Journal of Critical Reviews

ISSN- 2394-5125 Vol 7, Issue 13, 2020

COPD: SOME ASPECTS OF BASIC THERAPY IN REAL CLINICAL PRACTICE

Shchekina S.A.[1], Selezneva N.M.[2], Rebrushkin A.V.[3], Vidyashkin V.V.[4], Markunina M.V.[5], Bibikov V.P.[6]

[1]6th year student of the Medical Institute of the Federal State Budgetary Educational Institution of Higher Education "N. P. Ogarev's Mordovia State University", Saransk, Russia, 430005, Bol'shevistskaya Ulitsa, 68, 8(8342)351044, Email: s.a.shchekina@mail.ru

[2]Associate Professor, Candidate of Medical Sciences, Associate Professor of the Department of Hospital Therapy of the Medical Institute of the Federal State Budgetary Educational Institution of Higher Education "N. P. Ogarev's Mordovia State University", Saransk, Russia, 430005, Bol'shevistskaya Ulitsa, Email: nata_rm@mail.ru

[3]Clinical Resident of the Medical Institute of the Federal State Budgetary Educational Institution of Higher Education "N. P. Ogarev's Mordovia State University", Saransk, Russia, 430005, Bol'shevistskaya Ulitsa, 68, 8(8342)351044, Email: rarvik@yandex.ru

[4]6th year student of the Medical Institute of the Federal State Budgetary Educational Institution of Higher Education "N. P. Ogarev's Mordovia State University", Saransk, Russia, 430005, Bol'shevistskaya Ulitsa, 68, 8(8342)351044, Email: vvidyschkin@gmail.ru.

[5]5th year student of the Medical Institute of the Federal State Budgetary Educational Institution of Higher Education "N. P. Ogarev's Mordovia State University", Saransk, Russia, 430005, Bol'shevistskaya Ulitsa, 68, 8(8342)351044, Email: mutie@bk.ru

[6]6th year student of the Medical Institute of the Federal State Budgetary Educational Institution of Higher Education "N. P. Ogarev's Mordovia State University", Saransk, Russia, 430005, Bol'shevistskaya Ulitsa, 68, 8(8342)351044, Email: vladpulmo@mail.ru

Received: 22.06.2020 ***Revised: 14.07.2020*** ***Accepted: 06.08.2020***

Abstract.

Objective. To study the effect of tiotropium bromide / olodaterol on the effectiveness of therapy, the dynamics of some symptoms, quality of life, exercise tolerance in patients with COPD.

Materials and methods. The study included 27 male patients in remission, who were consulted within the framework of dispensary observation by a pulmonologist at the outpatient clinic of the Republican Clinical Hospital No. 4. To assess the condition of patients before and after therapy with tiotropium bromide/olodaterol, the CCQ clinical questionnaire for COPD, the CAT questionnaire, the mMRC dyspnea scale, the index of a smoker, the 6-minute walk test, spirometry and pulse oximetry data, the BODE index were used.

Results. During the ongoing therapy, patients noted a decrease in the severity of dyspnea on the mMRC scale by 0.5 ± 0.3 points, an increase in exercise tolerance (an increase in the distance covered in the 6-minute walk test by 14%). The BODE index in patients before treatment was 6.33 ± 0.64 points, the probability of 4-year survival in the study group of patients was 40 ± 8.48%. During the 14-day therapy, the BODE index decreased and amounted to 5.67 ± 0.53 points, the probability of 4-year survival increased by 13.3%.

Conclusion. The presented data of a clinical study show that the use of tiotropium bromide/olodaterol in patients with COPD reduces shortness of breath, as well as improves the quality and duration of patients' life.

Keywords: chronic obstructive pulmonary disease; tiotropium bromide/olodaterol; treatment; quality of life; COPD.

DOI: http://dx.doi.org/10.31838/jcr.07.13.641

INTRODUCTION

Chronic obstructive pulmonary disease (COPD) is a common disease characterized by respiratory symptoms and airflow restriction associated with bronchial and/or alveolar disorders, usually caused by a significant effect of damaging particles and gases [1].

