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Effects of a structured educational intervention in moderate-to-severe elderly asthmatic subjects

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ABSTRACT

Background: Adherence to inhaled drugs is linked to patients' satisfaction with their device, and an incorrect use can negatively affect the outcomes of asthma treatment. We speculated that this is particularly true in elderly asthmatic subjects.

Aim: We performed a national pre-post interventional multicentre study, enrolling moderate-to-severe asthmatic subjects aged ≥65 years treated with fixed inhaled combination drugs by dry powder inhaler (DPI) or pressurized metered dose inhaler (pMDI). Adherence and critical errors were evaluated by means of validated questionnaires at first visit (V1) and after 3–6 months (V2). At V1, subjects underwent intensive training on the correct use of their device by physical demonstration.

Results: A total of 411 asthmatics (F/M: 238/173, mean age±SD: 72 ± 5 years) participated to the study. At V1, 50% of the study subjects showed an Asthma Control Test (ACT) score ≤19 despite GINA step 3 and 4 treatment, and 40% had experienced at least one severe asthma exacerbation in the previous year. Poor adherence to treatment was recorded in 43% of subjects, and at least one error in using the device was registered in 56% of subjects. At V2, available for 318 patients, both the percentage of individuals with poor adherence and with at least one critical error significantly decreased (from 46% to 25%, and from 49% to 25%, respectively; $p < 0.001$ for both comparisons) with a significant increase of the ACT score (from 19 ± 4.9 to 20 ± 4.0, $p < 0.001$).

Conclusions: Asthma in the elderly is characterized by low levels of symptom control. Educational interventions are strongly advocated in this age group in order to increase adherence to treatment and inhaler techniques.

Introduction

Errors in inhaler handling, not taken into account in clinical trials, could impact on drug delivery and minimize treatment benefits. Approximately 50 billion US dollars (USD) are spent annually on inhalers in the USA, and 7 to 15 billion USD are wasted due to incorrect technique.[1] Lewis et al.[2] developed a model for estimating the impact of poor inhaler technique on the economic burden of asthma and COPD in Spain, Sweden and UK, and they attributed 2.2–2.7% of direct asthma and COPD costs of 105 million Euros to poor inhalation technique across the three countries studied.

In a previous study, we reported a high rate of uncontrolled asthma in elderly subjects[3] with possible explanations due to the well-known poor perception of dyspnea in the elderly[4] and the occurrence of

Abbreviations: ACT, asthma control test; EDUCA, elderly and device use in chronic asthma; LABA, long-acting β_2 agonist; ICS, inhaled corticosteroids; LAMA, long-acting muscarinic antagonists; SAE, severe asthma exacerbation; CFC, chlorofluorocarbons; PROs, patient-reported outcomes; AHDS, hospital anxiety depression scale; FVC, forced vital capacity; FEV_1, forced expiratory volume 1s second; SF12, short form health survey; PCS, physical health composite score; MCS, mental health composite score; mMRC, modified medical research council.

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comorbidities; of note, low adherence to therapy or improper use of inhaler devices, which are known to be associated with loss of asthma control,[5,6] were not explored. Among subjects with obstructive airway diseases, only less than one quarter are compliant with their medications (≥80% of prescribed doses) as reported by the Italian National Health Agency.[7] Moreover, correct use of the inhalation devices is essential to ensure the effectiveness of the treatment,[8] and a high rate of inhalation device mishandling has been reported in younger asthmatics, with an impact on asthma control.[9–11] It is logical to hypothesize that elderly asthmatic patients are more at risk of errors because of the higher frequency of comorbid conditions potentially affecting the correct use of the device, as recently reported by Usmani et al..[12] Interestingly, a recent meta-analysis from Maricoto et al.[13] reported a significant effect of inhaler educational programs in reducing exacerbations and in improving clinical control, specifically in subjects aged 65 and older with asthma or COPD. However, the authors also admitted to have failed in the attempt to uncover important information about the role of inhaler technique alone, due to the fact that studies included in the meta-analysis addressed a large variety of interventional approaches, making it harder to detect the contribution of incorrect inhaler maneuvers. Also, the majority of the studies did not control for the confounding effect of adherence itself, which may be more relevant than inhaler performance.

