study.

The INspira pilot trial provides data about the possibility to implement educational services in the routine practice of Portuguese community pharmacies. However, it has also highlighted some difficulties to fully engage pharmacies and patients with this type of interventions, traditionally not delivered in the community pharmacy setting. Aware of this circumstance, automatic visit reminders were developed to help pharmacies and patients to comply with the trial. However, due to a technical problem, these text reminders were not sent to patients. Nevertheless, pharmacists were alerted to schedule the visits by the INspira software add-on and could voluntarily call the patients for remind. Once these retention strategies proved to be quite ineffective, the motives and barriers that lead to patients' drop-out should have been systematically collected. Other approaches should be considered in further research. Moreover, pharmacists had no benefit or financial incentive for providing the service along with their regular tasks, what may have weighed for a divestment on the pilot. Lack of time and remuneration are factors frequently reported as barriers for pharmacist-led interventions [29] and could also have impacted the willingness to perform a close patient follow-up [36]. Additionally, pharmacy staff changes may also have impacted the ability to deliver the intervention, as in most pharmacies, there was only one pharmacist trained on trial procedures.

4.1. Limitations

Some limitations of this study must be mentioned. Firstly, this was a pilot study conducted only in three regions of mainland Portugal; therefore, our sample may not be representative.

Secondly, we had a high percentage of patients lost to follow-up (40.2% in the IG and 28.3% in the CG) which lowered the statistical power of the analysis and may have biased the results, decreasing the internal validity. However, when the patients who drop out were compared with those who completed the trial, no significant differences were found. This finding suggests that loss to follow-up may have not impacted the estimates of the effect of the intervention vs the control group. Thirdly, self-reported clinical data (e.g., medication, comorbidities) collected at baseline was not confirmed, as pharmacists do not have access to such data, and could have some degree of inaccuracy; however, it has already been validated that patients are aware of their disease [37]. Furthermore, patients were asked to report exacerbations and scheduled doctor appointments that had occurred in the previous 3 months to minimize recall bias. Fourth, inhalation technical skills from intervention pharmacists were not reassessed during the trial. This lack of retraining could have affected the pharmacists' performance and quality assessment in the intervention group compared to the control group, whose training was performed just before the 6-month assessment. However, it was unlikely to happen because the trial was held during a short time span and with several moments of teaching and evaluation of the inhalation technique.

Fifth, selection bias could have occurred, as a significant difference ($p = 0.0036$) was found between the gender distribution of patients who accepted to participate and those who refused. A major proportion of males refused to participate in the study which may explain the higher proportion of women found in COPD CG, given that the prevalence of COPD in Portugal is greater in men [16].

5. Conclusion

To our knowledge, this is the first RCT conducted in Portugal to pilot the effectiveness of an educational intervention on inhaler technique in asthma and COPD patients. Public health initiatives are essential to help patients and health providers to manage these high burden diseases. Study results suggest that pharmacist-led inhaler technique educational interventions can be introduced in the pharmacy's daily routine practice. Further research at national level with a larger sample size and this pilot learnings (related to intervention procedures, pharmacies and patient's recruitment) will be needed to define the essentials of future implementation in the community pharmacy and which patients would most benefit from this intervention.

Availability of data and materials

The datasets used and/or analysed during the current study are available from the corresponding author on reasonable request.

Funding

This research did not receive any specific grant from funding agencies in the public, commercial, or not-for-profit sectors. This study was funded by the Portuguese National Association of Pharmacies.

Role of the funder

The funder had no role in the design of the study; management, analysis, and interpretation of the data; preparation; review, or approval of the manuscript; and decision to submit the manuscript for publication.