According to a population-epidemiological study conducted in 12 regions of Russia (within the GARD program), with the participation of 7164 patients (average age – 42.4 years), the prevalence of COPD in Russia among people with respiratory symptoms reaches 21.8%, among persons from the general population – 15.3%. Thus, based on the data of expert assessments and research results, it can be assumed that at present in Russia the proportion of the population with a spirometrically confirmed COPD diagnosis is 15.3% of the total population of the country (about 20 million people) [4].

The disease has recently become the leading mortality factor in the world, causing significant economic and social damage [3]. Each year, about 3 million people die of COPD, which accounts for 5% of all causes of death [4]. The development of COPD can begin even before birth, since passive smoking during pregnancy is associated with an increased risk of COPD in adults, regardless of active and passive exposure to smoke in childhood, adolescence or adulthood [7]. In addition, people with respiratory failure in childhood are at increased risk of decreased lung function in adults. Although COPD is a chronic disease, a significant number of patients have exacerbations that require a change in treatment. Exacerbations are an important medical problem, for example, it is obvious that frequent severe exacerbations of COPD lead to adverse outcome of survival [16]. This determines the need of constant assessment and correction of ongoing therapy in patients with COPD.

The main goals of the treatment for COPD are: early detection and treatment of the disease, including prevention of severe exacerbations leading to hospitalization; prevention of disease progression, reduction of mortality from COPD and concomitant pathology, as well as reduction of clinical symptoms, improvements of exercise tolerance, improvement of the quality of life of patients with COPD [5]. The choice of a drug to start regular therapy for COPD depends on the

symptom load, at the same time long-acting bronchodilators – the combination of LAA/LABA or one of these drugs in monotherapy are indicated for all patients. Long-acting bronchodilators, anticholinergics (LAAs) and beta-2-agonists (LABA) form the basis of basic therapy for patients with COPD and should be used regularly [6].

However, at present, the majority of patients continue to use as the only therapy short-acting bronchodilators, which do not affect the mechanisms of hyperinflation, disease progression, the frequency of exacerbations, and, consequently, the prognosis [7].

The success of inhalation therapy depends not only on the properties of the drug, but also on the choice of its optimal delivery system. An ideal delivery device should provide a good deposition of the drug in the lungs, be reliable, easy enough to use, and affordable for use at any age and in severe disease stages. From this point of view, the inhaler of the Respimat system is a step forward in the field of inhalation therapy [8].

In the Russian Federation, only one inhaler of the Respimat system from the group of drugs LABA/LAA is officially registered – tiotropium bromide/olodaterol.

OBJECTIVE OF THE WORK

To study the effect of tiotropium bromide/olodaterol on the effectiveness of therapy in patients with COPD in real clinical practice.

RESEARCH OBJECTIVES

1. To study the dynamics of some stable COPD symptoms during treatment with the basic therapy drug of tiotropium bromide/olodaterol.
2. To assess the quality of life of stable COPD patients during treatment with the basic therapy drug of tiotropium bromide/olodaterol using a Clinical COPD Questionnaire (CCQ) and a CAT test (COPD Assessment Test).
3. To study exercise tolerance in stable COPD patients treated with the basic therapy drug of tiotropium bromide/olodaterol using the 6-minute walk test (6MWT, m).

MATERIALS AND METHODS

The study included 27 male patients in remission who were consulted within the framework of dispensary observation by a pulmonologist at the outpatient clinic of the Republican Clinical Hospital No. 4. The selection criteria for the study were the following: a diagnosis of COPD established at least 12 months before the visit of the patient; the presence of chronic symptoms (cough, sputum, shortness of breath); FEV1 indicator is less than 80% of the due one, but more than 30%, the presence of signs of fixed bronchial obstruction – TT is less than 0.7; stable course of COPD (stage of remission).

Thus, all patients met the criteria for moderate and severe COPD [13]. The study did not include patients with exacerbation of the disease, extremely severe stage of COPD, taking iGCS or GCS per os, severe concomitant diseases, as well as persons with acute diseases or exacerbations of other chronic diseases.

The informed consent of the patient during the study was required.

To relieve the symptoms of the disease, patients took the short-acting β2-agonist of Salbutamol or the combined drug of Berodual in the on-demand regimen.