The aim of our study was to evaluate the level of adherence and the rate of inhaler mishandling on a cohort of elderly asthmatics, and the effect of a structured one-visit educational intervention on asthma control assessed after a period of 3–6 months.

Methods

The EDUCA (**E**lderly and **D**evice **U**se in **C**hronic **A**sthma) Study, a pre-post interventional trial with a follow-up of 3–6 months, promoted by the Italian Respiratory Society (IRS), was carried out between June 2016 and June 2017 in 21 Italian Health Service Pulmonology and Allergy Clinics. To be consecutively enrolled in the study, subjects were required to have a physician-diagnosis of asthma based on the 2016 GINA guide,[14] be 65 yrs of age or older and using a combination of Long-Acting Beta-2 Agonists (LABA) and Inhaled Corticosteroids (ICS) in a fixed dose single device or in two different devices. As by GINA 2016[14] tiotropium was considered off-label for asthma, patients under treatment with tiotropium or another Long Acting Muscarinic Antagonist (LAMA) were excluded from enrollment. Data were recorded by researchers using a standardized questionnaire which included: 1) age, sex, height, weight; 2) smoking habit; 2) educational level; 3) the number of severe asthma exacerbations (SAEs) in the previous year, defined as "an asthma exacerbation requiring systemic corticosteroids for at least three days and/or hospitalization"[15]; the device or devices in use (with the exception of that for rescue medication, i.e. salbutamol); the daily ICS dosage expressed as low, medium, or high dosage of beclomethasone dipropionate CFC or equivalent according to GINA classification[14]; concomitant drugs for other diseases (arterial hypertension, chronic heart disease, diabetes, gastroesophageal reflux, osteoporosis) and the presence or arthritis on hands. In addition, the following Patient-Reported outcomes (PROs) were assessed by validate tools a) dyspnea (modified Medical Research Council (mMRC) dyspnea scale,[16] b) level of asthma control (Asthma Control Test ACT),[17] c) health status (SF 12),[18] d) adherence to treatment (Morinsky Medication Adherence Scale),[19] and e) anxiety and depression (Hospital Anxiety Depression Scale, HADS).[20]

At each visit, patients underwent a Forced Vital Capacity (FVC) maneuver according to the standardized technique[21] after proper wash-out period from bronchodilator drugs. At the end of the visit, patients were asked to use their device, and their maneuvers were analyzed following the check-list reported in Table 1, modified from the Inhaler Error Steering Committee Document[22] which we adopted when the study was designed. Whenever applicable, patients were immediately informed about their errors and re-checked until adequately instructed to handle correctly their device by physical demonstration.

Table 1
Check list for detecting errors with the device in use (modified from ref. 22).

MDI device
☐ Do not remove cap
☐ Do not handle correctly
☐ Activates before inspiring
☐ Activates at the end of inspiration
☐ Do not activate
☐ Do not inspire
☐ Inspires too quickly
☐ Inhales nasally
DPI device
☐ Do not remove cap
☐ Do not charge the dose correctly
☐ Charges the dose, but inverts the device before inhaling
☐ Charges the dose, but shakes the device (as a MDI)
☐ Expires (instead inspiring)
☐ Do not connect correctly with the mouthpiece of the device
☐ Do not inspire with proper velocity
☐ Do not inhale orally
☐ Inhales nasally
☐ Is not able to understand when the device is empty

The study was approved by the Coordinating Ethic Committee of Palermo, Italy, and a written informed consent was collected locally for each patient.

Data analysis

Data from each center were centralized to the investigators of Pavia, Italy (AMC), who were responsible for data quality control, and then submitted to the center of Milano, Italy (FDM and ST) for statistical analysis. The results are shown as mean ± standard deviation (SD), unless otherwise stated.

Lilliefors corrected K–S test was performed before the data analysis in order to examine the distribution of the residuals of the parametric tests. For continuous variables, two tailed paired *t*-test analysis was used to analyze the difference between first and second visit in terms of errors done with the device in use, ACT, mMRC and SF12. Unpaired Student's *t*-test analysis (test for equal variances) was used for comparisons between patients for continuous variables; for dichotomous variables Chi square or Fisher's exact test were used, as appropriate.