CRediT authorship contribution statement

António Teixeira Rodrigues: Conceptualization, Methodology, Writing – review & editing, Project administration. **Sónia Romano:** Methodology, Formal analysis, Investigation, Resources, Supervision,

Writing – original draft. **Mariana Romão:** Methodology, Formal analysis, Investigation, Resources, Writing – review & editing. **Débora Figueira:** Formal analysis, Writing – original draft. **Carolina Bulhosa:** Data curation, Formal analysis, Writing – review & editing. **Anabela Madeira:** Investigation, Writing – review & editing. **Luis Rocha:** Conceptualization, Writing – review & editing. **José Alves:** Conceptualization, Writing – review & editing.

Declaration of competing interest

The authors declare the following financial interests/personal relationships which may be considered as potential competing interests: ATR, SR, MR, DF, CB and AM are employees of Infosaude, a company owned by Portuguese National Association of Pharmacies..

Acknowledgements

The authors are grateful to all community pharmacies who participated in the study and all participants who voluntarily agreed to complete the trial. The authors thank to AstraZeneca®, Novartis®, Teva®, Boehringer Ingelheim® and GlaxoSmithKline® for providing placebo devices.

Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.rmed.2021.106507.

References

[1] European Respiratory Society, European lung white book. https://www.erswhitebook.org/chapters/the-burden-of-lung-disease/, 2020. Accessed December 2, 2020.
[2] A.S. Melani, M. Bonavia, V. Cilenti, et al., Inhaler mishandling remains common in real life and is associated with reduced disease control, Respir. Med. 105 (6) (2011) 930–938, https://doi.org/10.1016/j.rmed.2011.01.005.
[3] G.K. Crompton, P.J. Barnes, M. Broeders, et al., The need to improve inhalation technique in europe: a report from the aerosol drug management improvement team, Respir. Med. 100 (9) (2006) 1479–1494, https://doi.org/10.1016/j.rmed.2006.01.008.
[4] F. Lavorini, A. Magnan, J. Christophe Dubus, et al., Effect of incorrect use of dry powder inhalers on management of patients with asthma and COPD, Respir. Med. 102 (4) (2008) 593–604, https://doi.org/10.1016/j.rmed.2007.11.003.
[5] Global Initiative for Asthma (Gina), At-A-Glance Asthma Management Reference for adults, adolescents and children 6–11 years. https://ginasthma.org/wp-content/uploads/2016/04/GINA-at-a-Glance_2016.pdf. Accessed December 10, 2020. Glob Initiat Asthma. Published online 2016.
[6] P. Arora, L. Kumar, V. Vohra, et al., Evaluating the technique of using inhalation device in COPD and Bronchial Asthma patients, Respir. Med. 108 (7) (2014) 992–998, https://doi.org/10.1016/J.RMED.2014.04.021.
[7] S.L. Klijn, M. Hiligsmann, S.M.A.A. Evers, M. Román-Rodríguez, T. Van Der Molen, J.F.M. Van Boven, Effectiveness and success factors of educational inhaler technique interventions in asthma & COPD patients: a systematic review, npj Prim Care Respir Med 27 (24) (2017). 10.1038/s41533-017-0022-1.
[8] I.A. Basheti, H.K. Reddel, C.L. Armour, S.Z. Bosnic-Anticevich, Improved asthma outcomes with a simple inhaler technique intervention by community pharmacists, J. Allergy Clin. Immunol. 119 (6) (2007) 1537–1538, https://doi.org/10.1016/j.jaci.2007.02.037.
[9] M.A. Crane, C.R. Jenkins, D.P. Goeman, J.A. Douglass, Inhaler device technique can be improved in older adults through tailored education: findings from a randomised controlled trial, npj Prim Care Respir Med 24 (March) (2014) 1–5, https://doi.org/10.1038/npjpcrm.2014.34.
