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CLINICAL STUDY

Characteristics of COPD patients treated with single-inhaler triple therapy in real-life clinical practice

Lassan S[1], Keszegh J[2], Lassanova M[3]

Institute of Pharmacology and Clinical Pharmacology, Faculty of Medicine, Comenius University, Bratislava. **monika.lassanova@fmed.uniba.sk**

ABSTRACT

BACKGROUND: Inflammation associated with chronic obstructive pulmonary disease (COPD) causes narrowing of the airways and destruction of the lung parenchyma. The triple therapy (ICS+LABA+LAMA) may improve lung function, patient-reported outcomes, and exacerbation risk in a specified subset of GOLD group D patients. A better understanding of the factors leading to the single-inhaler triple therapy (SITT) prescription in real-life scenario is still an unmet need.

METHODS: We assessed the characteristics of 838 GOLD group D patients treated with SITT and way of how those patients had been routinely managed before in their outpatient settings. The cross-sectional observational survey was based on an assessment of routine practice patterns and retrospective collection of anonymous medical data.

RESULTS: Severe and very severe forms of airflow obstruction were experienced by 52 % and 34 % of patients, respectively. The mean number of exacerbations during the 12-month period antecedent to SITT prescription was 2.01. Before starting SITT, various combinations of COPD medications were prescribed: LABA (95 %), followed by ICS and LAMA. Compared to patients with 0-1 exacerbation, the patients with ≥2 exacerbations had higher levels of mMRC and CAT scores (2.47 vs 2.69 and 16.02 vs 19.31, respectively, both $p < 0.001$), worse treatment adherence and higher need for rescue medication (4.7 vs 3.9 units, $p = 0.0011$). The driver for switching the treatment to SITT was an expected improvement in lung function followed by reduction in dyspnoea and number of exacerbations.

CONCLUSIONS: Despite current treatment, the burden of COPD remains significant in GOLD group D patients. The lung function, symptoms burden and exacerbation history are among the most important factors involved in the decision for stepping up to SITT with potential roles of both bronchodilator and anti-inflammatory components *(Tab. 2, Fig. 9, Ref. 66)*. Text in PDF *www.elis.sk*

KEY WORDS: chronic obstructive pulmonary disease, observational retrospective survey, real-life setting, single-inhaler triple therapy, factors for treatment escalation.

Introduction

Chronic obstructive pulmonary disease (COPD) is a progressive and debilitating respiratory disease. The chronic airflow limitation in COPD is caused by a mixture of small airways disease and parenchymal destruction (emphysema). Chronic inflammation causes structural changes, narrowing of the small airways and destruction of the lung parenchyma, which leads to the loss of alveolar attachments to the small airways and decreases the lung elastic recoil (1). Nowadays, COPD is highly prevalent worldwide (2) and represents the fourth leading cause of death (3). Despite considerable progress in the field of prevention and treatment, COPD continues to pose a major public health challenge also in Slovakia. According to the data annually published by the National Centre for Health Information, more than 80 thousand patients suffering from COPD are registered at Slovak pulmonary outpatient clinics with an estimated prevalence of 1,500 per 100,000 (4).

Current pharmacological therapies have been shown to improve quality of life and symptoms and reduce exacerbations in patients with COPD. During recent decades, the number of pharmacological agents available for inhalation treatment of COPD has increased significantly (5). These became the cornerstone of therapy for chronic airway diseases. In contrast, the number of pharmacological classes present in treatment algorithms has not changed markedly (6) and the progress corresponded mostly to improvements in the pharmacokinetic profiles of molecules, design of new inhalation devices (7) and combination of different pharma-

[1]Department of Pneumology, Phthisiology and Functional Diagnostics, Slovak Medical University and Bratislava University Hospital, Bratislava, [2]CEEOR SK, s. r. o., Bratislava, and [3]Institute of Pharmacology and Clinical Pharmacology, Faculty of Medicine, Comenius University, Bratislava, Slovakia

Address for correspondence: M. Lassanova, MD, PhD, Institute of Pharmacology and Clinical Pharmacology, Faculty of Medicine, Comenius University, Sasinkova 4, SK-81108 Bratislava, Slovakia.
Phone: +421.905236107, Fax: +421.2.90119508

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cological classes within the same device (8). Despite advances in COPD therapy, various patient characteristics such as age, cognitive abilities, breathing pattern, airway diameter, disease severity, inspiratory flow including aerosol characteristics (inhaler device and inhaled drug characteristics), pharmacokinetics and pharmacodynamics have an impact on the optimal treatment outcomes (9). Patients must be properly and repeatedly instructed about the device handling and proper use because not all patients will perform in the correct way due to either cognitive or physical reasons, or both. When an inhaler device is not used properly, it affects lung deposition, which may lead to a lower efficacy and possibly increased chances of topical side effects. Another important issue represents the unsatisfactory level of adherence to COPD medication which worsens the clinical and economic outcomes (10).

