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ORIGINAL ARTICLE

COPD: Analysing factors associated with a successful treatment

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Abstract
Objectives: To evaluate if non-adherence to inhaled medications, inhalers mishandling or the prescribers' non-adherence to GOLD strategy are associated with mMRC grade, CAT score, COPD acute exacerbations or FEV_1%.
Methods: A cross-sectional study on COPD was conducted in the ambulatory pulmonary clinic of Hospital de Guimarães. Patients ≥40 years diagnosed according to GOLD criteria were recruited consecutively. A survey of demographic and clinical data was used. Adherence was assessed by using the Measure of Treatment Adherence (MTA) questionnaire. Inhalation technique was evaluated by using checklists of correct steps and critical errors, and inhalers' misuse was defined when one or more critical errors were made, whatever the number or types of inhalers in use. To evaluate the prescriber non-adherence to GOLD strategy, the patients' current medication was compared with therapeutic standards proposed by the GOLD 2017 strategy for the same ABCD groups. A statistical analysis was performed with IBM SPSS Statistics for Windows, Version 23.0. Armonk, NY: IBM Corp.
Results: We studied 303 participants, 79.5% males, mean age = 67.5 years. A total of 285 completed the MTA questionnaire. Non-adherence was referred by 47 (16.5%) patients, and a significant negative association was found between adherence and CAT score and FEV_1%. 285 patients performed 499 inhalations manoeuvres with 10 different IDs. Inhaler misuse was observed in 113 (39.6%) patients, and was not associated with CAT score, mMRC grade, ECOPD or FEV_1%. We found deviations from the GOLD strategy in 133 (44.3%) patients, which were negatively related to CAT score, mMRC grade and ECOPD.

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Conclusions: In the present study we failed to prove a positive association between non-adherence to medication, inhalers mishandling or prescribers' non-adherence to GOLD strategy with symptoms, exacerbations and airflow limitation. Conversely, more symptomatic and more obstructed patients were more adherent to medication, previous ECOPD seems to improve prescribers' adherence to treatment guidelines, and symptoms, ECOPD and FEV_1% were not significantly associated with inhaler technique.

Background and objectives

Chronic Obstructive Pulmonary Disease (COPD) is the only leading cause of death with rising mortality and morbidity,[1] and currently represents one of the most significant health problems at international level. It is a chronic and incurable disease, but symptoms significantly improve with inhaled therapy, even though it is unlikely that most patients remain asymptomatic. Lung function also improves with medication, and acute exacerbations can be prevented or mitigated. Symptoms, acute exacerbations and airflow limitation are important treatment outcomes. Treatment can be described as successful if an appropriate change is measured in an appropriate outcome.[2] Some factors relying on patients, on health-care providers or on the physician–patient relationship can be significantly related to poor clinical outcomes. Some of them are common and modifiable. Non-adherence to medications in COPD has been related to mortality, poor disease control and poor quality of life. In the LASSYC study,[3] poor adherence was associated with more exacerbations. Vestbo et al., using data from the TORCH study, also found significant differences in survival and risk of severe exacerbations according to the degree of patient adherence.[4] Inhaled medication is the mainstay of COPD management. Inhaler misuse has been associated with increased rate of severe COPD exacerbations,[5] but the overall impact on clinical outcomes remains currently unknown. It would appear to be predictable that poor clinical outcomes is related to non-adherence to guidelines, but the relationship between adherence to guidelines and some clinical outcomes, such as the number of acute exacerbations, may be different than expected.[6,7]

The objective of this study was to assess whether non-adherence to inhaled medications, inhaler mishandling or prescriber non-adherence to the Global Initiative for Chronic Obstructive Lung Disease (GOLD) strategy are associated with medical Research Council Dyspnoea Questionnaire (mMRC) grade, COPD Assessment Test (CAT) score, COPD acute exacerbations and FEV_1%.

Methods

Study design and population

A cross-sectional study was conducted in the outpatient respiratory care of Hospital de Guimarães, Portugal, between March 2016 and May 2017. Stable patients over 40 years old and diagnosed as suffering from COPD according to the GOLD criteria were consecutively included, after having given their written informed consent. Exclusion criteria were the refusal to participate and the inability to understand simple questionnaires. The study was approved by the Hospital's Ethics Committee, the Research Ethics Committee of Minho University and the Portuguese Data Protection Agency. We followed the STROBE guidelines for reporting observational studies.[8]