[10] E. Mossialos, E. Courtin, H. Naci, et al., From "retailers" to health care providers: transforming the role of community pharmacists in chronic disease management, Health Pol. 119 (5) (2015) 628–639, https://doi.org/10.1016/j.healthpol.2015.02.007.
[11] M.M. Castel-Branco, A. Fontes, I.V. Figueiredo, Identification of inhaler technique errors with a routine procedure in Portuguese community pharmacy, Pharm. Pract. 15 (4) (2017) 1072, https://doi.org/10.18549/PharmPract.2017.04.1072, 1072.
[12] A. Milosavljevic, T. Aspden, J. Harrison, Community pharmacist-led interventions and their impact on patients' medication adherence and other health outcomes: a systematic review, Int. J. Pharm. Pract. 26 (5) (2018) 387–397, https://doi.org/10.1111/ijpp.12462.
[13] Instituto Nacional de Estatística, Número de habitantes por médico e por outro pessoal de saúde Lisboa, Portugal, 2020. https://www.pordata.pt/Portugal/M%c3%a9dicos+e+outro+pessoal+de+sa%c3%bade+por+100+mil+habitantes-639. Accessed December 10, 2020.
[14] Oecd, The looming crisis in the health workforce - how can OECD countries respond?. https://www.who.int/hrh/migration/looming_crisis_health_workforce.pdf, 2008. Accessed December 10, 2020.
[15] D.M. Dawoud, A. Haines, D. Wonderling, et al., Cost effectiveness of advanced pharmacy services provided in the community and primary care settings: a systematic review, Pharmacoeconomics 37 (10) (2019) 1241–1260, https://doi.org/10.1007/s40273-019-00814-4.
[16] Institute for Health Metrics and Evaluation (Ihme), GBD Compare Data Visualization. Seattle, IHME, University of Washington, 2021. http://vizhub.healthdata.org/gbd-compare. Acedido em: 11 março 2021.
[17] R.A. Nathan, C.A. Sorkness, M. Kosinski, et al., Development of the Asthma Control Test: a survey for assessing asthma control, J. Allergy Clin. Immunol. 113 (1) (2004) 59–65, https://doi.org/10.1016/j.jaci.2003.09.008.
[18] Global Initiative for Asthma, Global strategy for asthma management and prevention. www.ginasthma.org, 2019. Accessed December, 16 2020.
[19] J.C. Bestall, E.A. Paul, R. Garrod, R. Garnham, P.W. Jones, J.A. Wedzicha, Usefulness of the Medical Research Council (MRC) dyspnoea scale as a measure of disability in patients with chronic obstructive pulmonary disease, Thorax 54 (7) (1999) 581–586, https://doi.org/10.1136/thx.54.7.581.
[20] D. Kovelis, N.O. Segretti, V.S. Probst, S.C. Lareau, A.F. Brunetto, F. Pitta, Validação do Modified Pulmonary Functional Status and Dyspnea Questionnaire e da escala do Medical Research Council para o uso em pacientes com doença pulmonar obstrutiva crônica no Brasil, J. Bras. Pneumol. 34 (12) (2008) 1008–1018, https://doi.org/10.1590/S1806-37132008001200005.
[21] P.W. Jones, G. Brusselle, R.W. Dal Negro, et al., Properties of the COPD assessment test in a cross-sectional European study, Eur. Respir. J. 38 (1) (2011) 29–35, https://doi.org/10.1183/09031936.00177210.
[22] P.W. Jones, G. Harding, P. Berry, I. Wiklund, W.H. Chen, N. Kline Leidy, Development and first validation of the COPD assessment test, Eur. Respir. J. 34 (3) (2009) 648–654, https://doi.org/10.1183/09031936.00102509.
[23] C. Torre, Guerreiro, A. José Pedro Madeira, F. Lopes, et al., Pharmacy-Based Intervention in COPD Patients – Portuguese Pharmacists Can Effectively Improve Inhalation Technique! *FIP World Congr 31 August - 5* Sept Dublin, 2013.