Referring to the Global Initiative for Chronic Obstructive Lung Disease (GOLD) 2020 document (11), the step up in inhalation treatment to long-acting beta2 agonists (LABA) plus long-acting muscarinic antagonists (LAMA) plus inhaled corticosteroids (ICS) (triple therapy) can occur in form of various approaches (12). The triple inhalational therapy may improve lung function, patient-reported outcomes and exacerbation risk (13, 14, 15, 16, 17, 18). A recent systematic review showed the extent of improvements that can be achieved with inhaled triple therapy, namely in form of an increase in trough forced expiratory volume (FEV1) ranging from not significant (NS) to 147 ml, improvement in health status using the St. George's Respiratory Questionnaire (SGRQ) from NS to 8.8 points, and reduction in exacerbation risk-risk ratio (RR) from NS to 0.59 for all exacerbations versus single or double therapies with a variability in the response, depending on the specific combination, and comparison group. The proportion of adverse effects was similar between study groups, the exception being the increase in pneumonia for some ICS-containing groups (19). On the other side, some trials utilizing triple combinations in comparison to LAMA, LAMA plus LABA or LABA plus ICS have reported a mortality reduction with triple therapy (20, 21, 22). Especially patients with a high symptom burden, severe-to-very severe airflow obstruction and history of frequent or severe exacerbations are likely to benefit from these effects.

In one study, the single-inhaler triple therapy (SITT) presumably outperforms the three individual components given via two separate inhalers (23). The additional benefit of a fixed triple LABA/LAMA/ICS combination is related to convenience for the patient, and possibly improved compliance. Moreover, the simultaneous delivery to the target organ of three agents with different mechanisms of action may contribute to synergistic interactions leading to improved efficacy. In addition, the triple therapy might improve physical activity levels through bronchodilation or reduced breathlessness, and thereby improve respiratory muscle strength and impact upon disease progression (24). The initiation of triple therapy may be justified at least after a COPD exacerbation because it can reduce health care costs and subsequent exacerbation rate as compared with late initiation (25).

Based on the available efficacy and safety data, the GOLD 2019-2020 recommendations suggest escalation to triple therapy should the response to initial dual combination treatment be not appropriate. The escalation to triple therapy should be undertaken if patients remain symptomatic despite LABA plus ICS treatment or continue to experience a high exacerbation frequency on LABA plus LAMA or LABA plus ICS combinations (11, 26). However, adding ICS to the treatment schedule is particularly successful in patients with blood eosinophils count higher than 100 cells/µl (11). Apart from the GOLD recommendations for COPD management, the majority of European countries have their own national guidelines which are often not updated in time and may differ from the current state of art. Moreover, respiratory physicians often do not adhere to the guidelines, which results in a significant gap in applying evidence to practice. For certain, numerous published papers show that adherence to the guidelines in the COPD management needs improvement. (27). An inadequate prescription may affect the eficacy/safety profile of drugs used to treat COPD while likely influencing treatment adherence triggered by the patient´s perception of limited benefit (28). The use of triple therapy exposes patients to a long-term use of ICS, which is already reported to be widely used in patients with GOLD A and B where it is not clinically indicated (29, 30, 31, 32, 33) except for patients with concomitant asthma. This can lead to appearance of known side effects associated with ICS, (34, 35, 36, 37), in particular pneumonia (38, 39, 40).

The GOLD Report indicates that there is a significant population of COPD patients belonging to the GOLD group D, who are appropriate candidates for inhaled triple therapy and are likely to profit from it. A better understanding of the factors that trigger the escalation to single-inhaler triple therapy (SITT) in real-life is an unmet need, and with respect to this fact, the aims of our observational survey were as follows: 1. to assess the characteristics of COPD patients currently under the treatment with SITT in a large cohort; 2. to assess how those patients were routinely managed prior to switching to SITT (pharmacological treatment, education and compliance monitoring, etc.) in order to identify and evaluate factors that influenced the treatment choice in a real-life scenario.

Methods

Data source

In contrast to many other European countries, in the Slovak republic, the care of patients suffering from COPD is almost exclusively in hands of physicians specialized in respiratory medicine (pulmonologists). The project utilized a data collection from a quality-controlled survey carried out within inpatient and outpatient respiratory clinics in Slovakia by gathering information from 65 Slovak pulmonologists. It can be stated that approximately 31 % of all practicing Slovak pulmonologists were involved in the survey.

No active involvement of patients was required and the survey was designed as an observational, cross-sectional, retrospective collection of anonymous data provided by participating physicians. In their introductory part, these data contained information on routine practice at the sites (e.g., treatment of COPD at individual stages, education about proper use of inhalers, etc.) while the clinical part contained information on patients´ clinical data and basic patients´ demographics, stratification according to GOLD

Tab. 1. DemoFig.ic data on group D patients whose treatment was switched to single-inhaler triple therapy (at the time of treatment change).

