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Behaviour of COPD patients
when involved in the inhaler device selection process, relative to the level of
technical skills and inhaler device used

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CONTENT

Abbreviations

ACOS – Asthma and Bpoc overlap syndrome

AVC – Stroke

BADLA – Long - acting betamimetics

BADSA – Short - acting betamimetics

BD – Bronchodilator

Copd – Chronic obstructive pulmonary disease

CAT – Bpoc assessment test

C19 – COVID19

CSI– Corticosteroid inhaler

DPI – Dry powder inhalers

DZ – Diabetes mellitus

FEV1 – Forced expiratory volume in the first second

GA – Chosen group

GR – Recommended group

HRQL – Quality of life questionnaire

HTA – Hypertension

IMC – Body mass index

LAMA – Long-acting anticholinergics/antimuscarinics

LABA – Long-acting betamimetics

mMRC – Modified Medical Research Council

NYHA – New York Heart Association

OLD – Long-term oxygen therapy

OMS – World Health Organization

PaO2 – Oxygen partial pressure

pMDI – Pressurised metered dose inhaler

PDE4 – Phosphodiesterase inhibitor 4

RFG – Glomerular filtration rate

SpO2 – Peripheral blood oxygen saturation

SUA – United States of America

SGRQ – Chestionarul St George's Chestionarul respirator

T0 – Initial monitoring at study entry

T6 – Six-month monitoring

T12 – 12 - month follow-up

VEMS – Maximum expiratory volume per second

VNI – Non - invasive ventilation

VNP23 – 23 - valent polysaccharide vaccine

VNC13 – Vaccine conjugate 13

Introduction

Treatment of Copd is predominantly using inhaled drugs, administered with inhaler devices. The correct use of inhaler devices by patients is one of the many challenges patients face after the diagnosis of Copd (1). A wide range of inhaler devices are available for the administration of inhaler therapy to patients with Asthma and Copd, unfortunately a very large number of patients diagnosed with these respiratory conditions do not use their inhaler devices correctly and this has a significant impact on the effectiveness of the medication administered, ultimately resulting in poor disease control and frequent episodes of exacerbation (2). In recent years, more and more evidence has emerged to support the idea of patient empowerment in the choice of inhaler device. With this idea of empowering patients by involving them in the inhaler device selection process, there is increasing discussion of the answer to the question "Which is more important, the inhaler device or the medication administered with the device?".

Although we are talking about a respiratory disease that affects millions of people, not much research is available to address the issue of inhaler misuse through the lens of patient involvement in the inhaler device selection process.Given the need to correlate information received from patients on the correct use of inhaler devices and their implementation in practice, we have not identified scientific evidence correlating technical skill level, inhaler device type and inhaler device handling errors, exacerbation rates, smoking cessation and adherence to inhaler treatment. The particularity of the present research is to empower patients by involving them in the inhaler device selection process and pre-measuring technical skills using a standardised test, in an attempt to identify a link between this and the behaviour of patients with Copd.

The motivation for the implementation of this study came from medical practice, where we found that most patients with Asthma and Copd who presented to the consultation for escalating respiratory symptoms, although using their inhalers daily, continued to make mistakes in their use. Analysing the published scientific evidence on inhaler misuse among patients with Asthma and Copd, we found that in the majority, the inhaler device was recommended by the physiciancaregiver without taking into account the patient's preference for a particular inhaler device. In order to be able to identify the behaviour of Copd patients when they are responsible for and involved in the inhaler device selection process, we analysed in two separate studies the behaviour of patients already diagnosed with Copd and the behaviour of patients newly diagnosed with Copd.

I. General Part

In the general part of the paper, we have made a foray through the literature on the state of knowledge about Copd and the state of knowledge about inhaler misuse, exacerbation episodes, adherence to inhaler treatment and smoking cessation.All the research on inhaler devices reviewed concluded that; the perfect inhaler does not exist. Each inhaler has its pluses and minuses, which is why inhalers should also be chosen according to the patient's preference and understanding, as correct and long-term management of asthma and obstructive chronic obstructive pulmonary disease depends to a very large extent on the correct use of inhalers and therefore on correct inhaler technique (3).In his review, Piyush Arora (4), determined that 82.3% of the patients analysed committed at least one error in inhalation technique. The published data are in agreement with the study by Maria Luiza Souza (3), in which the authors identified an error in inhalation technique in 93.4% of patients. The age group 51-60 years was found to have a wrong inhalation technique in percentages of up to 86.0%, likewise patients with a low level of education or poor socioeconomic condition were found to make inhalation mistakes in up to 96.4%.Worryingly, many of the mistakes patients made in inhalation technique that the authors identified in many of their analyses suggested that the instruction provided by the medical staff may not have been sufficiently clear or understood by patients due perhaps also to context - age, co-morbidities, impact of diagnosis, ”white coat” effect, to which can be added factors relating to the medical staff, the patient and the inhaler device.Among the first inhalation devices introduced for the treatment of asthma and obstructive lung disease are pMDIs, which are still the most widely used types of inhalation devices, but are relatively difficult to use due to the need to coordinate inhalation with the release of the active substance(s), and are thus associated with a misuse rate of between 7 and 71% (5).

Dry powder inhalation devices (DPI), are inspiratory flow dependent devices and require less coordination between patient and device, and are therefore more appreciated and less prone to major errors in inhalation technique (5). Comparative analyses between the two types of devices mentioned above concluded that both are equally effective in delivering treatment to patients with Asthma and Copd, provided the inhalation technique is correct. A very interesting analysis and very relevant to the discussion on the misuse of inhaler devices was published by Maria Luiza de Moraes Souza (3).When asked about inhaler technique, all patients with Asthma and 98% of those with Copd claimed to use

their inhaler correctly. Verification of the inhaler technique of these patients revealed that 94.2% of patients with Asthma and Copd made at least one error in the administration of inhaler therapy.