Variables that resulted in p values < 0.15 were used in a multivariate logistic regression model to predict factors that were associated with at least one error in the use of inhaler. The odds ratios (OR) and their 95% confidence intervals were also derived. All tests were two-sided, and $p < 0.05$ were considered statistically significant. Asthma control was defined as optimal, partially or poorly controlled for ACT score ≥20, 16–19, or ≤15, respectively.[23] Statistical tests were performed using the Statistical Package for Social Sciences (version 21.0; SPSS, Chicago, IL).

Results

A total of 452 asthmatic subjects were enrolled and 411 subjects were retained for the statistical analysis as 41 were excluded, a) because under treatment with LAMA, b) for inconsistency of therapy between visit 1 and 2, and c) inclusion criteria not respected (i.e. age <65 years).

Table 2 summarizes demographic, clinical and functional data of the subjects. The number of females was higher than that of males, and an ACT score ≤19 occurred in 49% of the subjects, with at least one SAE in 40% of them. The devices in use were a pMDI in 41% and a DPI in 59% of subjects, the latter represented by Diskus (39%), Turbohaler (31%), Nexthaler (17%) and Ellipta (13%). The second device in use, not including salbutamol as rescue medication, was reported in a negligible percent of patients (36 patients, 9% of the whole population), in whom a non-fixed LABA/ICS combination was the option. During the first clinical evaluation (V1), at least one error was reported in 56% of the subjects, and a low adherence was detected in 43% of them. At least one comorbidity was present in 80% of the subjects, and more than a quarter (30%) of them suffered from hand arthritis. HADS score was 7 ± 4 and 8 ± 4 for

Table 2
Demographic, clinical and functional data of the study subjects.

	All patients (n = 411)
Age, yrs	72 ± 5
Male/female, n (%)	173 (42)/238 (58)
BMI, kg/m^2	27 ± 5
BMI≥30, n (%)	89 (22)
Smoke History	
Current/former/no smoke, n (%)	26(6)/147(36)/236 (57)
Pack-years	18 ± 17
>20 P/Y, n (%)	46(37)
Subjects with SAE, n (%)	167 (40)
Education	
Primary School, n (%)	113(29)
Secondary, n (%)	149(37)
High school, n (%)	105(26)
Degree, n (%)	31(8)
Lives alone, n (%)	72 (17%)
mMRC, (median, IQR)	1(1,2)
ACT, score	19 ± 4.7
ACT≤19, n (%)	197 (49)
FEV_1, % predicted	80 ± 24
Comorbidity, n (%)	334 (81)
Hand Arthritis, n (%)	113(30)
Clinically relevant depression, n (%)	81(20)
Clinically relevant anxiety, n (%)	129(31)
Morinsky, score	1.03 ± 0.96

Data are expressed ad mean ± standard deviation if not otherwise stated. mMRC: modified Medical Research Council dyspnea score; SAE, Severe Asthma Exacerbation. ACT: Asthma Control Test; Comorbidity: any of gastroesophageal reflux, arterial hypertension, osteoporosis, heart disease; IQR: interquartile range. Clinically relevant depression/anxiety: evaluated with HADS scale.

anxiety and depression, clinically relevant in 20% and 31% of the patients enrolled, respectively.

Effect of training on the correct use of device (Table 3)

During follow-up visit (Visit 2), both the percentage of patients with poor adherence and that of patients who committed at least one error decreased significantly ($p < 0.001$), from 40% to 23% and from 52% to 23%, respectively. A significant reduction in the percentage of at least one error was reported also in the subset of patients with clinically relevant anxiety or depression. A parallel clinically significant increase of 1.46 ± 3.02 (95%CI: 1.13–1.79, $p < 0.001$) was also observed in the ACT score (from 18.85 ± 4.88 to 20.32 ± 4.04).

Table 3
Effects of educational training on outcome variables (N = 318 patients).

	Visit 1	Visit 2	Mean ± SD (95% CI)	p value
Error, n	0.74 ± 1.02	0.38 ± 0.56	−0.37 ± 0.88 (0.26–0.47)	<0.001
Error ≥1, n (%)				
• All patients	167 (52)	102 (32)		<0.001
• Patients with clinically relevant anxiety or depression at visit 1	74 (66)	49 (42)		<0.001
Low Adherence, n (%)	130 (41)	74(23)		<0.001
SF-12				
PCS	38.90 ± 10.36	40.16 ± 10.21	1.27 ± 7 (0.48–2.05)	<0.001
MCS	48.03 ± 10.92	50.73 ± 10.07	2.69 ± 7.96 (1.81–3.58)	<0.005
ACT	18.85 ± 4.88	20.32 ± 4.04	1.46 ± 3.02 (1,13–1,79)	<0.001
mMRC	1.33 ± 0.99	1.09 ± 0.88	0.24 ± 0.63 (0.17–0.31)	<0.001