Characteristics	N	%	Mean	SD	95 % CI	Median	Min./Max.
Gender							
Men	583	69.57					
Women	255	30.43					
All	838	100					
Age (years)			67.1	9.1	66.5–67.7	68	33/91
Smoking status							
Smoker	289	34.49					
Ex-smoker	469	55.97					
Non-smoker	80	9.55					
Professional exposition to inhaled pollutants							
Yes, persisting	29	3.46					
Yes, past	201	23.99					
No	608	72.55					
Body-Mass-Index (BMI)			27.0	5.8	26.6–27.4	26.4	12.5/54.8
COPD duration			11	6.9	10.56–11.52	10	1/42
Completed education							
Elementary	135	16.11					
Practical	336	40.1					
High school	265	31.62					
University	47	5.61					
Unknown	55	6.65					
Pulmonary function tests							
FVC (L)			2.16	0.74	2.11–2.21	2.1	0.43/4.84
FEV1 (L)			1.08	0.4	1.06–1.11	1.00	0.23/2.77
FEV1/FVC			0.52	0.11	0.51–0.53	0.53	0.12/0.69
Mild airflow obstruction (FEV1 ≥ 80 % of predicted value)	3		0.3				
Moderate airflow obstruction (50 % ≤ FEV1 <80 % of predicted value)	112		13.35				
Severe airflow obstruction (30 % ≤ FEV1 <50 % of predicted value)	435		51.85				
Very severe airflow obstruction (FEV1 <30 % of predicted value)	289		34.45				
mMRC and CAT scores							
mMRC score			2.63	0.76	2.6–2.7	3	1/4
CAT score			18.59	6.25	18.03–19.15	18	1/38
Exacerbation history (exacerbations during previous year)							
All			2.01	1.01	1.94–2.08	2	0/5
0	53	6.32					
1	169	20.17					
2	404	48.21					
3	154	18.38					
4	44	5.25					
5 and more	14	1.67					
0–1 exacerbations	222	26.49					
≥ 2 exacerbations	616	73.51					
Hospital admissions (during previous year)							
Yes	361	43.12					
No	477	56.88					
Use of ATB (during previous year)							
Number of packages/12 months			2.91	1.83	2.73–3.09	3	0/12
Rescue medication use (during previous year)							
Number of packages/12 months			4.5	2.9	4.27–4.66	4	0/13
Co-morbidities							
Depression	101	12.05					
Diabetes	190	22.67					
Cancer	52	6.21					
Osteoporosis	67	8					
Cardiovascular	537	64.08					

Values were mean ± SD unless otherwise specified.
FEV1 – forced expiratory volume in the first second; FVC – forced vital capacity; ATB – antibiotic

2018 (most recent and widely used version at the time of the survey) and patients´ compliance/adherence monitoring conducted by pulmonary specialists. This section also included questions on information on the characteristics associated with the underlying disease (COPD duration, exacerbation history, hospital admissions, mMRC dyspnoea and COPD Assessment Test scores, lung functions, rescue medication use, etc.), relevant co-morbidities likely to influence the course of COPD and baseline medication prior to switching to SITT.

The collected data and their format rendered the identification of patients impossible. After completing the survey, the data were centrally assessed for consistency. Logical data discrepancies were discussed with the respondents.

Design and patients

Cross-sectional observational survey is based on the assessment of routine practice patterns of the participating physicians and retrospective collection of anonymous medical data. The survey contained data from physicians on the population of COPD patients in their outpatient settings. The survey itself was designed as an observational, retrospective collection of anonymous data not meeting the criteria for biomedical research, as defined in the national Act No. 576/2004 Coll., as amended. The data collection was carried out in two waves, namely in periods of May to September 2018 and March to June 2019. Upon completion of the basic questionnaire intended for evaluation of general COPD management patterns at individual sites, the participating physicians were asked to report anonymous data of 10 consecutive patients who were receiving SITT at the time. In total, data from 943 patients were recorded while 838 GOLD group D patients with COPD were included to the final analysis.

The analysis included patients ≥40 years of age at initial date of COPD diagnosis with spirometry data supportive of the COPD diagnosis (FEV1/forced vital capacity <0.7). GOLD 2018 group classification was utilized in this survey coupled with spirometric data. Patients were classified into GOLD A–D groups based on CAT or mMRC scores and baseline exacerbation frequency 12 months before assigning the patient to the appropriate group. COPD medication was determined in groups A–D. COPD baseline therapy was defined as pharmacological therapy prescribed at least 3 months prior to switching to SITT. Interviews with physicians were also performed to explore additional issues about treatment and adherence to the GOLD guidelines. The assessment of treatment adherence covered the period of the last 12 months. The adherence to therapy was assessed with the help of medical records containing electronic or paper-based prescription entries and evaluation by the participating physician.

Analysis of data

In the first step, the data were analysed for the entire population of managed COPD patients by participating physicians. Subsequently, the data obtained from the GOLD group D patients with prescribed SITT were furthermore deeply processed. Summaries were produced for all characteristics as at the day of data collection.

The treatment marked as baseline therapy was defined as a sum of inhalation therapies prescribed at least 3 months prior to the first commencement of SITT. Based on electronic or paper-based prescription records, we collected data on brand/commercial name of inhaler(s) used.

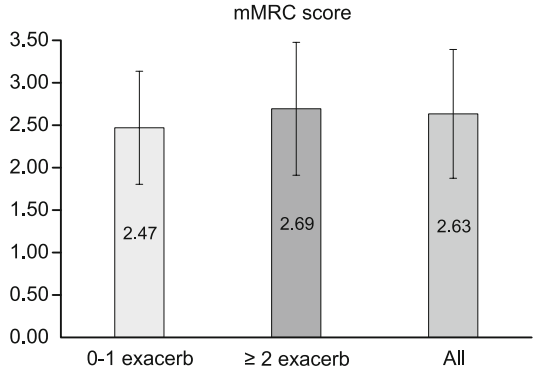
Lung function limitation, mMRC and/or COPD Assessment Test were calculated during the year prior to and at the date of switching to SITT. The exacerbation history referred to the corresponding 12 months.