Some meta-analyses have shown that drugs from the same class are approximately equally effective clinically, provided they are used correctly (6,7). Translating this evidence into real life, the difference in full control of obstructive lung disease is made by the inhaler device, which is why it should be chosen according to patient preference, bearing in mind that the patient is the ultimate beneficiary of the inhaler device (6-8).The current trend is for these drugs to be given in combination with a single inhaler to minimise the likelihood of a misinhalation technique identified in patients using multiple devices. In addition to the major benefit derived from a less error-prone inhaler technique, the administration of inhaler treatments in combination with the same device increases the efficacy of therapeutic formulations and encourages adherence to treatment.

Among the most common mistakes identified in users of inhaler devices were:

- Failure to exhale before inhaling the drug;

- Absence of apnea after inhalation;

- Inadequate inspiratory flow;

- Absence of tank shaking before use;

- Poor co-ordination between inspiration and drug release for pMDI type devices;

- Inadequate preparation of DPI type devices;

- Absence of oral cavity lavage after inhalation for patients using combinations of drugs containing ICS;

Summarising the "Current state of knowledge about the misuse of inhaler devices" the following observations can be made:

1. Regardless of the inhaler device used, errors observed in patients with Asthma and Copd varied from study to study, and their frequency was identified in more than 50% of users.

2. In most analyses comparing inhaler devices, the inhaler device was recommended by the investigating physician, thus not knowing the patients' "preference" for a particular inhaler device.

3. A great deal of data is available on the mistakes patients make in using inhaler devices recommended by their doctor, but there is very little published evidence on the impact of patient involvement in the inhaler device selection process on the frequency of inhaler device mistakes, frequency of exacerbation episodes and adherence to inhaler therapy.

4. The impact of the level of technical skills in handling inhaler devices in terms of inhaler device misuse, exacerbations, adherence to inhaler treatment and smoking cessation is unknown.

Original part

II. Personal contributions

The personal contributions part focuses mainly on the results obtained in this research and the future perspectives it opens in the approach to the treatment of Copd patients. The main objective of the present research was "To identify the behaviour of Copd patients when they are empowered and involved in the inhaler device selection process, related to the level of education and technical skills of patients on the correct inhaler technique, assessed by the frequency of inhaler device misuse, frequency of exacerbations, smoking cessation and adherence to inhaler treatment".In order to achieve the proposed objective, two studies were designed in which newly diagnosed Copd patients and already diagnosed Copd patients on inhaler treatment were included.

To achieve the main objective, four working hypotheses were established in each study:

Working assumptions - Study 1

H1:Empowering patients by involving them in the inhaler device selection process improves the frequency of inhaler device misuse, exacerbations and adherence to inhaler therapy.

H2: Assessment of inhaler technique at regular intervals reduces the frequency of inhaler device misuse and the frequency of exacerbations (1,3-7,9-22).

H3: Diversified training and re-training practiced at regular intervals on the correct way to use inhaler devices and encouraging patients to administer their inhaler treatment daily has a significant impact on the frequency of misuse of inhaler devices and the annual frequency of exacerbations (3,6,16,19,23-30).

H4: Impact of education level and technical skills on Copd patients' behaviour in relation to inhaler device use and disease progression under the four aspects monitored: inhaler device misuse, annual exacerbations, adherence to inhaler treatment and smoking cessation (1,31).

Working assumptions - Study 2

H1: Differences between the doctor's "opinion" and the patient's "opinion" about the "most suitable" inhaler device are a serious warning signal about the high number of inhaler device misuse and the increased frequency of exacerbations (3-7,11-18,21,24,32-36).

H2: Empowering patients by involving them in the inhaler device selection process increases the chances of selecting an inhaler device that is compatible with the patient's level of understanding, thereby creating the prerequisites for correct inhaler technique (9,10,20-22).

H3: Incorrect use of inhaler devices is the main reason for poor control of obstructive diseases. Approaching treatment from the perspective of patient empowerment in the inhaler device selection process reduces the frequency of misuse and thus exacerbations with significant impact on symptom control and quality of life of these patients (3,16,25-28).

H4: Technical skill levels shape Copd patients' behaviour in relation to inhaler device misuse, exacerbations, treatment adherence and smoking cessation.

Working methodology - Study 1

The target group was patients with no history of obstructive lung disease or history of bronchodilator treatment. Thus, 180 patients newly diagnosed with Copd risk group B and C were enrolled in the study according to the inclusion criteria [4]. Six (6) groups of 30 subjects each were thus created. For each device investigated - Genuair, Respimat and Breehzhaler a working group and a control group were formed. Upon entry into the study, patients were asked to solve a standardized technical skills test, which comprised 10 questions, with a working time of 30 minutes.Patient entry into the study was randomised 1:1 in the sense that the first patient entered into the study was recommended the inhaler device by the doctor, thus the patient was included in the control group of the recommended inhaler device. The second patient was left to choose/decide for himself the type of inhaler device he considered 'most suitable' for him.Thus, by choosing one of the three analysed devices - Genuair, Respimat and Breehzhaler, he assigned himself to the working group of the chosen/decided device. While patients in the working groups received an interim follow-up at T6, during which they were reinstructed on the correct

way to use the inhaler device, patients in the control groups were instructed on the correct way to use the inhaler devices only at T0 and T12.

