

THE IMPACT OF TECHNICAL SKILLS AND EDUCATION ON EXACERBATIONS, ADHERENCE TO TREATMENT AND THE CHOICE OF INHALER DEVICE IN PATIENTS WITH COPD

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Abstract

Introduction. *The largest challenge for patients with COPD is the correct use of inhaler devices. In COPD, inhalation therapy has a key role in symptom control, reducing the exacerbation rate, hospitalization and improving the quality of life. Choosing the active substance(s) administered by inhaler devices is an easy task because of the Gold guideline recommendations, but, when it comes to choosing the inhaler device, it is much more difficult to get recommendations.*

Methods. *Our analysis included 200 subjects divided into two groups and its objective was the identification of some mechanisms that connect education, exacerbation and adherence to treatment, placed in the context of measuring technical skills and patients' preference for a particular inhaler device. All subjects included in the analysis were subjected to a technical skills test that included a set of 10 questions with a 30-minute solving time. The subjects in the working group were put in the position of deciding factor for the choice of an inhaler device, and implicitly for the treatment they would follow during monitoring.*

Results. *In both groups, the lowest treatment dropout rate at T12 was recorded among those with higher levels of education, while those with poor education levels recorded very high dropout rates. In both groups we noticed that, as the level of education increased, technical skills were also increasingly better. Both in the control group and in the working group, dropout subjects at T12 had significantly lower technical skills compared to subjects who did not drop out. The level of technical skills was significantly lower in both groups in subjects with exacerbations. Statistical analysis proved the relationship between the low level of technical skills and exacerbation. The subjects with lower technical skills proved to be more prone to dropout of inhaler therapy as well. The proportion of subjects with exacerbations in the control group was significantly higher than the proportion of those with exacerbations in the work group. The proportion of subjects with exacerbations in the control group was significantly higher than the proportion of those with exacerbations in the work group.*

Conclusions. *The authors consider that the involvement of the patient in choosing the inhaler device had a positive impact on disease control and reducing the rate of exacerbations.*

Keywords: COPD, technical skills, education, RespiMAT, Genuair, Breezhaler, adherence.



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Rezumat

Introducere. Cea mai mare provocare pentru pacienții cu BPOC o reprezintă utilizarea corectă a dispozitivelor inhalatorii. În BPOC, tratamentul administrat pe cale inalatorie are un rol central în controlul simptomatologiei, reducerea ratei de exacerbare, spitalizare și ameliorarea calității vieții. Alegerea substanței/lor active administrate cu ajutorul dispozitivelor inhalatorii este o misiune ușoară datorită recomandărilor ghidului Gold, însă, când vine vorba de alegerea dispozitivului inhalator, este mult mai dificil să se obțină recomandări.

Metodă. Analiza noastră a inclus 200 de subiecți împărțiți în două grupuri și a avut ca obiectiv identificarea unor mecanisme de legătură între educație, exacerbare și aderența la tratament, puse în contextul măsurării abilităților tehnice și preferinței pacienților pentru un anumit dispozitiv inhalator. Toți subiecții incluși în analiză au fost supuși unui test de abilități tehnice care a cuprins un set de 10 întrebări cu timp de rezolvare 30 de minute. Subiecții din grupul de lucru au fost puși în postura de factor decident al dispozitivul inhalator și implicit tratamentul pe care aveau să-l urmeze pe parcursul monitorizării.

Rezultate. În ambele grupuri rata cea mai mică de abandon a tratamentului la T12 s-a înregistrat în rândul celor cu educație superioară, în timp ce, cei cu educație precară înregistrează rate de abandon foarte crescute. În ambele grupuri se observă că, pe măsură ce nivelul de educație crește, se constată și abilități tehnice din ce în ce mai crescute. Atât în grupul martor, cât și în grupul de lucru, cei care au renunțat la tratament la momentul T12 au avut abilități tehnice semnificativ mai scăzute comparativ cu cei care nu au renunțat. Nivelul abilităților tehnice a fost semnificativ mai scăzut în ambele grupuri la cei cu exacerbări, analiza statistică demonstrând legătura între nivelul scăzut al abilităților tehnice și exacerbare. Subiecții cu abilități tehnice mai scăzute s-au dovedit a fi mai predispuși la abandonarea și tratamentul inhalator.