Descriptive statistics for baseline data were presented as percentage or mean and SD. When the distribution of continuous data was not normal, the median (minimum–maximum) was used instead. To conduct statistical inference in key explanatory variables of interest, we used the Mann–Whitney test where the data were obtained from an arbitrary scale, and central estimates of group were compared. Frequency counts were compared by means of Fisher´s exact test. Data management and statistical analyses were performed using IBM-SPSS Statistics software.

Results

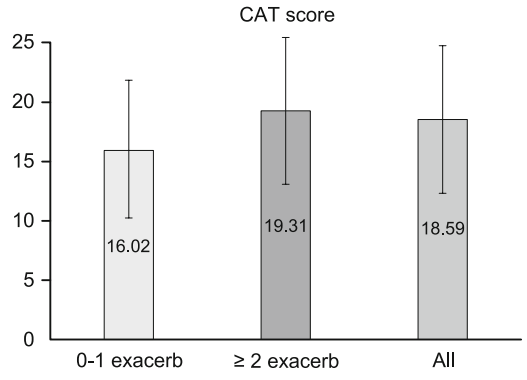
Patients from target population

On average, the participating physicians followed up approximately 1,830 patients (Median: 1,305 patients, Maximum: 10,000 patients) of whom 32 % suffered from COPD. One third of the pulmonologists took care of more than 600 COPD patients. The highest proportion of COPD patients were in GOLD Group B (48 %), while GOLD group D patients represented just approximately 15 %. GOLD A and C groups accounted for approximately 19 % and 18 % patients, respectively. Since triple therapy is expected to be primarily used in patients meeting the GOLD group D criteria,



mMRC score	N	Mean	SD	95% CI		Median	Min	Max
0-1 exacerb	199	2.47	0.67	2.4	2.6	2	1	4
≥ 2 exacerb	543	2.69	0.78	2.6	2.8	3	1	4
All	742	2.63	0.76	2.6	2.7	2	1	4

Fig. 1. The mMRC score in patients with no or single exacerbation compared with patients with ≥ 2 exacerbations during the year prior to switching to single-inhaler triple therapy. p < 0.001 for the difference between patients with ≥ 2 exacerbations during the 12-month period prior to fixed triple therapy prescription, and patients with no or single exacerbation.



CAT score	N	Mean	SD	95% CI		Median	Min	Max
0-1 exacerb	106	16.02	5.75	14.93	17.11	15	0	36
≥ 2 exacerb	377	19.31	6.24	18.68	19.94	17	0	38
All	483	18.59	6.25	18.03	19.15	18	0	38

Fig. 2. CAT score in patients with no or single exacerbation compared with patients with ≥ 2 exacerbations during the year prior to switching to single-inhaler triple therapy. p < 0.001 for the difference between patients with ≥ 2 exacerbations within the 12-month period prior to fixed triple therapy prescription, and patients with no or single exacerbation.

we were focused on the group D of patients whose treatment has been changed to SITT following the decision of their physician.

The demographic data on 838 of these patients are shown in Table 1. A typical COPD group D patient was a 60–80-year-old male with a lower level of education who has been suffering from COPD for approximately 11 years. The predominance of men over women in this disease group was obvious. Patients aged over 80 years were relatively rare. The GOLD group D patient population was primarily associated with smoking. Only a small proportion of patients have never smoked. Occupational exposure was reported in almost one quarter of all patients, representing an important causative factor after smoking. The average GOLD group D patient was slightly overweight, and in this respect, the characteristic did not differ from the national average (4). One third of these patients maintained their weight within the normal range. After excluding patients who were evidently not meeting the criteria for GOLD group D, the analysis revealed a mean FVC of 2.16 L and a FEV1 of 1.08 L. More than a half of group D patients suffered from severe airflow obstruction (30 % ≤ FEV1 < 50 % of predicted value). There were no significant differences among patients with 0–1 or ≥ 2 reported COPD exacerbations during the previous year.

Majority of the GOLD group D patients had breathing problems even during normal walking (mMRC score ≥ 2). Indeed, the largest group of patients had the mMRC score of "3". A proportion of the participating pulmonologists (42 %) did not use the COPD Assessment Test (CAT). When CAT was used, a vast majority of patients achieved scores > 10, i.e., the disease had a significant burden on patients´ lives. In patients with ≥ 2 exacerbations within the period of 12 months prior to SITT prescription, the mMRC and CAT scores were higher than those in patients with no or single exacerbation (2.47 vs 2.69 or 16.02, p < 0.001 vs 19.31, respectively, p < 0.001) (Figs 1 and 2).

About 41 % of the participating physicians declared that they endeavour to educate patients about the proper use of inhalers at each visit; 31 % of them mentioned that they tried to educate patients twice a year, which however, may be related to the frequency of controls at pulmonologists' offices. In any case, majority of participating pulmonologists (95 %) answered that they endeavoured to educate patients regularly and continuously at least once a year (Fig. 3).