Results Study 1

At the end of the monitoring period, only 21.6% of the subjects in the working groups still made inhaler device errors, significantly fewer than in the control groups where inhaler device errors were identified in 50.0% of the subjects.

			Mistakes - T12		Total
			No	Yes	
Group	Working	Count	58	16	74
		% within Grup	78,4%	21,6%	100,0%
	Control	Count	24	24	48
		% within Grup	50,0%	50,0%	100,0%
Total		Count	82	40	122
		% within Grup	67,2%	32,8%	100,0%

χ^2=10,64; df=1; p=0,001

Table5.5. Comparative evaluation of T12 errors

Analysis of exacerbations at the end of the follow-up period identified a significantly lower percentage of exacerbations among patients who chose their own inhaler device compared to control groups where the inhaler device was recommended by the investigating physician.

			No	Yes	
Group	Working	Count	76	14	90
		% within Grup	84,4%	15,6%	100,0%
	Control	Count	38	52	90
		% within Grup	42,2%	57,8%	100,0%
Total		Count	114	66	180
		% within Grup	63,3%	36,7%	100,0%

χ^2=34,54; df=1; p<0,001; Cramer's V=0,325

Table5.9. Comparison of exacerbations between the two groups

And in terms of adherence to inhaler treatment, patients involved in the inhaler device selection process, collaborating with interim monitoring at T6, resulted in only 17.8% of all patients included in the working groups stopping inhaler treatment before T12, while 47.8% of patients in the control groups stopped treatment.

			STOP Treatment		Total
			Nu	Da	
Group	Working	Count	74	16	90
		% within Grup	82,2%	17,8%	100,0%
	Control	Count	47	43	90
		% within Grup	52,2%	47,8%	100,0%
Total		Count	121	59	180
		% within Grup	67,2%	32,8%	100,0%

Table 5.1. Stop treatment before T12

Correlating the results of the technical skills test with the number of mistakes in the use of inhaler devices shows a higher level of technical skills among those who made no mistakes at time T12, while the average level of technical skills of those who made mistakes at time T12 was much lower.

Group Statistics					
	Mistakes - T12	N	Mean	Std. Deviation	p
Technical skills	No	82	3,32	2,398	0,001
	Yes	40	2,05	1,648	

Table 5.2. Correlation between technical skills test and inhaler device errors

Smoking cessation was significantly higher among patients who chose their inhaler device themselves (25.6%), compared to patients for whom the device was recommended by their doctor (14.8%).

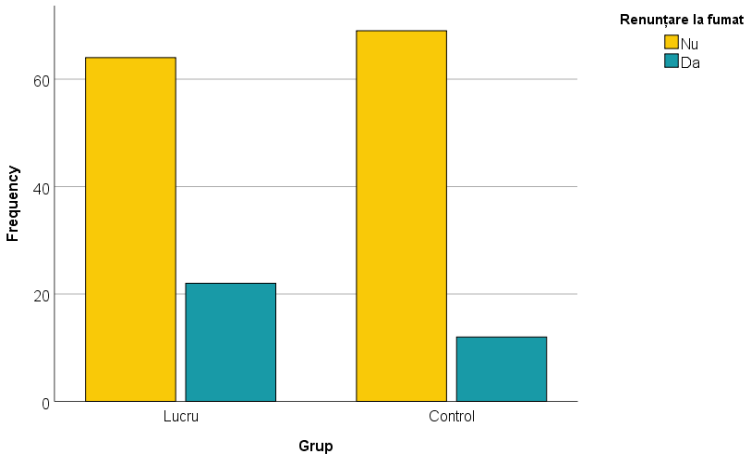

Figure 5.32. Comparison of smoking habits between the two groups

Statistical analysis according to CAT evolution identified a significantly greater decrease in CAT 2 (T12) in patients who chose their own inhaler device - positive evolution, compared to the decrease in CAT in patients in whom the device was recommended by the physician.

Group Statistics					
	Group	N	Mean	Std. Deviation	p
CAT evolution	Working	90	-8,92	6,547	<0,001
	Control	90	-2,90	8,619	

Table 5.11. Comparative analysis of CAT 2 (T12)

Methodology Study 2

The target group was patients already diagnosed with Copd on long-acting inhaled bronchodilator and inhaled corticosteroid (ICS+LABA) treatment, although according to the Gold diagnostic and treatment guidelines (8) they would have been indicated for inhaled treatment with LAMA+LABA. In this study, 200 patients were enrolled, divided into two groups of 100 subjects each. The first group was called the recommended group (RG) because the inhaler device was recommended to the patients by the pulmonologist. The second group was called the chosen group (GA), because in this group, it was the patients who chose/decided for themselves the inhaler device they considered "most

suitable" for them.The monitoring period was also 12 months. Patients in this study, were all monitored at T6, unlike Study 1, where only patients in the working groups were monitored at T6. Patient entry into the study was also randomised 1:1 in the sense that the first patient was recommended the inhaler device by the doctor and the second patient was responsible for choosing/deciding for himself the type of inhaler device he considered "most suitable" for him.After presenting the three inhalation devices and explaining the correct inhalation technique for each device, patients were given demonstration inhalation devices to familiarise themselves with and practice the correct inhalation technique. Subsequently, subjects in the recommended group were asked to indicate which type of inhaler device they would "opt for" if given the choice. Subjects in the chosen group were asked to choose/decide for themselves the type of device they considered "most suitable" for them.As patients practiced with the demonstration inhaler devices provided, the doctor wrote down the type of inhaler device he or she would "opt for" for each patient in the chosen group.

Results Study 2

In terms of gender representation, the two groups were similar. The same was true for age. In both groups, more than 50% of the patients included in the analysis had their inhaler and initial treatment with ICS+ LABA prescribed by pulmonologists.