On the first day, all patients completed the CCQ clinical COPD questionnaire (Table 1), the CAT questionnaire (Table 2) and the mMRC dyspnea scale (Table 3) on the first day, independently or with the help of a doctor.

Table 1. The Chronic Obstructive Pulmonary Disease Clinical Questionnaire (CCQ).

Please **circle** the number corresponding to the answer that best describes your physical and emotional well-being in **the past 7 days**. (Please mark only **one** answer for each question).							
On average, how often have you experienced in the last 7 days:	have not experienced at all	rarely	from time to time	sometimes	often	very often	almost constantly
1. Shortness of breath while at rest?	0	1	2	3	4	5	6
2. Shortness of breath on exertion?	0	1	2	3	4	5	6
3. Anxiety that you might catch a cold or that your breathing will get worse?	0	1	2	3	4	5	6
4. Depressed mood due to breathing problems?	0	1	2	3	4	5	6
In general, how often in the last 7 days:							
5. Have you coughed?	0	1	2	3	4	5	6
6. Have you sputum?	0	1	2	3	4	5	6
On average, over the past 7 days, how limited were you in the following activities due to breathing problems:	not limited at all	quite a bit limited	a bit limited	moderately limited	very limited	extremely limited	completely limited or was not able to do it
7. Heavy physical activity (for example, climbing stairs, rushing, playing sports)?	0	1	2	3	4	5	6
8. Moderate physical activity (for example, walking, doing housework, carrying things)?	0	1	2	3	4	5	6
9. Daily activities at home (for example, dressing, washing)?	0	1	2	3	4	5	6

10. Communication with people (for example, chatting, staying with children, visiting friends/relatives)?	0	1	2	3	4	5	6

The final score is calculated from the sum of points received when answering all the questions, and divided by 10. If its value is <1, the symptoms are assessed as not expressed, and if it is ≥ 1, they are marked, i.e. influencing the patient's life.

Table 2. Questionnaire for assessing the severity of COPD symptoms (CAT)

I never cough	0 1 2 3 4 5	I cough constantly	Points
I have no sputum (mucus) in my lungs at all	0 1 2 3 4 5	My lungs are filled with sputum (mucus)	
I have no chest tightness at all	0 1 2 3 4 5	I have a very strong feeling of tightness in my chest	
When I walk uphill or climb one flight of stairs, I have no shortness of breath	0 1 2 3 4 5	When I walk uphill or climb one flight of stairs, I have severe shortness of breath	
My daily activities within the house are not limited	0 1 2 3 4 5	My daily activities within the house are very limited.	
Despite my lung disease, I feel confident when I leave the house	0 1 2 3 4 5	Due to my lung disease, I don't feel confident at all when I leave the house	
I sleep very well	0 1 2 3 4 5	Because of my lung disease, I sleep very badly	
I have a lot of energy	0 1 2 3 4 5	I have no energy at all	

0-10 points – Minor impact of COPD on the patient's life
11-20 points – Moderate impact of COPD on the patient's life
21-30 points – Strong impact of COPD on the patient's life
31-40 points – Extremely strong impact of COPD on the patient's life

Table 3. Dyspnea point according to the Medical Research Council Scale (MRC) Dyspnea Scale.

Degree	Severity	Description
0	none	I only feel short of breath on intense exertion
1	mild	I gasp when walking fast on a level surface or climbing a gentle hill
2	medium	Shortness of breath makes me walk on a level surface more slowly than people of my age, or my breathing stops when I walk on a level surface at my usual pace
3	severe	I gasp after walking about 100 m or after walking for a few minutes on a level surface
4	very severe	I have too much shortness of breath to leave the house or I gasp when I dress or undress

We assessed the smoking index (SI) of a person, expressed in packs/years: SI (packs/years) = (number of cigarettes smoked per day x smoking experience (years)) / 20. If SI is more than 10 packs/years, the patient belonged to the group of heavy smokers, which is a significant risk factor for the development of COPD [6].

The general condition of the patient was assessed by the attending physician on a 6-point scale. 1-2 points – bad, 3-4 – satisfactory, 5-6 – good.