The highest frequency of verification of patient´s compliance and adherence to treatment was that done at each visit (58 %). As with the case of education on proper use of the inhaler, nearly all physicians reported checking patients' compliance regularly at least once a year (Fig. 4).

Management of GOLD group D patients

Before starting SITT, the group D of patients used various combinations of COPD medications (Tab. 2). In regular treatment we most often found LABA (95 %), followed by ICS and LAMA. The use of PDE4 inhibitors and antileukotrienes was reported just occasionally (Fig. 5). With reference to data available on 448 patients, the most frequent pharmacological combinations before switching to SITT were various combinations forming multiple-inhaler triple therapy (MITT; i.e., containing ICS, LABA and LAMA) with or without methylxanthines (173 and 106 cases, respectively) and dual bronchodilator combinations (LABA plus LAMA) in 60 cases (Tab. 2). Based on interviews with participating pulmonologists, smaller proportions of COPD patients in other groups were similarly on MITT (1.97 % in group A, 11.93 % in group B and 23.97 % in group C as compared with 59.1 % in group D patients).

The adherence in the subgroup of patients with 2 and more COPD exacerbations

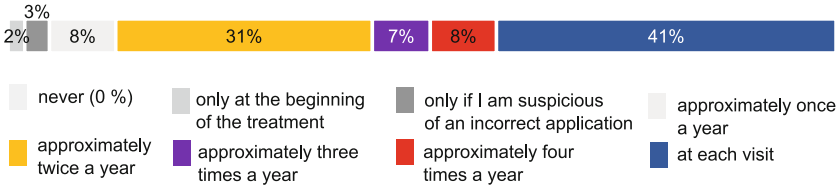


Fig. 3. Frequency of education about proper use of inhalers by pulmonologists.

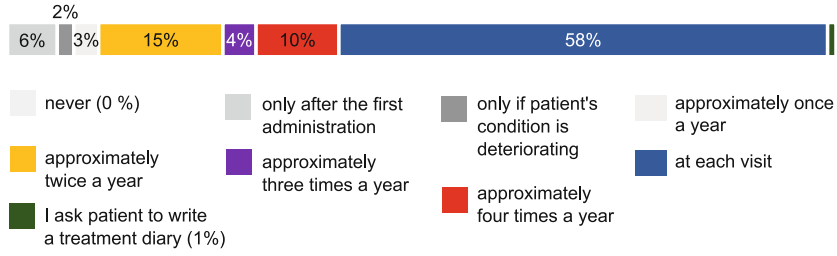


Fig. 4. Checking the frequency of patients´ compliance with treatment.

Tab. 2. Pharmacological treatment before switching to single-inhaler triple therapy (classes of pharmacological agents alone or in combinations except for fixed triple combinations); Data available on 448 subjects.

Treatment before switching to single-inhaler triple therapy	Number of patients (%)
ICS, LABA, LAMA	173 (38.6 %)
ICS, LABA, LAMA, methylxanthines	106 (23.6 %)
LABA, LAMA	60 (13.4 %)
ICS, LABA	22 (4.9 %)
LABA, LAMA, methylxanthines	19 (4.2 %)
ICS, LABA, LAMA, iPDE4	18 (4.0 %)
ICS, LABA, methylxanthines	13 (2.96 %)
ICS, LABA, LAMA, methylxanthines, iPDE4	6 (1.3 %)
LAMA	6 (1.3 %)
ICS	3 (0.7 %)
ICS, LABA, iPDE4	3 (0.7 %)
ICS, LABA, LAMA, montelukast	3 (0.7 %)
ICS, LAMA	2 (0.4 %)
ICS, LABA, LAMA, methylxanthines, Montelukast	2 (0.4 %)
ICS, LABA, montelukast	2 (0.4 %)
ICS, LABA, methylxanthines, montelukast	2 (0.4 %)
ICS, methylxanthines	1 (0.2 %)
LABA, LAMA, iPDE4	1 (0.2 %)
LABA, LAMA, methylxanthines, iPDE4	1 (0.2 %)
LABA	1 (0.2 %)
SAMA	1 (0.2 %)
ICS, LABA, LAMA, anti-IgE	1 (0.2 %)
LAMA, iPDE4	1 (0.2 %)
LABA, methylxanthines	1 (0.2 %)

iPDE4 – PDE4-inhibitors

during the 12-month period before starting SITT was significantly worse ($p < 0.001$) in comparison to the group of patients with no or single exacerbation (Fig. 6). Only 6 % of patients experienced no COPD exacerbation during the period of 12 months prior to switching the treatment. The mean number of exacerbations was 2.01. In the group of patients with 2 or more exacerbations, the proportion of subjects having undergone at least 1 hospital admission was significantly higher ($p < 0.001$) (Fig. 7).

Rescue medication is an integral part of the management of symptomatic COPD patients. As many as 95 % of patients received at least 1 unit of a rescue bronchodilator during the year prior to starting a fixed triple therapy. More than 40 % of patients were prescribed 3–4 inhalers per year, while 17 % of patients can be considered as heavy users with more than 6 packages per year. The mean number of rescue medication packages used by patients with 2 or more exacerbations was significantly higher ($p = 0.0011$) than in patients with no or single exacerbation (Fig. 8).