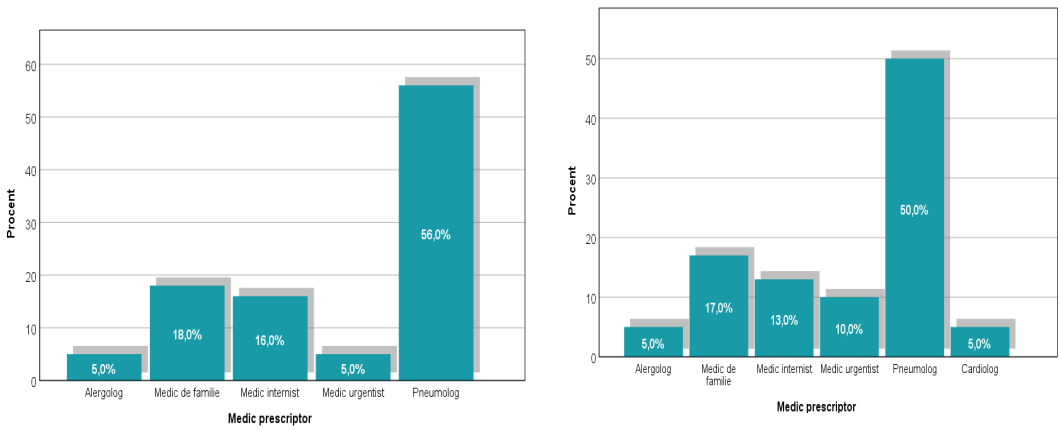

Figure 6.2A. și 6.2B. Graphical representation of patients according to the specialty of the initial prescriber of the inhaler device

Responsiveness to the proposal to change the initial device and therefore the inhaler treatment was over 80% in both groups. The most receptive category of patients to the

change of inhaler device, and by default treatment, were patients with a history of inhaler device use between 3 years and 4.11 years.

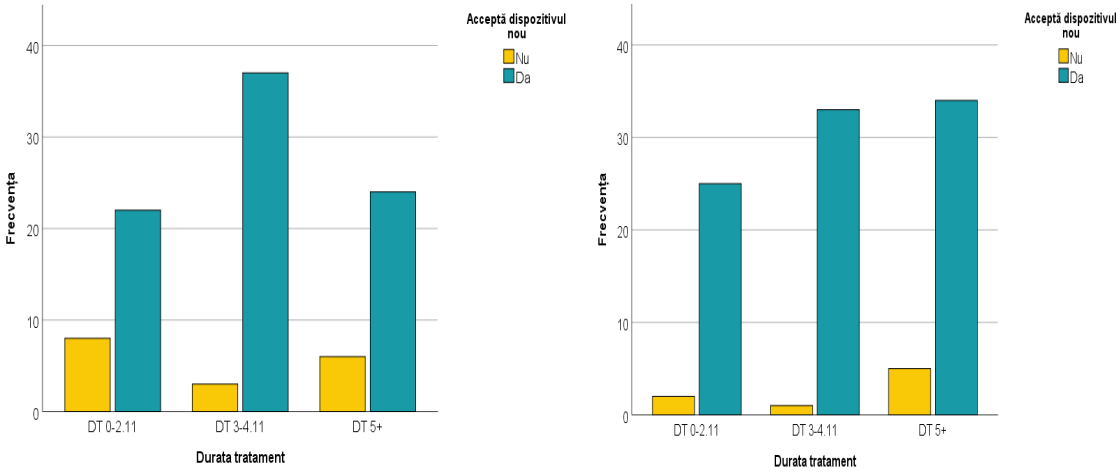

Figure 6.4A. și 6.4B. Acceptance of change of inhaler devicedepending on the age of use of the original device

Given the paucity of research on patient preference for a particular inhaler device, I wasinterested to find out what the differenceisbetween patient 'opinion' and doctor 'opinion' on the 'most suitable' inhaler device. Thus, in the group where the device was recommended by the doctor, only in 30% of cases was the patient's 'choice' similar to the pulmonologist's recommendation, while in the group where patients chose their own inhaler device, only in 51% of cases was the patient's decision similar to the pulmonologist's 'choice' for a particular type of inhaler device.

"Doctor/patient "option					Total
			Similară	Diferită	
Grup	Recommended	Frecvența	30	70	100
		% din Grupul	30,0%	70,0%	100,0%
	Chosen	Frecvența	51	49	100
		% din Grupul	51,0%	49,0%	100,0%
Total		Frecvența	81	119	200
		% din Grupul	40,5%	59,5%	100,0%

χ^2=9,15; df=1; p=0,004; Cramer's V=0,214

Tabel 6.2. Comparative analysis of our subjects

Analysing the 'choice' of the patients in the recommended inhaler device group if they had the possibility to choose/decide their inhaler device themselves, it is found that: none of the three inhaler devices stands out in the patients' preferences. However, in the group where patients were able to choose their own inhaler device, 51% of patients' choices went to the Genuair device, and the remaining 49% were split equally between the remaining two devices.