Demographic and clinical characteristics

A questionnaire of demographic and clinical data was used. Symptoms were evaluated using the Portuguese versions of the CAT questionnaire and the mMRC scale. Results were later dichotomised according to GOLD thresholds for considering more or less symptomatic impact of COPD. A variable''symptoms'' was created and dichotomised into fewer symptoms (mMRC <2 and CAT <10) or more symptoms (mMRC $\geq$2 and/or CAT $\geq$10). The number of COPD acute exacerbations (ECOPD) registered in the previous year was evaluated. We defined ECOPD according to GOLD, as an acute worsening of respiratory symptoms that result in additional therapy,[9] but also requiring an unplanned medical visit, whatever the severity of symptoms. The number of ECOPD were also dichotomised according to GOLD as <2 exacerbations and $\geq$2 exacerbations or $\geq$1 hospitalisation. All participants performed spirometry according to the American Thoracic Society and the European Respiratory Society recommendations for standardised lung function testing,[10,11] and referenced according to Global Lung Function Initiative prediction equations (GLI 2012).[12] The diagnosis of ACO was not considered in the present

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study, because neither its definition nor the clinical characteristics or diagnostic criteria are universally accepted, and they changed during the period the project was conceived and developed, and data was collected and interpreted.[13]

Adherence to medication

Adherence to inhaled medication was assessed using the Measure of Treatment Adherence (MTA), a psychometric tool validated for the Portuguese population in 2001, with a reported Cronbach's alpha of 0.74. It consists of a seven items questionnaire, reflecting common patterns of non-adherent behaviours. Answered on a 6-point Likert scale (with 1 = always, 2 = almost always, 3 = often, 4 = sometimes, 5 = rarely and 6 = never), points are summed, and total scores range from 6 to 42, with higher scores indicating higher self-reported adherence. Non-adherence was defined by a score $\leq$5, after dividing the total score by the number of questions. This cut-off was validated by the MTA authors.[14]

Inhaler technique

Inhaler technique was assessed using previously defined checklists developed according to the instructions provided by the manufactures and to previous literature,[15] and also including essential steps and critical errors (Table 1). Errors considered critical were related to priming/loading or the inhalation manoeuvre, and could substantially affect drug delivery to the lungs. These included lack of inhalation through the mouthpiece for all devices, slow and not forceful inhalation for dry powder inhalers (DPI) and rapid or forceful inhalation for pressurised metered-dose inhalers (pMDI) or soft-mist inhalers (SMI). Device-dependent critical errors are listed in Table 2.

Participants were invited to demonstrate the use of their prescribed inhaler devices, just as they do it at home, and the correct steps and critical errors were recorded. Inhaler misuse was defined when one or more critical errors were made, whatever the number or types of inhalers in use.

Adherence to guideline

The prescribers' adherence to GOLD 2017 strategy was assessed by comparing the patient's current medication with the therapeutic standards for the same ABCD groups. Current medication was evaluated using the hospital data base, the health data platform, or patient self-reported information. Patients were categorised as GOLD-concordant or GOLD-discordant based on criteria presented in Table 3.

Statistical analysis

The statistical association between dichotomous variables was assessed with the Chi-square test and intensity of linear association with the Pearson's correlation coefficient. Statistical analysis was performed with IBM SPSS Statistics for Windows, Version 23.0. Armonk, NY: IBM Corp.

Table 1 Check-list of steps and critical errors.

1.Correct priming or loading (Incorrect priming or loading were considered critical error)
2.Exhalation before inhalation (No-exhalation before inhalation was not considered critical)
3.Correct inhalation (Incorrect inhalation were considered critical error)
4.Hold the breath a few seconds after inhalation (except when using a spacer) (Not holding the breath or exhalation through the mouthpiece was not considered critical)
5.Finalisation (clean the mouth-piece, remove used capsule after verifying that no powder remains, check colour changing in control window, close ID and wash the mouth if necessary)

Table 2 Critical errors in different IDs.

1. Aeroliser®, Breezhaler®, and Handihaler®: failure to insert the capsule, failure to press and release buttons, powder remaining in the capsule after inhalation.
2. Diskus®: failure to open the cover, to slide the lever until it clicks, or not keeping inhaler horizontally.
3. Ellipta®: failure to slide cover down until a click is heard or block air vent with fingers.
4. Genuair®: failure to remove the cap, to press and release the button until the control window has changed to green, not holding inhaler horizontally, and not changing control window to red after inhalation.
5. pMDI: failure to remove cap, not shaking the inhaler (suspensions only), not holding the inhaler in the upright position, poorly synchronised hand actuation and inhalation (except using a spacer), inhalation through the nose, actuation against teeth, lips or tongue.
6. Respimat®: lack of cartridge in the device, failure to open the cap, twisting the base or pressing the dose-release button, poorly synchronised hand actuation and inhalation.
7. Spiromax®: failure to hold the inhaler in upright position, failure to open mouthpiece cover until a click is heard or blocking air vent with fingers.
8. Turbuhaler®: failure to remove cover, to hold the inhaler upright when twisting the grip (tolerance $\pm 45^{\circ}$) until a click is heard.