Data are expressed and mean ± standard deviation if not otherwise stated. mMRC: modified Medical Research Council dyspnea score; SF12: Short Form Health Survey; PCS: Physical Health Composite Score; MCS: Mental Health Composite Score; ACT: Asthma Control Test; SD: standard deviation. $p < 0.050$ in bold. Two tailed paired *t*-test analysis for continuous variables and Chi square test for dichotomous variables.

Correlation between errors and asthma outcomes

Differences between subjects with at least one error and without any error are described in Table 4. Variables that were significantly associated with errors were used in a multivariate logistic regression model to identify independent factors able to predict critical errors in the use of inhaler. As shown in Table 5, comorbidities, a low educational status and the presence of an asthma exacerbation in the last six months were factors independently associated to commit at least one error with the device.

Discussion

The main findings of our study are that in a large cohort of elderly moderate to severe asthmatics half of them had features of uncontrolled disease despite optimal treatment, and that a similar proportion of subjects were poor adherents to treatment and misused their device. In this context, a one-visit educational training was shown to improve symptom control and adherence to inhaled therapy in subjects with at least one error in the use of their inhaler.

The current findings are in line with the well-known poor control of asthma in the elderly.[24] It is noteworthy that our subjects had uncontrolled asthma despite having been prescribed optimal treatment according to GINA guidelines. Potential explanations for the lack of asthma control in our cohort of elderly patients could be the well-known poor perception of dyspnea in the elderly,[25] and low level of adherence to therapy or improper use of inhaler devices.[5,6] The reason for the increased adherence at the follow-up visit in the absence of a specific intervention promoting adherence could lie in the well-recognized bias, the Hawthorn effect, originally described in an industrial setting.[26] This suggests that the subjects' behavior may be modified by the subjects' awareness that they are being studied and for which they receive additional attention.

Poor technique has been associated with age, sex, educational level and emotional problems.[27] In asthma, device-handling errors have already been described, as well as their association with poor disease control.[10,20–30] A high rate of inhalation device mishandling has been reported in younger asthmatics, with an impact on asthma control.[11,31] In elderly COPD patients, high rates of inhaler device mishandling and their potential impact on COPD on exacerbation were recently described by Molimard et al.,[32] where an underestimation of handling errors of device (>50% of the subjects) was associated with an increased rate of severe exacerbations (Odds Ratio of 1.86). Moreover, data on elderly asthmatic populations are lacking, although Melani et al.[10] reported a significant association between inhaler mishandling and older age.

Recently, educational interventions of inhaler technique were reviewed[33] and found to be effective, at least on the short-term (with an average follow-up of 5 months). The authors concluded that, as expected, effectiveness of interventions holds true for patients with an insufficient inhaler technique, whereas interventions may be less valuable for patients with an already moderate to good technique. Therefore, considering constrains on budget available and time available, they suggested to pursue an educational intervention only in those in whom errors were documented, as in the present study. A recent Cochrane review on interventions to improve inhaler technique[34] concluded that confirmatory trials are required, as the maximum duration of follow-up was only 26 weeks. Ideally, studies should report all critical descriptive statistics, and inhaler technique should be checked by persons blinded to group allocation. Also, the authors suggest to focus efforts on poor controlled asthma and/or on poor inhaler technique. Very recently, Maricoto et al.[13] carried out a systematic review and meta-analysis on studies conducted in older subjects, specifically addressing the role of education on inhaler technique on disease control and exacerbation rates. Although the

Table 4
Characteristics of enrolled patients according to the presence of at least one error in the use of inhaler.