Ponderea celor cu exacerbări din cadrul grupului martor este semnificativ mai mare comparativ cu ponderea celor cu exacerbări din cadrul grupului de lucru. Ponderea celor cu exacerbări din cadrul grupului martor este semnificativ mai mare comparativ cu ponderea celor cu exacerbări din cadrul grupului de lucru.

Concluzii. Autorii consideră că implicarea pacientului în procesul de alegerea a dispozitivului inhalator a avut un impact pozitiv asupra controlului boli și reducerii ratei exacerbărilor.

Cuvinte cheie: BPOC, abilități tehnice, educație, exacerbare, Respimat, Genuair, Breezhaler, aderență.

Introduction

COPD is a chronic obstructive disease, perfectly preventable by early smoking cessation or by not starting the habit of smoking. The disease has a progressive evolution, characterized by airway obstruction and decreased lung function as a result of chronic inflammation from smoking or from exposure to professional or household air pollutants⁽⁷⁾.

The administration of treatment by inhalation is the most used way in patients with COPD due to its rapid therapeutical advantages and reduced systemic effects. The largest challenge for patients with COPD is the correct use of inhaler devices. As a multitude of studies have highlighted, the importance of the correct use of inhaler devices is essential for symptom control, reducing the rate of exacerbations and improving quality of life⁽²⁸⁾.

In recent years, more and more published studies have emphasized the importance of patients' preference for and satisfaction with a particular inhaler device when it comes to adherence⁽¹⁾. More and more evidence comes to light, supporting the idea of choosing the inhaler device depending on each individual patient. Obviously, there are many voices that brought forth the question: "What is more important, the inhaler device or the substance(s)?"

Choosing the active substance(s) administered by inhaler devices is an easy task because of the Gold guideline recommendations⁽¹¹⁾ but, when it comes to choosing the inhaler device, it is much more difficult to get recommendations. It is suggested that patients that use the preferred inhaler, in addition to making fewer errors, would achieve a much larger therapeutic benefit. Starting from the idea

that the patient is the final beneficiary of the inhaler device, the manufacturers of inhaler devices became more and more interested in patients' opinion. Involving the patients in the decision of choosing the inhaler device would not only reduce the errors in device use, but also contribute to reducing the rate of exacerbations and would increase the adherence to inhalation treatment^(10,28).

Unfortunately, COPD cannot be cured, but effective symptom control has a decisive role in slowing the disease progression and improving the quality of life for these patients^(11,19).

Disease management from the point of view of the therapeutical solutions is pretty easy, considering the myriad of medical studies and the multitude of active substances available, which can be administered in mono-, dual or triple therapy⁽²⁵⁾. The management of COPD gets complicated when it comes to choosing the inhaler device, reducing the errors in the use of inhaler devices and the adherence to treatment. The adherence rate to inhalation treatment among patients with COPD is proven to be low and an explanation could be that this category of patients has a lot of comorbidities, for which they take daily several medicinal products⁽¹³⁾.

Randomized studies have proven that long-acting bronchodilator treatment reduces the symptoms, reduces the exacerbations and improves the quality of life for COPD patients. However, interrupting the bronchodilator treatment was associated with the depreciation of the respiratory function, with an increase in the frequency of visits to the doctor, of hospitalizations and with an increase in medical care costs^(5,14,28). In COPD, inhalation therapy has a central role in symptom control, reducing the exacerbation rate, hospitalization, and in improving the



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quality of life⁽¹⁷⁾. It is well known that many patients have a low adherence to inhalation treatment. Several studies have reported that an average of 60% of COPD patients do not adhere to the prescribed therapy, added to which are the errors of use of inhaler devices, thus increasing the reduction of inhalation treatment efficacy^(12, 15, 16, 27). The GOLD guideline⁽¹¹⁾ highlights the importance of prevention and treatment of exacerbations as primary objectives for COPD control, emphasizing the harmful effects of exacerbations on the respiratory function and on healthcare due to increased costs^(10,11, 28).

The inhalation administration of treatment presents a series of advantages: easy administration, rapid action, achieving high local concentrations with low doses of active substance and decreased side effects compared to systemic administration^(24,27).