The most important driver for the switch to SITT was the expected improvement in lung function. Other important reasons include "expected reduction in dyspnoea" and "expected reduction in the number of exacerbations" (Fig. 9).

Discussion

Our findings show that COPD continues to pose a significant public health burden in Slovakia, where approximately one third of patients attending respiratory outpatient clinics suffer from this progressive difficult-to-treat disease. The most demanding group requiring healthcare and economic resources are patients with a severe course of the disease belonging to the GOLD group D, representing 15 % of all COPD patients. When compared to other cohorts, the proportion of group D patients appears to be lower, even when compared to distributions in general practice (41, 42, 43, 44).

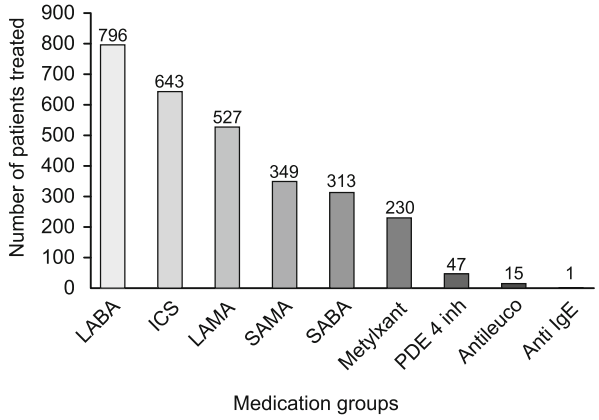


Fig. 5. Long-term treatment used over 3 months before switching to single-inhaler triple therapy.
LABA – long-acting beta-2-agonsits; LAMA – long-acting antimuscarinics; ICS - inhaled corticosteroids; SABA – short-acting beta-2-agonists; SAMA – short-acting antimuscarinics; Metylxant – methylxanthines; PDE 4 inh – PDE-4 inhibitors; Antileuco – antileukotrienes; Anti IgE – anti-IgE biological treatment.

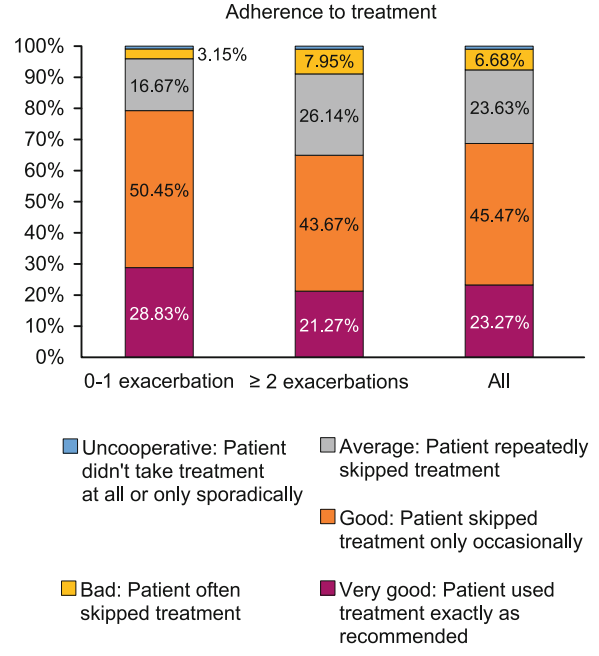


Fig. 6. Adherence to treatment before switching to single-inhaler triple therapy. $p < 0.001$ for the difference between patients with ≥ 2 exacerbations within the 12-month period prior to fixed triple therapy prescription, and patients with no or single exacerbation.

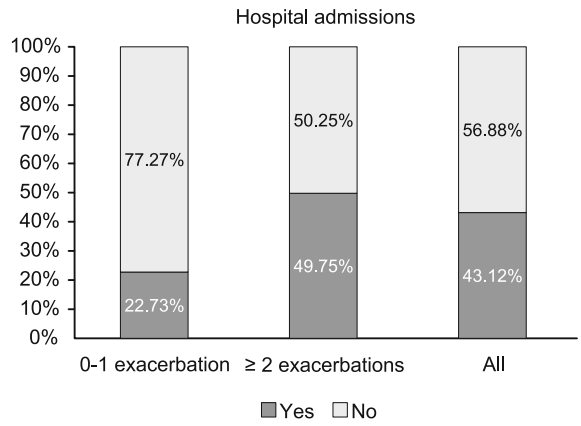


Fig. 7. Number of reported hospital admissions due to COPD during the year prior to switching to single-inhaler triple therapy. p <0.001 for the difference between patients with ≥ 2 exacerbations within the 12-month period prior to fixed triple therapy prescription, and patients with no or single exacerbation.

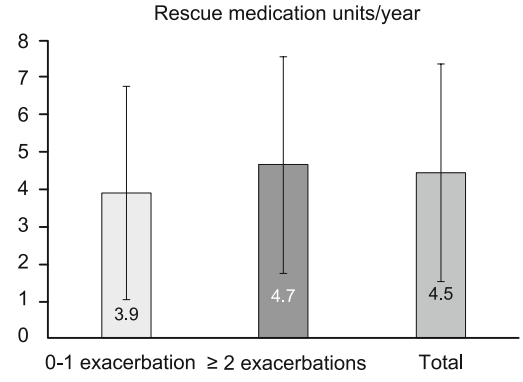


Fig. 8. Rescue medication consumption (units/year) during year prior to switching to single-inhaler triple therapy. p=0.0011 for the difference between patients with ≥2 exacerbations within the 12-month period prior to fixed triple therapy prescription, and patients with no or a single exacerbation.