[24] O.S. Usmani, F. Lavorini, J. Marshall, et al., Critical inhaler errors in asthma and COPD: a systematic review of impact on health outcomes, Respir. Res. 19 (1) (2018) 10, https://doi.org/10.1186/s12931-017-0710-y.
[25] C. Gregoriano, T. Dieterle, A.-L. Breitenstein, et al., Use and inhalation technique of inhaled medication in patients with asthma and COPD: data from a randomized controlled trial, Respir. Res. 19 (1) (2018) 237, https://doi.org/10.1186/s12931-018-0936-3.
[26] L. Guénette, M.C. Breton, J.P. Grégoire, et al., Effectiveness of an asthma integrated care program on asthma control and adherence to inhaled corticosteroids, J. Asthma 52 (6) (2015) 638–645, https://doi.org/10.3109/02770903.2014.999084.
[27] E. Tommelein, E. Mehuys, T. Van Hees, et al., Effectiveness of pharmaceutical care for patients with chronic obstructive pulmonary disease (PHARMACOP): a randomized controlled trial, Br. J. Clin. Pharmacol. 77 (5) (2014) 756–766, https://doi.org/10.1111/bcp.12242.
[28] A. Hämmerlein, U. Müller, M. Schulz, Pharmacist-led intervention study to improve inhalation technique in asthma and COPD patients, J. Eval. Clin. Pract. 17 (1) (2011) 61–70, https://doi.org/10.1111/j.1365-2753.2010.01369.x.
[29] K.W. Ruud, S.W. Rønningen, P.K. Faksvåg, H. Ariansen, R. Hovland, Evaluation of a structured pharmacist-led inhalation technique assessment service for patients with asthma and COPD in Norwegian pharmacies, Patient Educ. Counsel. 101 (10) (2018) 1828–1837, https://doi.org/10.1016/j.pec.2018.05.018.
[30] X. Jia, S. Zhou, D. Luo, X. Zhao, Y. Zhou, Y min Cui, Effect of pharmacist-led interventions on medication adherence and inhalation technique in adult patients with asthma or COPD: a systematic review and meta-analysis, J. Clin. Pharm. Therapeut. 45 (5) (2020) 904–917, https://doi.org/10.1111/jcpt.13126.
[31] S. Axtell, S. Haines, J. Fairclough, Effectiveness of various methods of teaching proper inhaler technique: the importance of pharmacist counseling, J. Pharm. Pract. 30 (2) (2017) 195–201, https://doi.org/10.1177/0897190016628961.
[32] A. Shakshuki, R.U. Agu, Improving the efficiency of respiratory drug delivery: a review of current treatment trends and future strategies for asthma and chronic obstructive pulmonary disease, Pulm Ther 3 (2) (2017) 267–281, https://doi.org/10.1007/s41030-017-0046-2.
[33] J. Van Der Palen, J.J. Klein, C.L.A. Van Herwaarden, G.A. Zielhuis, E.R. Seydel, Multiple inhalers confuse asthma patients, Eur. Respir. J. 14 (5) (1999) 1034–1037, https://doi.org/10.1183/09031936.99.14510349.
[34] E. Mehuys, L. Van Bortel, L. De Bolle, et al., Effectiveness of pharmacist intervention for asthma control improvement, Eur. Respir. J. 31 (4) (2008) 790–799, https://doi.org/10.1183/09031936.00112007.
[35] T. Maricoto, L.V. Rodrigues, G. Teixeira, C. Valente, L. Andrade, A. Saraiva, Assessment of inhalation technique in clinical and functional control of asthma and chronic obstructive pulmonary disease, Acta Med. Port. 28 (6) (2015) 702–707, https://doi.org/10.20344/amp.5905.
[36] V.B. Petkova, Pharmaceutical care for asthma patients: a community pharmacy-based pilot project, Allergy Asthma Proc. 29 (1) (2008) 55–61, https://doi.org/10.2500/aap2008.29.3083.
[37] T. Oksanen, M. Kivimäki, J. Pentti, M. Virtanen, T. Klaukka, J. Vahtera, Self-report as an indicator of incident disease, Ann. Epidemiol. 20 (7) (2010) 547–554, https://doi.org/10.1016/j.annepidem.2010.03.017.