Unfortunately, few things are known about the factor which drive the adherence to inhalation treatment among COPD patients⁽⁵⁾. Adherence to treatment is defined as the initiation, the implementation and the continuation of treatment, and is fundamental in managing symptom control, in reducing the rate of exacerbation, and in preventing the decline of pulmonary function⁽²⁴⁾. In some studies, the female gender has been associated with a high risk of error of use of inhalers and with a high proportion of males that correctly use the

inhalers and who have a correct inhalation technique⁽³⁾. However, other studies have revealed a weaker performance among men concerning the correct manipulation of inhalers, while other studies did not identify any difference between the two genders^(6,8,23).

There are published analyses that support the idea of patient involvement in choosing the inhaler devices, given the results obtained in asthma patients that had better control of the disease⁽²⁴⁾. Improving adherence to inhaler treatment and reducing the number of errors in the handling of inhaler devices lead to a better efficiency of treatments with a positive impact on exacerbation rate and healthcare costs^(10, 27,28). Because studies that highlight the measurement of technical skills, the level according to which inhaler devices can be recommended, remain few: The objective of this study was the identification of some mechanisms that connect the patients' preference for a particular inhaler device, exacerbation, and adherence to treatment according to the level of education and technical skills.

Material and method

The present research combines two particularities: 1. All subjects included in the analysis were subjected to a technical skills test that included a set of 10 questions with a

30-minute solving time. For each correct answer one point was awarded. The maximum score that could be obtained was 10 points. And 2. The subjects in the working group were put in the position of deciding factor for the choice of inhaler device they would use during the monitoring. The authors were interested in the impact that technical skills and the level of education have on the disease evolution considering the exacerbations and the adherence to treatment in the context of patient involvement in the process of selection of the inhaler device.

Inclusion criteria. The patients enrolled in the study were smokers, ex-smokers and/or with an important exposure to professional air pollutants, aged over 40, diagnosed with COPD at least 12 months prior, and under inhaler treatment with a long-acting bronchodilator and corticosteroid. All patients enrolled in the study presented themselves in the pneumology service on their own initiative for assessment, complaining of respiratory symptoms while under background treatment.

Exclusion criteria. The absence of smoking history and/or exposure to professional air pollutants, radiological image suggestive for associated diseases, heart failure class III-IV NYHA, angina pectoris, heart rhythm disorders, a history of myocardial infarction and stroke in the previous 12 months, chronic kidney disease - $\text{eGFR} < 60 \text{ mL/min/1.73 m}^2$, uncontrolled diabetes mellitus - $\text{HbA1c} > 7.5\%$, obesity class II and III - $\text{BMI} > 35 \text{ kg/m}^2$, alcohol addiction, psychiatric disorders, patients with rheumatological and orthopedic pathology (difficulty in executing fine movements with their upper limbs), patients with stroke sequelae, a history of SARS-CoV-2 infection in the previous 6 months, and patients with major difficulties in understanding the differences between the

inhalers presented etc. The study spanned over a period of 4 years (2018-2022) and the monitoring period of enrolled patients was 12 months. During the study the patients were monitored three times: T0, T6 and T12. The identification of eligible patients was performed by the two authors and the introduction and monitoring in the study was performed by only one investigating doctor in order to reduce to a minimum the multi-individual approach in the relationship between doctor and patients. For the two groups to be comparable, the patient introduction into the study was randomized 1: 1 in the sense that: for the first patient introduced into the study, the doctor would recommend the inhaler device, and the following patient would have the responsibility of choosing the type of inhaler device that they considered the best for themselves.

The target group was represented by patients already diagnosed with COPD, on inhaler treatment with a long-acting bronchodilator and a corticosteroid, although according to the GOLD guideline they would have had indication for inhaler treatment with a long-acting bronchodilator and a long-acting muscarinic antagonist.

At the start of the study and during the study, there were three inhaler devices available in Romania - Genuair, Respimat and Breezhale - with which patients could administer the combination of long-acting bronchodilator and long-acting muscarinic antagonist. For studying the three inhaler devices, two comparable groups of patients have been formed, each group including 100 subjects. The first group was named the control group because the treatment was recommended to the subjects of this group by the classical method, i.e. 0 by the investigating pulmonologist. The second group was named



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the work group. The patients in this group were made available all three analyzed inhaler devices for familiarization and surveilled going through all the stages of handling in order to correctly administer the inhaler treatment.