	Without any error N = 181	With at least one error N = 230	mean (95%CI)	OR (95%CI)	p value°
Age, yrs	72 ± 5	72 ± 6	0,74 (−1.82–0.32)		0.171
Gender, female, n (%)	74 (43)	92 (41)		1.16 (0.75–1.61)	0.613
Higher education[a], n (%)	74 (43)	62(27)		0.50 (0.33–0.76)	**0.001**
Living alone, n (%)	30(17)	43(19)		1.18 (0.70–1.98)	0.600
Poor adherence to therapy[b], n (%)	130 (56)	49(27)		3.05 (2.30–5.30)	**<0.001**
SAE ≥1, n (%)	46(25)	121 (53)		3.36 (2.18–5.17)	**<0.001**
Comorbidity, n (%)	132 (73)	202 (87)		2.41 (1.40–4.13)	**<0.001**
BMI ≥ 30 Kg/m^2	53(30)	567 (30)		1 (0.65–1.57)	0.810
Rhinitis, n (%)	106 (62)	114 (50)		0.63 (0.42–0.94)	**0.026**
DPI, n (%)	105 (58)	137 (60)		1.09 (0.74–1.61)	0.687
MDI, n (%)	76 (42)	93 (40)		0.92 (0.62–1.36)	0.687
Clinically relevant anxiety, n (%)	40(22)	89 (39)		2.22 (1.4–3.43)	**<0.001**
Clinically relevant depression, n (%)	22(12)	59(26)		2.49 (1.46–4.25)	**0.001**

$p < 0.05$ in bold, ° unpaired Student's *t*-test analysis for continuous variables, Chi square test for dichotomous variables, binomial logistic regression to calculate odds ratio for dichotomous variables.

[a] From high school.

[b] Evaluated with Morinsky scale; SAE: Severe Asthma Exacerbation.

Table 5
Significant univariate and multivariate logistic regression analyses of predictors for at least one error in the use of the inhaler.

Variable	UNIVARIATE			MULTIVARIATE		
	OR	95% CI	p*	OR	95%CI	p**
Lower education	1.97	1.30–3.01	**0.001**	1.77	1.13–2.77	**0.012**
SAE	3.29	2.13–4.97	**<0.001**	2.84	1.82–4.43	**<0.001**
Comorbidity	2.67	1.60–4.47	**<0.001**	2.46	1.39–4.34	**0.002**
Hands arthritis	1.16	0.75–1.82	0.493	–	–	–
Poor adherence to therapy	1.37	0.92–2.04	0.111	–	–	–
Clinically relevant anxiety	2.22	1.43–3.43	**<0.001**	1.28	0.75–2.19	0.352
Clinically relevant depression	2.49	1.46–4.25	**0.001**	1.78	0.94–3.39	0.076

$p < 0.05$ in bold.

*Binomial Logistic Regression Analysis for univariate analysis.

**Multiple Regression Analysis for multivariate analysis.

findings confirmed the efficacy of educational interventions in reducing the rate of exacerbations in older individuals, the heterogeneity of the included studies did not allow to assess the contribution of improved inhaler technique education alone. Taken together, these observations advocate for future studies specifically designed to compare different educational interventions on clinical outcomes in vulnerable populations, such as older asthmatics. From a clinical standpoint, providing the most suitable and efficacious time interval for regular follow-up is the main challenge.

The presence of comorbidities has been demonstrated to influence quality of life in adults with asthma,[35] which in turn can affect adherence to treatment. In this context, specific comorbidities, such as arthritis, may also impair the ability to use inhalation devices.

Some limitations should be considered in the interpretations of our results. First, this is an open (not blinded) study, with the lack of a control group and, as such, both patients' behaviors and researchers' judgements could have been influenced to some extent. However, the collection of the items in a single database and the analysis of the data were conducted by two independent teams. Second, the results are limited to a very short period of observation and cannot be extrapolated to longer lengths of time: the 6 months effects on adherence due to the targeted intervention may potentially vanish afterwards as expected by findings from other real-life studies on duration of adherence. Third, the educational action was conducted during outpatient visits by well-trained pulmonologists and allergists, which may have affected the outcomes. Moreover, one can observe that not all errors are similar. For example, failure to remove the inhaler cap is a critical error, as opposed to failure to hold the inhaler upright. However, the document of the Inhaler Error Steering Committee[22] did not distinguish between these two types of error and defined as critical an error "when a patient performs an error, displays imperfect technique or lacks knowledge on usage or maintenance of the inhaler device that is likely to significantly impair the delivery of adequate medication on all occasions". However, recently Price et al.[36] were able to identify in the CRITIKAL Study which errors are critical, meaning that they negatively impact on asthma outcomes. In our study, the most frequent error for the MDI device was "activating before inspiring" (36%), and for DPI "not inspiring with proper velocity" (32%), both of which were demonstrated to be correlated with uncontrolled asthma in the CRITIKAL study.[36] Also "inspiring too quickly" (25%), "not handling correctly (16%) and "activating at the end of inspiration" for MDI, were judged as critical in the study by Price et al.[36]