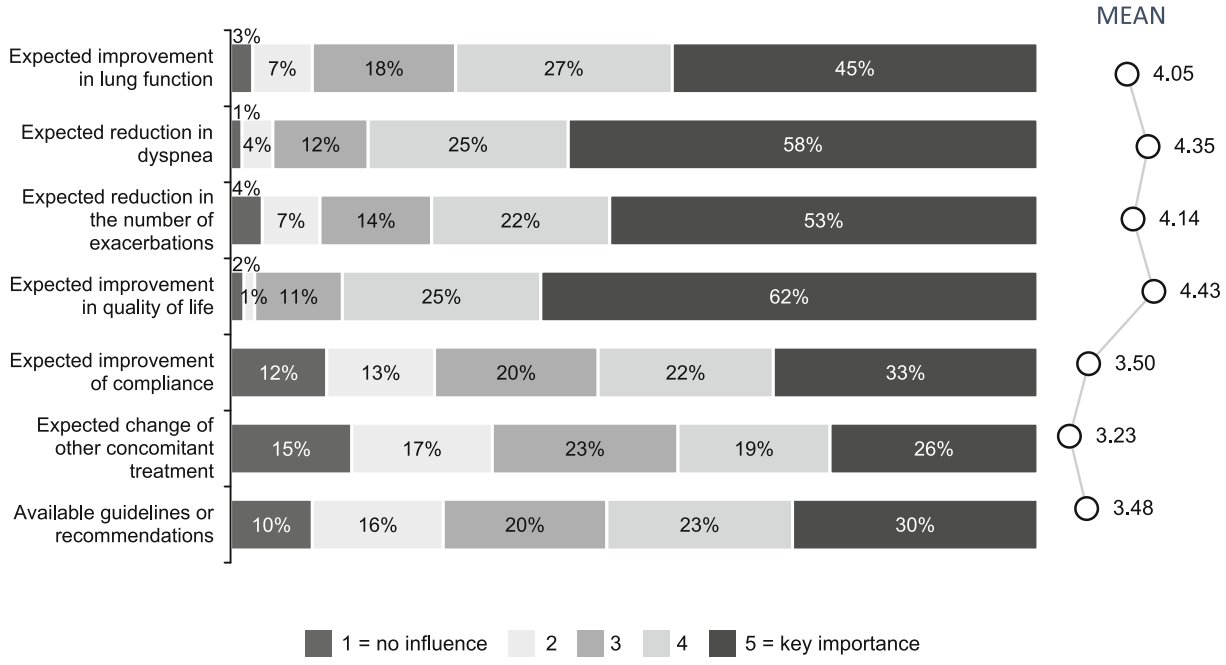


Fig. 9. Factors influencing the switch to single-inhaler triple therapy in group D patients.

Not surprisingly, the Slovak group D patients remain highly symptomatic, suffer mostly from severe or very severe airflow obstruction and repeated exacerbations despite the pulmonologist-driven comprehensive management comprising pharmacological therapy supported by efforts aimed at improvement in patients´ compliance to treatment, and education about proper use of prescribed inhalers. In terms of pharmacotherapy, basically every GOLD group D patient was on a single or dual long-acting bronchodilator treatment, with nearly 60 % of patients in this group already receiving MITT before the physician´s decision to switch to the SITT regimen. In line with other middle and eastern European countries (45), triple-inhaler therapy prescription is frequently present also in groups other than GOLD group D. However, the proportion of COPD patients treated in that fashion is lower, indicating at least a partial adherence to recommendations.

When we focused on the characteristics of patients indicated for SITT, the most prominent difference between those, who experienced 2 or more exacerbations during the last 12 months compared with those with no or single exacerbation, was poor adherence to the pharmacological treatment (65 % vs 79 % of patients with good or very good adherence to treatment) indicating either the need for placing stronger emphasis on adherence im-

provement at routine visits or switching to a simplified treatment regimen with a higher probability to be more likely accepted and adhered to by a patient. Although three quarters of the patients indicated for SITT reported 2 or more exacerbations and more than 40 percent of patients were hospitalised, which suggests frequent life-threatening events, the most important drivers for the treatment upgrade were expected improvement in lung functions and reduction in dyspnoea.