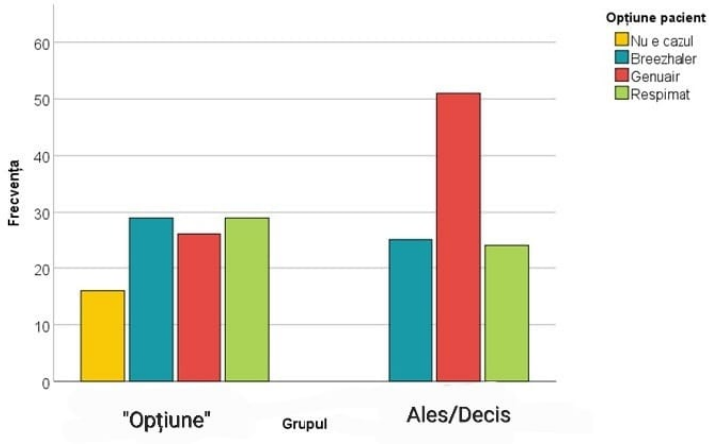

Figure 6.5. Option and choice of inhaler device

Comparative analysis of inhaler device misuse (Appendix 5) revealed that at T0, the proportion of those who made mistakes in the administration of treatment was similar in the two groups. But at time T6, things change radically. In the group, where the device was chosen by the patients, the percentage of those who still made mistakes in taking the treatment was significantly lower (47%), compared to those in the group where the device was recommended by the doctor (59%). The difference between the two groups in terms of mistakes in the use of inhalation devices was also maintained at the follow-up at T12.

Mistakes at T12			Not the case	Yes	No	Total
Group	Recommended	Frecvența	14	50	36	100
		% din Grupul	14,0%	50,0%	36,0%	100,0%
	Chosen	Frecvența	8	31	61	100
		% din Grupul	8,0%	31,0%	61,0%	100,0%
Total		Frecvența	22	81	97	200
		% din Grupul	11,0%	40,5%	48,5%	100,0%

χ^2=12,53; df=2; p=0,002; Cramer's V=0,250

Table 6.4. Erroranalysis at T12

Analysis of exacerbations and adherence to inhaler treatment by patient gender has sparkedmuch discussion about whichgenderismostexacerbating and least adherent to inhaler treatment. The present analysis, revealed at T12, that women had significantly more exacerbations compared to men. Regarding adherence to inhaler treatment at T12, in the recommended group, the difference between the gender sisblurring, with 56.6% of men still following treatment and only 47.1% of women following treatment. However, in the group, where the device was chosen by the patients, the gender difference is maintained, with 64.2% of men still on treatment and only 21.1% of women on treatment.

In terms of reducing exacerbations at T12, empowering patients by involving them in the inhaler device selection process contributed significantly to lowering the frequency of exacerbations among patients in the patient chosen group.

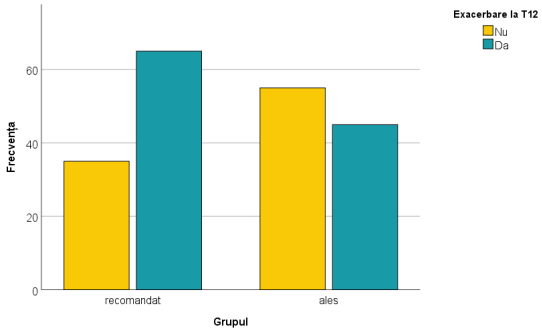

Figure 6.8. Exacerbation at T12

In the present analysis, the Breezhaler device was associated with the most user errors, starting at time T0 and ending at time T12, in subjects in both groups. The result also correlates with the higher number of exacerbations accounted for among users of this device, but also with a lower level of technical skill level documented in users of this inhaler device. Analysing the statistical relationship between the two groups analysed in terms of patients' technical skill levels, we find that patients in whom an exacerbation episode was documented had significantly lower technical skill levels compared to those in whom no exacerbation episodes were documented.

Group		Exacerbation	N		Standard deviation	p
Recommended	Technical skills	No	35	2,97	2,728	0,005
		Yes	65	1,65	1,824	
Chosen	Technical skills	No	55	2,07	2,276	0,013
		Yes	45	1,56	2,095	

Table 6.15. Technical skill level and exacerbation

In the present analysis, we found that those who stopped inhaler treatment at T12 had significantly lower mean technical skills compared to subjects who were on treatment at the end of the follow-up period.

Technical skills	Treatment at T12	N	Media	Standard deviation	p
	No	45	1,60	1,827	0,035
	Yes	55	2,53	2,501	

Table 6.17. T12 treatment adherence and technical skill level

The results obtained on the link between age and exacerbation are in line with already published evidence on this issue. Thus, most exacerbations were counted in older patients and the fewest in younger patients.

Analyzing the statistical data from both groups, we found a statistically significant association between smoking cessation and exacerbations. Further more, in the recommended group, of those who quit smoking only 28.6% had exacerbations, and of those who continued smoking, 94.6% had exacerbations. In the selected group, the situation is roughly similar for exacerbations in smokers and non-smokers. Of those who quit smoking, only 16.7% had exacerbations, and of those who continued smoking, 57.1% had exacerbations. In both groups, patients who had exacerbations had a significantly lower level of technical skills compared to patients who did not have exacerbations.

Compared to patients with hypertensionand DZ, the overall adherence to inhaled treatment of patients with Copd was low in both groups. Only 55% in the recommended group and 56% in the chosen group were still taking treatment at T12. The results, being consistent with the data obtained by most studies that have focused on analysing adherence to inhaler treatment.

			Treatment at T12		Total
			Nu	Da	
Group	Recommended	Frecvența	45	55	100
		% din Grupul	45,0%	55,0%	100,0%
	Chosen	Frecvența	44	56	100
		% din Grupul	44,0%	56,0%	100,0%
Total		Frecvența	89	111	200
		% din Grupul	44,5%	55,5%	100,0%

χ^2=0,02; df=1; p=0,887

Tabel 6.28. Treatment adherence in T12

Smoking cessation showed a significant decrease at T12 compared to T0. The decrease in our analysis ranked well above most of the published smoking cessation data. As the percentage of those who quit smoking was approximately similar in the two groups, it is clear that patient involvement in the inhaler device selection process did not influence smoking cessation, but other reasons did. We concluded that the relationship the investigating physician developed with patients during the study, together with the audio-video materials made available to patients, in which the benefits of smoking cessation in Copd patients were presented, played a central role in obtaining these results.