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Table 3 Type and number of deviations from the GOLD strategy.

Type of deviations	Number of deviations
1. Underuse	
1.1. Absence of medication (in B, C and D groups; in A group if symptoms or exacerbations)	3
1.2. Under-medication (under-therapeutic bronchodilation; only SAMA or SABA as need in B, C or D groups)	13
2. Overuse	
2.1. Doubling medication (2 or more different LAMA, LABA or ICS)	8
2.2. Overuse of bronchodilators (LABA + LAMA in A group)	34
2.3. Inhaled corticosteroids overuse (in A or B groups)	98
3. Inappropriate bronchodilation (only LABA in C or D groups)	1

Note: A total of 157 deviations from GOLD guideline were found in 133 patients: occasionally different deviations overlap in the same patient.

Results

Adherence to medication

A total of 303 COPD outpatients were included in the study. The most important demographic, clinical and functional characteristics of the patients are presented in Table 4.

A total of 285 participants completed the MTA questionnaire, and 47 (16.5%) were considered non-adherent to inhaled medications. The distribution of non-adherent patients were respectively 17.0%, 53.3%, 25.5% and 2.1% from GOLD I to IV ($p = 0.002$) and 34.0%, 36.2%, 4.3% and 25.5% from A to D of GOLD 2017 classification ($p = 0.53$). No association between adherence and mMRC score was found; an association between non-adherence and CAT score was found (26.5% of patients with CAT score <10 and 12.8% ≥10 were non-adherent, $p = 0.023$). A significant relationship was found between non-adherence and FEV_1% (the mean FEV_1% of non-adherent and adherent patients were respectively 62.3 and 49.9, $p < 0.001$). Non-adherence was respectively found in 19.3% and 12.4% of patients reporting <2 and ≥2 ECOPD, however without statistical significance ($p = 0.087$). When controlling for age, gender, education level, monthly income, Graffar classification, active smoking, symptoms and FEV_1%, FEV_1% was the only variable significantly associated with adherence (Table 5).

Inhaler technique

285 patients carried out 499 inhalations manoeuvres with 10 different IDs (Aeroliser®, Breezhaler®, Diskus®, Ellipta®, Genuair®, Handihaler®, pMDI, Respimat®, Spiromax® and Turbuhaler®) in a total of 66 (13.2%) pMDI, 128 (25.7%) single-dose inhalers (sDPI), 228 (50.8%) multiple dose inhalers (mDPI) and 77 (15.4%) SMI-Respimat®. Misuse due to critical errors was observed in 113 (39.6%) patients. It was significantly related to the type of inhaler device and was observed respectively in 53.6%, 28.4%, 26.2% and 24.2% demonstrations using a pMDI, SMI, mDPI or sDPI ($p < 0.001$). Neither was any statistically significant association found between inhaler misuse and CAT score, mMRC grade, FEV_1% and ECOPD. When controlling for age, gender, education level, monthly income, Graffar classification, active smoking, symptoms and FEV_1%, only age, gender and Graffar classification were significantly associated with inhaler technique (Table 5). There was also no statistical relationship

Table 4 Demographic, clinical and functional characteristics of COPD patients.

Characteristics	$n = 303$
Male gender	241 (79.5)
Mean age (years)	67.5 ± 10.2
Age ≥ 65 years	186 (61.4)
Very low education level ≤ 3 school years	89 (29.4)
Graffar social classification	
Graffar 1	2 (0.7)
Graffar 2	13 (4.3)
Graffar 3	106 (35.5)
Graffar 4	174 (58.2)
Graffar 5	4 (1.3)
Very low monthly income (<530 Euros)	197 (65.7)
Mean smoking amount (pack/years)	49.3 ± 32.4
mMRC grade ≥ 2	185 (61.1)
CAT score ≥ 10	152 (72.4)
Frequent ECOPD (≥2/last year)	115 (38.0)
Post-bronchodilator mean FEV_1%	53.2 ± 19.7
GOLD stage	
I	30 (9.9)
II	127 (41.9)
III	106 (35.05)
IV	40 (13.2)
GOLD 2017 classification	
A	70 (23.1)
B	120 (39.6)
C	7 (2.3)
D	106 (35.0)

Note: Data shown as mean ± SD or *n* (%).
Abbreviations: mMRC, medical Research Council Dyspnoea Questionnaire; CAT, COPD Assessment Test; ECOPD, COPD exacerbations; GOLD, Global Initiative for Chronic Obstructive Lung Disease.