Based on this evidence, there is an ongoing unmet need to improve the treatment outcomes. Due to limited alternatives in the field of pharmacological treatment, the SITT with its proven benefits may be a suitable solution for at least some patients. We can hypothesize that SITT could help improve poor adherence to COPD medications which often resulted in frequent exacerbations, persistent symptoms, and poor economic outcomes (46). Before the introduction of SITT, a UK study showed that only 45.6 % of COPD patients had adequate adherence over 1 year based on the assessment of five classes of maintenance therapy (47). In general, patients receiving specific treatments for COPD demonstrate low persistence with more than a half of them stopping the treatment within 12 months (48). Another study reported 1-year non-adherence rates from 16.2 % with LAMA to 43.8 % with ICS, and even 42.8 % with inhalers combining ICS and LABA (49). A large longitudinal cohort study with more than 14,000 patients showed that patients with COPD had low adherence to and persistence with MITT in a real-world setting. Mean proportion of days covered for each single inhaler component was higher than the mean value observed with MITT (from 49 to 54 % for components at 12 months vs 14 % for complete multiple-inhaler triple therapy) (50). The nonadherence to treatment may also be, in part, a reflection of regimen complexity. The use of a single inhaler has been associated with improved adherence and persistence compared with using more than one inhaler (51). Reducing the number of inhalers may improve overall adherence to the intended triple therapy. In our survey, the level of adherence to pharmacologic agents was assessed individually by participating physicians and the reference period covered the last 12 months. A higher adherence of Slovak GOLD group D patients could be explained by frequent reviewing and adjusting of prescribed pharmacological agents and corresponding inhalers in a vulnerable group of patients with a severe course of the disease. Such interventions were performed by pulmonologists as the management of COPD patients in Slovakia is almost exclusively in the hands of respiratory outpatient clinics.

Numerous factors contribute to poor adherence among COPD patients, including treatment complexity, factors such as dosing frequency, number of medications, and ease of using the inhalers (52). In addition, many patients with COPD are older, have comorbidities, and receive polypharmacy (28, 53). Moreover, the need to learn and cope with different inhaler techniques may further lower the adherence (54). In accordance with this evidence, Slovak COPD group D patients tend in the same way to be older and suffer from comorbidities, especially cardiovascular diseases and diabetes. All these factors justify partly the time-consuming interventions targeted at optimization of pharmacological treatment, its proper use, and prevention of possible drug interactions.

Compared with LAMA/LABA or LABA/ICS, the treatment with SITT results in fewer moderate and severe exacerbations, more QALYs gain with a small incremental cost, especially in symptomatic patients with the history of exacerbations (55). Clinical studies with SITT consequently demonstrated significantly better clinical outcomes when compared with long-acting bronchodilators alone or in combination with inhaled corticosteroids (20, 56, 57, 58). Since the classes of drugs present in MITT have long been available for use in clinical practice, it is not surprising, that respiratory physicians tend to over-prescribe them to patients with insufficient control of the underlying disease. Combinations of ICS, LABA and LAMA were already prescribed for majority of patients with GOLD group D before switching to SITT. However, triple therapy in other GOLD groups was significantly less common. This apparent relation demonstrated that the disease control based on symptoms, respiratory function and exacerbation history are clearly associated with escalating combinations of inhalation treatments. Only a few studies assess the factors associated with treatment choices in COPD. Recently published analyses found out that the intensity of treatment using the total number of COPD medications is associated with exacerbation rate as well as with gas trapping and airway wall thickness on CT-scan (59). The importance of exacerbations as triggers of ICS prescription has been emphasized in several other studies (60, 61, 62). Many of these also identified associations between symptoms burden and treatment intensity (61, 63, 64). Drawing on our evidence, the most important reason for the switch to fixed triple therapy was the requested improvement in lung function. Other important reasons include reduction in dyspnoea and number of exacerbations. Available guidelines or recommendations were a much weaker reason for the treatment decision. In line with our findings, a recent French study demonstrated a similar association between multiple-inhaler maintenance treatment prescription and respiratory function, symptom burden as well as exacerbation history (65). The guidelines are largely not followed, and physicians make treatment choices more often depending on their clinical judgement where exacerbations appear to be the key reason for escalating the treatment (66). Although MITT combinations are likely to produce effects similar to SITT alternatives, there are several scientifically and clinically proven arguments supporting a simultaneous delivery of active substances to the lungs (24).

One limitation of this survey is that the studied sample cannot be considered fully representative of the Slovak population of patients with COPD for several reasons. Investigators were exclusively clinicians agreeing to participate instead of a random sample of the Slovak population of respiratory physicians. A considerable proportion of the cohort's population could not be fully studied since some of required data were not available. A more extensive characterization of patients could have revealed other potential determinants of treatment choice (e. g. blood eosinophils count). Finally, several factors other than scientific evidence and current guidelines could influence prescription decisions. These factors include, e.g., age, gender, comorbidities and co-treatments. Further analyses may help explain how these variables interact as determinants of switching the treatment to SITT.

Conclusion

This real-life cross-sectional survey of pulmonologists shows important results regarding the therapeutic and diagnostic approach to specialized care of COPD patients in Slovakia. We found out that a considerable proportion of COPD patients, especially those belonging to the GOLD group D, receive multiple maintenance treatments. MITT is common although its indications are limited to specific populations in recent guidelines. Understanding the reasons why and which COPD patients are prescribed specific drug combinations in form of triple therapy, may help improve the COPD management and clinical outcomes. For this reason, the identification of the profile of real-life patients who are prescribed specific classes of drugs becomes relevant in the effort to improve the strategy of provided therapy and quality of COPD patients´ lives. Due to persistency of unmet needs and lack of satisfactory control over COPD in a large number of patients, the switch to SITT may be a logical decision in escalation of treatment. Lung function, symptoms burden and exacerbation history are among the most important factors involved in the decision for stepping up therapy in COPD. The optimization of pharmacological treatment must be supported by placing greater emphasis on promoting adherence and proper use of inhalers.

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