In conclusion, we found that a one-visit targeted educational intervention may enhance asthma control in the elderly, presumably by increasing adherence to treatment and inhaler techniques. The intervention is effective also in patients with clinically relevant anxiety and depression, which have been associated to a lower confidence in device usage.[37] A check-list for potential critical errors may be helpful to identify the subjects candidates to educational efforts.

Author contributions

MM, SN, FDM, AC, IB, AM conceived the idea and designed the study.

MM and SN wrote the manuscript.

ST and IB contribute substantially to the analysis and interpretation of data.

All authors revised the work critically.

All authors approved the final version.

Conflicts of interest

Authors declare that there is no conflicts of interest.

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References

1. Fink JB, Rubin BK. Problems with inhaler use: a call for improved clinician and patient education. *Respir Care*. 2005 Oct;50(10):1360–1374. discussion 1374-5.
2. Lewis A, Torvinen S, Dekhuijzien P, et al. The economic burden of asthma and chronic obstructive pulmonary disease and the impact of poor inhalation technique with commonly prescribed dry powder inhalers in three European countries. *BMC Health Serv Res*. 2016;16:251.
3. Milanese M, Di Marco F, Corsico AG, et al. Asthma control in elderly asthmatics. An Italian observational study. *Respir Med*. 2014;108:1091–1099.
4. Janssens J, Pache JC, Nicold LP. Physiological changes in respiratory function associated with ageing. *Eur Respir J*. 1999;13:197–205.
5. Castaldi PJ, Rogers WH, Safran DG, Wilson IB. Inhaler cost and medication non adherence among seniors with chronic pulmonary disease. *Chest*. 2010;138:614–620.
6. Baptist AP, Ross JA, Yang Y, Song PXK, Clark NM. A randomized controlled trial of self-regulation intervention for older adults with asthma. *J Am Geriatr Soc*. 2013;61:747–753.
7. The medicines utilization monitoring centre. *National Report on Medicines Use in Italy. Year 2017*. Rome: Italian Medicine Agency; 2018. available on http://agenziafarmaco.gov.it. Accessed March 16, 2019.
8. Global Initiative for Asthma (GINA). *Global Strategy for Asthma Management and Prevention*; 2018. Available from: https://ginasthma.org/2018-gina-report-global-strategy-for-asthma-management-and-prevention/. Accessed March 16, 2019.
9. Giraud V, Allaert FA, Roche N. Inhaler technique and asthma: feasibility and acceptability of training by pharmacists. *Respir Med*. 2011;105:1815–1822.
10. Melani AS, Bonavia M, Cilenti V, et al. Inhaler mishandling remains common in real life and is associated with reduced disease control. *Respir Med*. 2011;105:930–938.
11. Molimard M, Raherson C, Lignot S, et al. 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.
12. Usmani OS, Lavorini F, Marshall J, et al. Critical inhaler errors in asthma and COPD: a systematic review of impact on health outcomes. *Respir Res*. 2018;19:10.
13. Maricoto T, Montero L, Gama JMR, Correia-de-Sousa J, Taborda-Barata L. Inhaler technique education and exacerbation risk in older adults with asthma or chronic obstructive pulmonary disease: a meta-analysis. *J Am Geriatr Soc*. 2019;67:57–66.
14. Global Initiative for Asthma (GINA). *Global Strategy for Asthma Management and Prevention*; 2016. Available from: http://ginaasthma.org/.
15. Reddel HK, Taylor DR, Bateman ED, Boulet LP, Boushey HA, et al. An official American Thoracic Society/European Respiratory Society Statement. Asthma control and exacerbations. Standardizing endpoints for clinical asthma trials and clinical practice. *Am J Respir Crit Care Med*. 2009;180:59–99.
16. Mahler DA, Wells CK. Evaluation of clinical methods for rating dyspnea. *Chest*. 1988;93:580–586.
17. Nathan RA, Sorkness CA, Kosinski M, et al. Development of the asthma control test: a survey for assessing asthma control. *J Allergy Clin Immunol*. 2004;113:59–65.