Table 5 Predictors of adherence and inhalers misuse.

Logistic regression – predictors of adherence									
		B	S.E.	Wald	df	Sig.	Exp(*B*)	95% C.I. for Exp(*B*)	
								Lower	Upper
Step 1	Symptoms 0/1	.499	.405	1.518	1	.218	1.648	.745	3.647
	Age	.022	.019	1.472	1	.225	1.023	.986	1.061
	Ed. level 0/1	.349	.466	.560	1	.454	1.417	.569	3.532
	Gender	−.386	.425	.825	1	.364	.680	.295	1.564
	Curr. smok.	−.715	.432	2.730	1	.098	.489	.210	1.142
	FEV_1%	−.029	.010	9.367	1	.002	.971	.953	.990
	Income 0/1	.248	.382	.423	1	.515	1.282	.607	2.708
	Graffar 0/1	−.179	.413	.188	1	.665	.836	.372	1.878
	Constant	1.371	1.608	.727	1	.394	3.940		
Logistic regression – predictors of inhalers misuse									
		B	S.E.	Wald	df	Sig.	Exp(*B*)	95% C.I. for Exp(*B*)	
								Lower	Upper
Step 1	Symptoms 0/1	.366	.343	1.139	1	.286	1.442	.736	2.827
	Age	.039	.015	6.811	1	.009	1.039	1.010	1.070
	Ed. level 0/1	.084	.341	.061	1	.806	1.088	.557	2.123
	Gender	.736	.325	5.132	1	.023	2.087	1.104	3.946
	Curr. smok.	.266	.370	.519	1	.471	1.305	.632	2.696
	FEV_1%	−.002	.007	.044	1	.833	.998	.984	1.013
	Income 0/1	.215	.290	.547	1	.460	1.239	.702	2.190
	Graffar 0/1	−.775	.318	5.951	1	.015	.461	.247	.859
	Constant	−3.272	1.271	6.632	1	.010	.038		

a. Variable(s) entered on step 1: Symptoms 0/1 (symptoms = 0: mMRC <2 and CAT <10; symptoms = 1: mMRC ≥2 and/or CAT ≥10), age, education level 0/1 (<4 years at school = 0; ≥4 years = 1), gender, current smoking 0/1, FEV_1%, monthly income 0/1 (<530 Euros = 0; ≥530 euros = 1), Graffar social classification 0/1 (4 and 5 = 0; 1,2 and 3 = 1).

between inhaler technique and adherence to medications ($p = 0.328$).

Adherence to guideline

We found deviations from the GOLD 2017 therapeutic strategy in 133 (44.3%) patients, and they are described in Table 3. The most frequent deviations were related to the overuse of inhaled corticosteroids in GOLD A and B groups and the overuse of bronchodilators in the A group. Overuse of ICS and/or bronchodilators accounted for 88% of total prescriber deviations. It should be noted here that during the period of patient recruitment the 2017 GOLD version was published and 24,4% of patients moved from C and D to A and B groups. In the historical context in which they were treated, medications now considered excessive, could then have been appropriate. Table 6 describes the type of prescriber lack of agreement by GOLD 2017 ABCD groups.

We found no association between deviations from the GOLD guideline and FEV_1. However, 78.8% of the patients medicated according to GOLD and 62.2% of those not according to GOLD had a CAT score ≥10 ($p = 0.023$), and 68.5% of patients medicated according to GOLD and 53.0% of those not according had an mMRC grade ≥2 ($p = 0.024$). 58.7% of those who were medicated according to GOLD and 12.8% of patients medicated not according to GOLD referred to frequent exacerbations in the previous year ($p < 0.001$).

Discussion

Patient non-adherence to medications, inhaler mishandling and prescriber disagreement to therapeutic standards are common and modifiable factors which are likely to be related to poor clinical outcomes. Lung function, symptoms and acute exacerbations are important clinical outcomes among COPD patients, and they were measured in the present study. We found a negative association between adherence and the clinical or functional severity of the disease. No significant association was found between inhaler misuse and ECOPD, symptoms or FEV_1%. Lack of agreement with the GOLD strategy was more frequent than poor-adherence to medication or inhaler misuse, and previous ECOPD seems to improve prescriber adherence to treatment guidelines.

In the present study, adherence was significantly related to the clinical and functional severity of the disease. Patients who complained of more symptoms or airflow limitation adhered better to inhaled medications. This may be due to the fact that patient adherence to medication is based on their perceptions of symptoms severity. A positive association between poor-adherence behaviours and

Table 6 Prescribers disagreement to GOLD 2017 strategy by ABCD groups.