The patients were the ones who chose the device which they considered most appropriate for themselves. Patients both in the control group and in the work group were instructed during each monitoring visit regarding the correct way of using the inhaler device and the importance of daily administration of the inhaler treatment. For the statistical processing of study data, the IBM SPSS Statistics for Windows, Version 26.0 was used. Armonk, NY: IBM Corp. Continuous variables were analyzed for normality and then were expressed as mean value and standard deviation. The analysis of the association between the categorical variables was done using the cross table and the χ^2 (chi-square) test. If the results of the chi-square test were sufficiently altered so as not to be considered, Fisher's exact test was used. To compare means according to the dichotomous variables in the study, the independent samples t-test was used. To compare the parameter means between groups, One-Way ANOVA was used, followed by multiple comparison using the Bonferroni *post-hoc* test. A value of the coefficient of statistical significance $p < 0.05$ was considered significant.

The representativeness rate of the sample calculated using Cochran's formula for representing the sample size based on the Z score, indicates that in a general population in Romania of approximately 1,494,000 patients with COPD, with an acceptable sampling error of 6%, and an estimated proportion of assignment to the sample population of 50%, with a distribution error of 10%, generates a coefficient of determination relative to the sample size of 188 people, which means that the selected sample of 200 people is representative.

Results

From the point of view of representativeness by gender and average age, the two groups were comparable. In the control group 83% were men and 17% were women. The average age of the group was 63.65 years. In the work group 81% were men and 19% were women. The average age of the group was 65.14 years. The gender assessment of adherence to inhaler treatment at T6 in the control group revealed that: 68.7% of men were still under treatment, compared to only 11.8% of women. The gender difference is statistically significant ($\chi^2 = 18.89$; $df = 1$; $p < 0.001$; Cramer's $V = 0.435$). At T6, the gender difference is also statistically significant ($\chi^2 = 18.73$; $df = 1$; $p < 0.001$; Cramer's $V = 0.433$) in the work group, where

77.8% of men were still under treatment compared to only 26.3 of women. In the control group at time point T12, the gender difference diminishes and is not statistically significant - 56.6% of men and 47.1% of women were still under treatment at T12 ($\chi^2=0.52$, $df=1$; $p=0.594$). In the case of the work group, the statistically significant difference between the two genders is maintained. At T12, 64.2% of men and 21.1% were still under treatment ($\chi^2=11.62$; $df=1$; $p=0.001$; Cramer's $V=0.341$).

In the control group, although we see different percentages among those with exacerbation according to the education level, the result of the statistical analysis shows that the differences are not significant ($\chi^2=4.70$; $df=4$; $p=0.319$), therefore we cannot say that there is an association between exacerbation and the level of education in the control group.

However, from a percentage point of view, it is noted that: patients with a vocational school - 73.9% and middle school - 83.3% had exacerbations in a larger proportion compared to those with high school - 60.6%, college - 60.9% and PhD - 44.4%. In the work group, the situation is similar to that from the control group, although we see different percentages among those with exacerbation according to the education level, the result of the statistical analysis shows that the differences are not statistically significant ($\chi^2=4.15$; $df=4$; $p=0.385$), therefore we cannot say here whether there is an association between exacerbation and the level of education.

Those holding PhDs had exacerbations at a rate of 20%, those with high school studies 37.1%, those with college studies 50%, those with middle school studies 60%, while those with vocational studies had exacerbations at a rate of 45%. No statistically significant

association was noted ($\chi^2=1.75$; $df=4$; $p=0.781$) between the level of studies and treatment dropout at T12. But from a percentage point of view very high rates of treatment dropout were found among patients with a low level of education - middle school - 47.8%, vocational school - 58.3% and high school - 45.5%. The tendency to drop out decreases significantly in percentage in those with college - 39.1%, and PhD - 33.3% educations.

In the work group there is a statistically significant association ($\chi^2=12.86$; $df=4$; $p=0.012$; Cramer's $V=0.359$) between the education level and treatment dropout at T12. Those with higher education - college - 25%, PhD - 20% - dropped out of treatment in a smaller proportion compared to those with lower studies; middle school - 50%, vocational school - 75%, high school - 37.1%. In both groups, the lowest treatment dropout rate at T12 was recorded among those with higher levels of education, while those with poor education levels recorded very high dropout rates.

It is worth highlighting that the subjects from the work group, probably also due to their involvement in choosing an inhaler device, have much lower dropout rates at T12 than subjects in the control group. The statistical analysis of the two groups has identified a statistical relationship between the degree of education and the level of technical skills, both in the control group ($p<0.001$), and in the work group ($p<0.001$). In both groups we noticed that, as the level of education increased, technical skills were also increasingly better.