In both groups analysed, there was a significant percentage of patients who requested a return to the original device and therefore to the original treatment (ICS+LABA), although the FEV1 and CAT values measured during the study showed positive developments.

			CSI+LABA - Inițially		Total
			No	Yes	
Group	Recommended	Frecvența	68	32	100
		% din Grupul	68,0%	32,0%	100,0%
	Chosen	Frecvența	72	28	100
		% din Grupul	72,0%	28,0%	100,0%
Total		Frecvența	140	60	200
		% din Grupul	70,0%	30,0%	100,0%

χ^2=0,38; df=1; p=0,537

Table 6.35. Patients who have requested a return to the original device and treatment

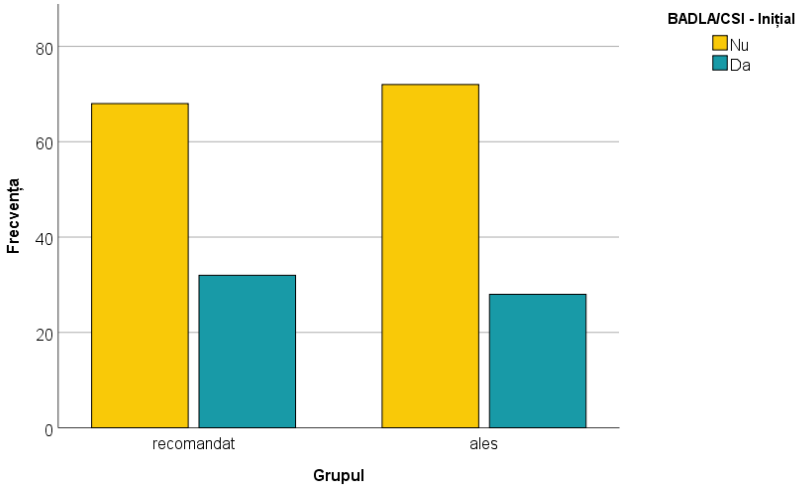

Figure 6.12. Patients requesting return to original device and treatment

Discussions

Choosing the most effective therapeutic formulation for each stage of Copd disease is a fairly easy task for physicians thanks to the Gold diagnostic and treatment guidelines (8), but choosing the "most appropriate" inhaler device for each individual patient is a difficult task and is an important structural element for controlling respiratory symptoms in Copd and especially for preventing exacerbation episodes (2,4,37). The efficacy of inhalation therapy can be dramatically altered by patient preference for a particular drug or inhaler device if the inhalation technique is not correct (38). The debate about what is more important between "drug and device" can be sliced by a wrong, partially correct or correct inhalation technique, and this can only be improved by prescribing inhalation devices according to patient preference, depending on patients' understanding of the correct inhalation technique and the level of patients' technical skills.

Many publications suggest that the benefits of Copd treatment are directly related to the correct use of inhaler devices, which is also demonstrated by the results obtained in the present analysis through the two studies (1,19,39), once again settling the dispute as to which is more important: the drug or the inhaler device. The correct inhalation technique depends on many aspects, but the most important element is the inhaler itself (26,40).

More and more published evidence is emerging on the need to select the inhaler device according to patients' realities and especially according to their understanding. The results of the present analysis join the little data already published on Copd patients' preference for a particular inhaler device, an attitude that has contributed significantly to

improving the frequency of inhaler device misuse and reducing the frequency of exacerbation episodes. The results strongly highlight the benefit of patient involvement in the inhaler device selection process and patient preference for a particular inhaler device (41-43). As expected, the present analysis identified that there is a significant difference between patient 'choice' and physician 'choice' of the 'most suitable' inhaler device, which has a significant impact in increasingfrequency of errors in the use of inhaler devices. Thus, it is becoming increasingly clear that a change of approach is needed in the way inhalers are recommended/chosen, and patient empowerment in the process of inhaler device selection opens the way for future research and, in all likelihood, this new approach will become part of current medical practice.

As stated in articles published in 2023 in Healthcare and the Romanian Journal of Internal Medicine (1,19), a correct inhalation technique is dependent on many factors, including: associated chronic diseases, neurological, rheumatological, orthopedic, psychiatric diseases, alcohol dependence, smoking, consumption of hallucinogenic substances and last but not least family and relatives.

Building on Darba et al's (44) idea of patient based selection of inhaler devices, we included in the present analysis the "element" of empowering patients by involving them in the inhaler device selection process and found that, in the group where the device was chosen by patients, a significant percentage of patients considered the Genuair device to be the most suitable for them, compared to the recommendation group, where patients' "choice" for a particular inhaler device was somewhat homogeneous.

Building on Miravitlles (41) analysis which revealed that more than 80% of prescribing clinicians of drugs administered with inhaler devices were aware of the importance of the inhaler device selection process, but continued their routine practice giving priority to bronhodilators over inhaler devices, in the present analysis, we put the patient in the position of the inhaler device decision maker and compared the results obtained with already published evidence in which the patient received the device without being consulted on inhaler device preference.

During the study, we revealed a very important point, which we did not find in many published studies, namely: the fewer the number of errors in the use of inhaler devices at T0, the lower the chances of the patient having an exacerbation episode. In my view, this result can be a strength and a starting point for future research, given that the thorough education of patients on the correct way to use inhalers is done on the "fast track" or even left to pharmacists or nurses, this aspect favours the development of a wrong or

partially correct inhaler technique, thus leaving the way open to errors in the use of inhaler devices and thus exacerbations.