	Group A	Group B	Group C	Group D
Guide-line concordant	26 (37.7)	44 (37.3)	5 (71.4)	92 (86.8)
Overuse	43 (62.3)	70 (59.3)	1 (14.3)	4 (3.8)
Underuse	0 (0)	4 (3.4)	0 (0)	10 (9.4)
Inadequate bronchodilator	0 (0)	0 (0)	1 (14.3)	0 (0)

Note: Results presented as number (%) of patients. $p < 0.001$; in 3 patients there was no information related to current medications.

poor treatment outcomes has been described in previous papers.[16,17] A previous study reported that patients are likely to alter the recommended medication based on how they feel,[18] and that the sentence ''I vary my recommended management based on how I am feeling'' was a significant predictor of non-adherence to medications.

We found inhaler mishandling disappointingly common but not related to patient clinical or functional characteristics. This is consistent with other published studies.[19,20] However, it was expectable a significant impact on clinical outcomes, such as symptoms and acute exacerbations. This is a surprising issue, and may be both because we have not analysed the specific medication affected by inhaler misuse and because of the substantial overuse of ICs and/or bronchodilators by a significant number of patients. In medical literature, a small number of studies report an association between critical errors and COPD outcomes.[21] In a recently published study the authors found inhaler misuse associated with an increased rate of severe COPD exacerbations,[22] and in two different cross-sectional studies inhaler misuse was related to increased risk of hospitalisation and emergency room visits.[23,24]

Prescribers not respecting guidelines was common in the present study and more frequent than poor-adherence or inhaler misuse, but there is currently no standard threshold of satisfactory adherence.[25] The most frequently found deviations were related to overuse of inhaled corticosteroids. This was to be expected because the diagnosis of ACO was not considered in the present study and the GOLD 2017 report was published while data was being collected, with many patients shifting from high to low risk groups. The overall non-adherence to GOLD guidelines seems to be very common, even though varying from country to country.[26] In previous studies, overuse of ICS was also the most common recorded deviation to international standards of therapy.[27,28] A previous published study found that exacerbations-related hospitalisations lead to improved adherence to GOLD guidelines.[6] In the present study, previous ECOPD seems to improve prescriber adherence to treatment guidelines, and patients medicated in non-agreement with the GOLD were less symptomatic and had fewer exacerbations. This is an intriguing issue, and can partly be due to fact that the present study did not control for features suggestive of airway hyperactivity. Moreover, because overuse of ICS and/or bronchodilators accounted for 88% of prescriber deviations, there were no reasons for patients medicated in non-agreement with guidelines to present more symptoms or more airflow limitation.

The present study draws attention to the choice of significant outcomes to evaluate responsiveness to treatment, and to the appropriate instruments to measure them.[29] Lung function, symptoms and acute exacerbations are important treatment outcomes in COPD. FEV_1 is a highly reproductive measurement strongly related to mortality. Dyspnoea is an important patient-centred outcome. However, it is very subjective, and the level of breathlessness depends on the level of patient activity. The mMRC scale, an instrument that has stood the test of time,[30] measures mainly dyspnoea-related disability, and, like other tools, may be not useful in evaluating responsiveness to treatment.[31] CAT has strong measurement properties in the overall impact of the disease, and the GOLD recommends its routine use in clinical practice. COPD exacerbations are the single most important feature of COPD, they indicate clinical instability and progression, and are related to increased mortality. It is an important outcome both from the physicians' and patients' perspectives. However, there is no standardised definition, and unreported exacerbations, not evaluated in the present study, have the same clinical relevance. A measure of self-reported adherence, the Test of the Adherence to Inhalers (TAI),[32] specifically designed to identify non-adherence to inhalers in asthma and COPD patients, is presently available in Portuguese-Brazilian language. To the best of our knowledge, MTA was the only validated instrument to measure adherence in the Portuguese language at the time patients were recruited for the present study. However, we acknowledge that factors related to adherence with inhaler therapy in COPD present some unusual features which makes the use of many unspecific questionnaires less appropriate.

Conclusions

In the present study, done in a real world context, we failed to prove a positive association between non-adherence to medication, inhaler mishandling or prescriber non-adherence to GOLD strategy with symptoms, exacerbations and airflow limitation. Conversely, more symptomatic and more obstructed patients adhered better to medication, previous ECOPD seems to have improved prescriber adherence to treatment guidelines, and symptoms, ECOPD and FEV_1% were not significantly associated with inhaler technique.

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Conflicts of interest

The authors have no conflicts of interest to declare.

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