Both in the control group ($m=1.60$) and in the work group ($m=1.20$), those who dropped out at T12 had significantly lower technical skills compared to those who did not drop out ($m=2.53$), ($m=2.34$). The level of technical



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skills was significantly lower in both groups in those with exacerbations, compared to those without exacerbations. The statistical analysis proved a strong relationship between the level of technical skills and exacerbation (Table 1).

The proportion of those with exacerbations in the control group is significantly higher (65%) than the proportion of those with exacerbations in the work group (45%). The difference between the two groups is significant from a statistical point of view ($\chi^2=8.08$; $df=1$; $p=0.007$; Cramer's $V=0.201$). This is another piece of evidence that involving the patient in choosing the inhaler device had a positive impact on disease control (Table 2).

The analysis of exacerbations on each device revealed the following results. In the control group most exacerbations were counted among subjects who were recommended the Breezhaler device - 76.9%. In second place were the users of the Genuair device - 63.6%. And in last place were the users of Respimat, with a percentage of 50.0% ($\chi^2=5.23$; $df=2$; $p=0.073$). In the work group, most exacerbations were counted also among Breezhaler users - 60.0%, followed by the Respimat users - 44.8%, and in the last position, the Genuair users - 26.3% ($\chi^2=13.47$; $df=3$; $p=0.004$; Cramer's $V=0.367$). A simple analysis shows that among the subjects from the work group, where the

inhaler device was chosen by the patients, the exacerbation rate was lower compared to subjects from the control group. The largest difference was recorded among the Genuair users - 37.3%.

The episodes of exacerbation were not proven to be related to the patients' background environment. Thus, in the control group - 69.1% of patients from an urban environment and 56.3% of patients from a rural environment had exacerbations ($p=0.208$). In the work group, 40.6% of patients from an urban environment and 52.8% of patients from a rural environment had exacerbations ($p=0.241$). The adherence to inhaler treatment at T12 was also unrelated to the patients' background environment. Our analysis showed that in the control group - 47.1% of those from an urban environment and 40.6% of those from a rural environment had stopped their treatment at T12 ($\chi^2=0.34$; $df=1$; $p=0.667$).

In the work group - 39.1% of those from an urban environment and 52.8% of those from a rural environment had stopped their treatment at T12 ($\chi^2=1.76$; $df=1$; $p=0.185$). We did not manage to identify a statistical relationship between the technical skills and each inhaler device in the control group, but in the work group, patients that opted for the Respimat device have a level of technical skills significantly higher than of those who would have opted for the other device ($p=0.001$).

Group		Exacerbation T12	N	Mean	Standard deviation	p
control	Technical skills	No	35	2.97	2.728	0.005
		Yes	65	1.65	1.824	
work	Technical skills	No	55	2.07	2.276	0.013
		Yes	45	1.56	2.095	

Table 1. The analysis of our subjects

			Exacerbation T12		Total
			No	Yes	
Group	control	Frequency	35	65	100
		% of group	35.0%	65.0%	100.0%
	work	Frequency	55	45	100
		% of group	55.0%	45.0%	100.0%
Total		Frequency	90	110	200
		% of group	45.0%	55.0%	100.0%

$\chi^2 = 8.08$; $df = 1$; $p = 0.007$; Cramer's $V = 0.201$.

Table 2. The analysis of our subjects



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Discussions

Considering that the proper use of inhaler devices was associated with the improvement of pulmonary function, of general health, and of quality of life, strategies to reduce user errors in the use of these devices should become a priority both for healthcare providers and for the patients. Current evidence suggests that the benefits of COPD treatment are directly related to the correct use of inhaler devices⁽¹⁵⁾. Inhaler devices are essential for the administration of bronchodilator drugs for managing the symptoms in COPD and the correct use needs a thorough initial training and a periodical assessment of the inhalation technique. Incorrect or partially correct inhalation techniques correlate with the decreased delivery of active substances in the bronchial tree, which leads to a poor control of the disease⁽¹⁶⁾.