The results in Bonini and Usmani's paper (45) correlate very well with the results of Study 1 in the present paper, and we can conclude that the establishment of regular intervals of 3-6 months for monitoring Copd patients could be a stepping stone in opening a new approach that would have as a main objective to increase adherence to inhalation treatment among Copd patients. Patient education, coupled with acceptance of the diagnosis of Copd and knowledge of disease progression, such as disease response to pharmacological and non-pharmacological treatment, confidence in treatment, effective patient-clinician interaction are essential elements for optimal treatment adherence among Copd patients.

The psychological component should not be neglected in patients with chronic diseases and with a high degree of dependence on caregivers and family. Anxiety-depressive disorders, frequently found among patients with Copd, play a major role in the neglect of inhaler treatment, thus opening an unproductive spiral with escalating respiratory disease symptoms and associated comorbidities. Thus, as DiMatteo (46) argues, it is very likely that feelings of helplessness, increased dependence on family and caregivers, and dissatisfaction with low quality of life are factors that reduce adherence to inhaler therapy.

Conclusions and personal contributions

The first objective of the present research was to identify "(O1) Copd patients' behaviour when they are empowered and involved in the process of inhaler device selection and by default inhaler treatment". This aspect has been pursued and achieved in both studies, and the results obtained, besides being remarkable, open the way for future research on much larger groups of patients, approaching Copd patients from the perspective of their empowerment and involvement in the inhaler device selection process.

Analyzing the results obtained in both newly diagnosed patients with Copd and patients already known to have Copd through the lens of the tracked items - inhaler device misuse, exacerbation episodes, adherence to inhaler treatment, role of education, role of technical skills, and smoking cessation - we find that involving patients in the inhaler device selection process radically altered the behavior of Copd patients when involved in the process of selecting which inhaler device to use.

The positive impact that this "atypical" approach of involving patients in the inhaler device selection process has had can be seen in the chapter on the results of the two studies (Study 1 and Study 2), where inhaler device misuse and exacerbation episodes were significantly lower and well below the average published evidence of inhaler device misuse in the groups where the inhaler device was chosen by the patients and not recommended by the physician. All these results can be seen in detail in the result chapters and thus validate objective number two: "(O2) Evolution of inhaler device misuse, exacerbations, adherence to inhaler treatment and smoking cessation in patients involved in the inhaler device selection process".

The third major objective proposed in this research: "(O3) The role of education level and technical skill level in increasing adherence to inhaler therapy, reducing the number of inhaler device misuse, reducing exacerbation rates and improving smoking habit" has been achieved and explored, both from the perspective of patient empowerment in the inhaler device selection process and from the classical and widely used perspective of physician recommendation of the inhaler device.

In terms of the level of technical skills as measured by a standardised test, the present research through the two component studies established that: patients with lower levels of technical skills made more mistakes in the use of inhaler devices compared to patients with higher levels of technical skills - Study 1. The situation is similar when it comes to exacerbation episodes and adherence to inhaler treatment - Study 2. Patients with lower levels of technical skill had more exacerbations and were less adherent to inhaler treatment compared to subjects with higher levels of technical skill. Contrary to expectations and in contrast to the positive results obtained on items inhaler device misuse and exacerbations, although patients with higher levels of technical skills were more adherent to inhaler treatment compared to those with lower levels, patient involvement in the inhaler device selection process did not alter overall adherence to treatment. Analysing also the implications of education level on overall adherence to treatment, the results obtained in the present research reinforce previously published results, which established that patients with a lower level of education tended to be more likely to drop out of inhaler treatment compared to patients with a higher level of education.

The present research has set as its fourth general objective: "(O4) To identify patients' preference for a particular inhaler device when placed in the position of inhaler device decision maker". In Study 2, patients who were put in the position of choosing/deciding for themselves the type of inhaler device they wanted to use during the

study, more than half opted for the Genuair device. Comparing the results of inhaler device misuse and exacerbation episodes in Genuair users, in the group where the device was recommended by the doctor versus the group where the device was chosen/decided by the patients, one can easily observe significantly better percentages among patients who chose/decided their inhaler device themselves.

Also in the steps conducted to identify patients' preference for a particular inhaler device, the results of the two studies revealed that the Genuair inhaler device was associated with the fewest misuses and the fewest exacerbation episodes, while the Breezhaler inhaler device was associated with the most misuses and the most exacerbation episodes.

Last but not least, in the present research, we were interested in: "(O5) The impact of assessments at regular intervals and regular re-training of patients on the correct way of using inhaler devices on: inhaler device misuse, exacerbations, treatment adherence and smoking habit". In many published studies on hypertensionand DZ, the authors found that these categories of patients are much more adherent to treatment, and the only reasons identified for this better adherence were assessments at 3-6 month intervals. In light of this evidence in patients with hypertension and DZ, I was interested to find out whether assessments at shorter intervals also benefit patients with Copd. To achieve this goal, we created the design of Study 1, where the device was chosen by patients, they were assessed at T6 and T12, and patients where the inhaler device was recommended byby the doctor, they were only assessed at T12. The item tracked was inhaler misuse. Analysing the results of inhaler misuse at T6, among subjects in the groups, we find that they are significantly higher compared to T12, and the intervention at T6, when the inhaler technique was corrected, resulted in a significant percentage of 15.1% not making inhaler misuse at T12. The results obtained regarding assessments at shorter time intervals had a significant impact on inhaler misuse and exacerbation episodes, thus being in indirect agreement with data obtained in groups of patients with hypertension and DZ, who had better adherence to treatment due to more frequent monitoring.