18. Gandek B, Ware JE, Aaronson NK, et al. Cross-validation of item selection and scoring for the SF-12 health survey in nine countries: results from the IQOLA project. International quality of life assessment. *J Clin Epidemiol*. 1998;51:1171–1178.
19. Morisky DE, Ang A, Krousel-Wood M, Ward HJ. Predictive validity of a medication adherence measure in an outpatient setting. *J Clin Hypertens*. 2008;10:348–354.
20. Costantini M, Musso M, Viterbori P, et al. Detecting psychological distress in cancer patients: validity of the Italian version of the Hospital Anxiety and Depression Scale. *Support Care Canc*. 1999;7:121–127.
21. Miller MR, Hankinson J, Brusasco V, et al. Standardisation of spirometry. *Eur Respir J*. 2005;26:319–338.
22. Inhaler Error Steering Committee, Price D, Bosnic-Anticevich S, et al. Inhaler competence in asthma: common errors, barriers to use and recommended solutions. *Respir Med*. 2013;107:37–46.
23. Jia CE, Zhang HP, Lv Y, et al. The Asthma Control Test and Asthma Control Questionnaire for assessing asthma control: systematic review and meta-analysis. *J Allergy Clin Immunol*. 2013;131:695–703.
24. Gibson PG, McDonald VM, Marks GB. Asthma in older adults. *Lancet*. 2010;376:801–813.
25. Janssens J, Pache JC, Nicold LP. Physiological changes in respiratory function associated with ageing. *Eur Respir J*. 1999;13:197–205.
26. Roethlisberger J, Dickson WJ. *Management and the Worker*. Cambridge, MA: Harvard University Press; 1939.
27. Rootmensen GN, van Keimpema AR, Jansen HM, de Haan RJ. Predictors of incorrect inhalation technique in patients with asthma or COPD: a study using a validated videotaped scoring method. *J Aerosol Med Pulm Drug Deliv*. 2010;23:323–328.
28. Price D, Roche N, Christian Virchow J, et al. Device type and real-world effectiveness of asthma combination therapy: an observational study. *Respir Med*. 2011;105:1457–1466.
29. Al-Jahdali H, Ahmed A, Al-Harbi A, et al. Improper inhaler technique is associated with poor asthma control and frequent emergency department visits. *Allergy Asthma Clin Immunol*. 2013;9(1):8.
30. Westerik JA, Carter V, Chrystyn H, et al. Characteristics of patients making serious inhaler errors with a dry powder inhaler and association with asthma-related events in a primary care setting. *J Asthma*. 2016;53:321–329.
31. Giraud V, Roche N. Misuse of corticosteroid metered-dose inhaler is associated with decreased asthma stability. *Eur Respir J*. 2002;19:246–251.
32. Molimard M, Raherison C, Lignot S, et al. Chronic Obstructive Pulmonary Disease exacerbation and inhaler device handling: real life assessment of 2935 patients. *Eur Respir J*. 2017;49:1601794.
33. Klijn SL, Hiligsmann M, Evers S, Roman-Rodriguez M, Van der Molen T, Van Boven J. Effectiveness and success factors of educational inhaler technique interventions in asthma and COPD patients: a systematic review. *Primary Care Respir Med*. 2017;27:24.
34. Normansell R, Kew KM, Mathioudakis AG. Interventions to improve inhaler technique for people with asthma. *Cochrane Database of Systemic Reviews*. 2017;(3). https://doi.org/10.1002/14651858.CD012286.pub2. art no CD011286.
35. Tay TR, Radhakrishna N, Hore-Lacy F, et al. Comorbidities in difficult asthma are independent risk factors for frequent exacerbations, poor control and diminished quality of life. *Respirology*. 2016;21:1384–1390.
36. Price DB, Romàn-Rodriguez M, McQueen RB, et al. Inhaler errors in the CRITIKAL study: type, frequency, and association with asthma outcomes. *J Allergy Clin Immunol Pract*. 2017;5:1071–1081.
37. Amin AN, Ganapathy V, Roughley A, Small M. Confidence in correct inhaler technique and its association with treatment adherence and health status among US patients with chronic obstructive pulmonary disease. *Patient Prefer Adherence*. 2017;11:1205–1212.