The assessment of the inhalation technique is complex and comprises an important dose of subjectivism from the evaluators, to which we can add the lack of a consensus between researchers regarding the definition of inhalation errors, and establishing some standardized lists for checking the correct inhalation technique⁽¹²⁾. Despite the GOLD guideline recommendations⁽¹¹⁾, after the initial prescription, patients' inhalation technique is rarely checked during visits. Some published

evidence suggests that patients' satisfaction and the ease of use of an inhaler device are among the most important attributes for increasing the rate of correct use of inhaler devices and of the adherence to the treatment⁽²⁴⁾. Since patients' preference for a particular inhaler device was associated with better results^(20, 21), it seems wise for the clinicians to keep in mind the patients' preference during the process of selection of the inhaler device. Even the GOLD guidelines⁽¹¹⁾ recommend that the selection of the inhaler device should be based not only on the availability of the medications, on costs and on the preference of the prescribing physician for a certain device, but also on the patient's preference and their ability to use the specific device^(11,22).

No matter the type of inhaler device, poor handling led to a decreased control of symptoms, exacerbations and frequent visits to the doctor or to the emergency room^(17, 22). The understanding of the practical aspects of the correct use of inhalers and the use of a correct inhalation technique are essential for the long term management of COPD patients⁽²⁹⁾.

It is interesting that several studies have emphasized the relationship between the characteristics of inhaler devices and the adherence to inhaler treatment. Therefore, selecting the inhaler devices according to the characteristics of each patient can have a

significant contribution to increasing the adherence, a better control of the symptoms and improving the quality of life⁽⁹⁾. The authors completely agree with the conclusions of Marc Miravittles⁽²⁰⁾, who considers that the relevance of inhaler characteristics also includes the COPD patients' preference for a certain inhaler device and that this has been relatively little investigated. More than 80% of inhaler prescribing physicians were aware of the importance of selecting the proper inhaler device for COPD patients, but yet they continued prioritizing the medicinal product to the detriment of the device⁽²⁰⁾. Similarly, Molimard *et al.*⁽²¹⁾ concluded that the patients' satisfaction and the ease of use were the most important attributes when selecting an inhaler device for patients. Patients with hypertension proved to be more prone to adherence to treatment, compared to COPD patients, which is plausible because these patients are monitored more frequently⁽²⁾.

Therefore we draw the conclusion that a periodical assessment of the inhalation technique and a periodical monitoring of FEV1 could contribute to increasing the adherence to inhaler treatment, but also to a better control of respiratory symptoms. It is a proven fact that smoking cessation is the most effective way of slowing down the progression of this disease⁽³⁾. Therefore, it is plausible to believe that patients who do not follow the recommendation to stop smoking do not follow the medication recommendations either⁽²⁶⁾.

Meek *et al.*⁽¹⁸⁾ proved that the current available strategies for educating patients on the correct use of inhaler devices result in error rates between 30% and 70%. This supports a need for improving the educational strategies for increasing the correct use of inhalers⁽⁸⁾. COPD patients are

more prone to handling errors of inhalers, probably due to older age and comorbidities that can significantly affect the inhalation technique. Moreover, the probability of poor handling is increased by the association of two or three inhaler devices used simultaneously⁽⁸⁾. A correct understanding of the relationship between inhalers and some specific patients' characteristics can be useful in clinical practice, adding value to a medical community with limited resources. However, choosing the right substances and the proper inhaler for each patient will continue to be a difficult problem to overcome.

Conclusions

The statistical analysis of the two groups has identified a strong relationship between the degree of education and the level of technical skills in both groups ($p < 0.001$). In both groups we noticed that, as the level of education increases, the technical skills are also increasingly better. In patients with exacerbations the level of technical skills was significantly lower than in those without exacerbations.

The lower level of technical skills in both groups proved to have a negative impact on the inhaler treatment at T12. Subjects with lower technical skills proved to be more prone to dropout of inhaler therapy compared to subjects with a higher level of technical skills. In our analysis we did not manage to identify a statistical relationship between the technical skills and each inhaler device in the control group, but in the work group, patients that opted for Respimat device had a level of technical skills that was significantly higher than of those who would have opted for the other device. The patients' environment did not prove to be an influencing factor on the



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exacerbation rate in the two groups. Our subjects analysis did not identify a statistical relationship between the patients' level of education and the exacerbation rate, but highlighted that patients with a low level of studies had a higher rate of exacerbations than the subjects with a higher level of studies - college and PhD.