Strengths, particularities and originality of the study

1. *Involving patients in the inhaler device selection process.*

One of the main features and originality of this work is the empowerment and involvement of patients in the inhaler device selection process. Basically, the patient analysed the inhaler device options and chose/decided which inhaler device is "best suited" for him/her. In this context, we followed the behaviour of patients with Copd, both newly diagnosed and those who were already known to have the disease and were undergoing inhaler treatment.

2. *Comparison of patients who chose their own inhaler device with patients whose inhaler device was recommended by their doctor.*

Another peculiarity and originality is that we compared patients who chose/decided their own inhaler device with patients who received a recommendation to use a specific inhaler device without being consulted on preference and we followed the behaviour and impact that involvement in inhaler device selection had on the four items followed: inhaler device misuse, exacerbation episodes, adherence to inhaler treatment and smoking habit evolution.

3. *Identify the difference between patient ”choice” and physician ”choice” of the ”most suitable” inhaler device.*

Among the justifying reasons we had when thinking about the subject of this research was the existing evidence on the high number of mistakes in the use of inhaler devices, with the direct consequence they have in the occurrence of exacerbations, to which was associated the observation of daily practice, in which pulmonologists recommend inhaler devices, without taking into account the characteristics of patients. Inevitably, I wondered: what is the difference in 'opinion' between doctor and patient on the 'most suitable' inhaler device?

4. *Measuring the level of technical skills using a standardised test.*

We identified a limited number of studies that assessed IQ and the impact that IQ level has among patients with Asthma and Copd in terms of inhaler device use, but found no evidence on the impact of the level of Technical Skills/Abilities in patients with Asthma and Copd. The standardised test measuring the level of Technical Skills/Aptitudes is a test combining IQ and the ability to put things into practice, and the correct use of inhaler devices depends very much on the ability to understand the correct handling of the inhaler device and put it into practice, materialised by correct use and impeccable inhaler technique.

5. *One investigating physician*

In the majority of studies that have tracked inhaler device misuse, exacerbation episodes, inhaler treatment adherence, and smoking cessation, multiple examining physicians were involved in the relationship with patients, and this can be interpreted as a "major limitation" because of the variability in the relationships each physician developed with patients over the course of the studies. Also under the heading of "great limitation" in those studies, it can be added that the patients included in these studies received different training on the correct use of inhaler devices, inhaler technique and were subject to variable assessment with a high degree of subjectivity, of errors in the use of inhaler devices, due to the involvement of several assessors. In the present study, in addition to the four particular and original strengths, the involvement of a single investigating physician in the whole process of: identification, selection, introduction, monitoring, assessment and management of exacerbation episodes eliminated variability in the multi-individual relationships between physicians and patients and greatly reduced subjectivism in assessing correct inhaler device use and practicing correct inhaler technique.

Future prospects

Further research from the perspective of patient empowerment in the inhaler device selection process and its impact on the four items analysed, over a period of 24-36 months.

Improve communication between doctor and patient in the inhaler device selection process, given the outcome of Study 2, which showed significant differences between the doctor's "opinion" and the patient's "opinion" on the "most suitable" inhaler device.

Physicians prescribing inhaler devices, in addition to patients' preferences for a particular inhaler device, should also take into account: the importance of inhaler devices and not only drugs, patients' age, associated comorbidities, their understanding of correct handling of inhaler devices and their understanding of inhaler technique.

In addition to the training provided by medical staff, doctors should also consider introducing modern patient education and re-education techniques - audio-video clips, written information materials (other than standard drug leaflets), inhaler handling workshops, etc. - into daily medical practice on: the correct way to handle inhalers, correct inhaler technique, why patients should take their inhaler treatment daily and why they should quit smoking.

Study limitations

1. Small number of inhalation devices - At the start of the study, but also during the course of the study, the three devices analysed: Genuair, Respimat and Breezhaler were the only devices approved in Romania and compensated 50% for the treatment of Copd risk group B and C, with which the combination of LAMA+LABA drugs could be administered, as recommended by the Gold diagnostic and treatment guidelines.
2. Monitoring period of 12 months;
3. Geographical area limited to four counties - Galați, Brăila, Tulcea and Vrancea;
4. Study conducted in a single health institution and health system;
5. Exclusion of a broad category of pathologies that are frequently associated with Bpoc patients;
6. My subjectivity about mishandling and wrong inhalation technique, even though I used checklists (Appendix 5).

Endnote

1. The study was conducted in accordance with the principles set out in the Helsinki Declaration and has the opinion of the Medical Council of the Military Emergency Hospital "Dr. Aristide Serfioti" Galati - RCM327/M1-544.
2. The full database and statistical reports are available on request.

List of scientific papers published as part of doctoral research:

1. COPD Patients' Behaviour When Involved in the Choice of Inhaler Device, *Healthcare* 2023, *11*(11), 1606; https://doi.org/10.3390/healthcare11111606, Received: 27 March 2023 / Revised: 25 May 2023/Accepted: 28 May 2023/Published: 30 May 2023. Impact factor 3.160.
   Paper prepared from personal contributions: Chapter 6. Study 2.
2. The impact of technical skills and education on exacerbations, adherence to treatment and the choice of inhaler device in patients with Copd, Internal Medicine 2023 vol. XX, No. 1, www.srmi.ro,10.2478/inmed-2023-0236. https://sciendo.com/pdf/10.2478/inmed-2023-0236, Impact factor 1.9.
   Paper prepared from personal contributions: Chapter 6. Study 2.

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