The proportion of subjects with exacerbations in the control group was significantly higher than the proportion of those with exacerbations in the work group. The difference between the two groups is statistically significant. The authors consider that the involvement of the patient in choosing the inhaler device had a positive impact on disease control and reducing the rate of exacerbations. More attention must be paid to the Breezhaler device that was shown to be associated with a high percentage of exacerbations in both groups. It is worth noting that the patients' involvement in the choosing of the inhaler device significantly contributed to the decrease of exacerbations in the work group for all devices. The largest difference was noted among the Genuair users.

Inhaler adherence results differentiated by gender revealed a statistically significant difference between men and women at T6, but this difference remains statistically significant in favor of men only in the work group at T12. A low level of education was proven to have a negative impact on the

dropout rate at T12. In the work group there was identified a strong relationship between education and treatment dropout. This aspect can also be interpreted by the process of patient's involvement in choosing the inhaler device.

Recommendations

Open communication between doctor and patient about the treatment and especially about the inhaler device should be the starting point for an effective and long term control of symptoms in COPD. The clinical practice proved that an adequate and periodical training at regular times is necessary for improving the inhalation technique and maximizing the advantages of each inhaler device. Inhaler devices-prescribing physicians should consider reducing the number of inhalers per patient as much as possible, because it is a known fact that a complex therapeutical formula increases the patients' tendency to drop out of the treatment.

The authors consider that in clinical practice choosing the inhaler device should also take into account certain characteristics of patients. The result of this research could have implications both for future research and for the daily medical practice. Additional research can be made concerning the behavior of COPD patients depending on the

level of technical skills and their preference for a particular inhaler device. And in clinical practice, it offers an effective alternative for choosing the inhaler device depending on the level of education, the technical skills and the patient's preference for a particular inhaler device.

Limitations of the study

Our study was made in a single medical institution and within a single health system. Therefore, the results should be interpreted with caution in the context of other nationalities. The geographical area limited to four counties (Galați, Brăila, Tulcea, and Vrancea) of origin of the patients, that can be interpreted as non-representative for the COPD patients' behavior in Romania. The study was limited to the three devices available in Romania, for administering the combination of long-acting bronchodilator and long-acting muscarinic antagonist - Breezhaler, Genuair and Respimat. Also to be considered is our subjectivism regarding a correct inhalation technique and the patients' honesty concerning the daily administration of inhaler treatment.

The subjects that did not pass the technical skills test by exceeding the work time of 30 minutes were excluded from the start from the study. Excluded were also patients that presented major difficulties of understanding the difference between the active substances from the inhaler devices (control medication and rescue medication or administered as needed). Also excluded from the study were patients where we suspected: alcohol addiction, psychiatric disorders, rheumatological and orthopedical disorders, stroke sequelae, limited financial capabilities, etc.

Author contributions

The conceptualization of the study was made by physicians A.C. and S.B. and brought to its final form through the significant contribution of physician S.B. The work methodology, creating the database and the statistical analysis were the work of A.C. The tasks of the investigator physician, filtering the resulting data, preparing and redacting the manuscript fell to S.B., and revising, editing and supervising were the work of A.C. Both authors read and agreed to the final form of the manuscript and its submission to publication.

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The budget covering the administrative costs of this project was covered by both authors from their own funds. This analysis did not benefit from external funding. All patients included in the analysis were insured by the public health system and they came to the hospital by their own initiative, due to their respiratory symptoms, following a reference from their General Practitioner. At the end of the examination, patients received a discounted prescription for the inhaler treatment that they would be taking during monitoring.

Institutional Review Board Statement

The study was conducted according to the principles of the Declaration of Helsinki and has the approval of the Medical Council of the "Dr. Aristide Serfioți" Military Emergency Hospital from Galați - RCM327/M1-544.

Informed Consent Statement

The subjects included in the analysis were diagnosed with COPD at the moment of presentation and they were treated at home with inhaled corticosteroid and long-acting



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bronchodilator. They were examined on demand for residual respiratory symptoms while on treatment, and would have received inhaler treatment with a combination of long-acting bronchodilator and long-acting muscarinic antagonist according to GOLD guidelines, even if they had not been included in the analysis. However, each patient was asked for a written agreement for taking part in the study for anonymized publication of the results.

Data Availability Statement. Databases that include the statistical anonymized data obtained from the patients included in the analysis are available upon request.

Declaration of conflicting interests. The authors do not declare any conflict of interest.

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