We studied spirometry and pulse oximetry data.

We performed a 6-minute walk test (6MWT) according to the generally accepted method. Load testing was supplemented by a study of the dynamics of arterial blood oxygen saturation. At the end of the test, the distance covered by the patient in 6 minutes was recorded. The distance traveled in 6 minutes was measured and compared with the proper value (6MWTi). The proper indicator was calculated using the formula:

For men (6MWTi) = 1140 – 5.61 x BMI – 6.94 x age, lower limit of the norm: 6MWDi – 153 m

We assessed the BODE index, which is a multiparameter system for scoring the condition of a patient with COPD, which allows predicting the risk of death from pulmonary pathology.

The BODE index includes an assessment of the following four parameters:

1. Restriction of air flow (forced expiratory volume in the first second - FEV1).
2. Distance covered in the 6-minute walk test.
3. Degree of dyspnea on the MRC scale.
4. Body mass index.

The index is calculated as follows. The value of each index and the point corresponding to this value are determined. Further, all points are summed up. The total can range from 0 to 10 (Table 4).

Table 4. Values of various parameters and the corresponding points used to calculate the BODE index*

Indicator	BODE index points			
	0	1	2	3
FEV1, % of the calculated one**	>65	50-64	36-49	<35
Distance covered in the 6-minute walk test, m	>350	250-349	150-249	<149
mMRC Dyspnea Scale&	0-1	2	3	4
Body mass index#	>21	<21	-	-

Note: * – breakpoints and their corresponding points are given for each parameter.
** – The breakpoints of FEV1 are given in accordance with the stages of pulmonary dysfunction of the American Thoracic Society.
& – The values of the Modified Medical Research Council Dyspnea Scale (mMRC) range from 0 to 4.
# – There are two values for body mass index, 0 or 1. This is due to the presence of a critical point in the feedback between survival and body mass index – 21.
The BODE index has a higher predictive accuracy than FEV1. Based on the value of this index, it is possible to predict the survival rate of patients with COPD (Table 5).

Table 5. Probability of 4-year survival rate of patients with COPD, depending on the value of the BODE index

BODE index value	4-year survival rate
0 – 2	80%
3 – 4	70%
5 – 6	60%
7 – 10	20%

All the above criteria were recorded at the patient's first visit to the pulmonologist and after 14 days of treatment. Statistical processing of the results was carried out using the "Student"-Fisher t-test.

RESEARCH RESULTS

27 male patients whose mean age was 55 ± 2.3 years (the minimum age was 48 years, the maximum age of the patient included in the study was 66 years) were observed. Thus, the patients included in the study were of working age.

19 patients were current smokers, 8 patients were former smokers. The smoking index was 33 ± 1.6 packs/years (maximum SI value – 40 packs/years, minimum – 25 packs/years). Thus, all patients were heavy smokers.

No occupational hazards were noted in past medical history in any case.

15 patients (55%) had concomitant diseases: arterial hypertension (8 patients – 30%), GERD (5 patients – 18%), a history of allergic reactions to penicillin antibiotics (2 patients – 7%).

All patients, according to the clinical guidelines of the Russian Respiratory Society [2], received prescribed treatment: smoking cessation; walks for at least 30 minutes a day; berodual/salbutamol on demand, but no more than 4 times a day; seasonal vaccination against influenza and pneumococcal infection.

As a basic bronchodilator therapy drug, all patients according to indications (COPD with marked symptoms (mMRC is more than 2) and frequent exacerbations) were prescribed T/O at a dose of 2.5/2.5: 2 breaths 1 time a day in the morning at the same time.

One of the main goals of COPD treatment is to reduce clinical symptoms, first of all, shortness of breath. All patients taking part in the study noted marked symptoms of the disease (they were diagnosed with dyspnea according to the mMRC scale at 2.4 ± 0.2 points) and frequent exacerbations of COPD (the number of exacerbations in the previous year was 2.4 ± 0.3). During the ongoing therapy, a decrease in the severity of dyspnea according to the mMRC scale to 1.98 ± 0.3 points was noted.

The attending physician assessed the general condition of the patients at the first visit as "satisfactory" (3.4 ± 0.2), and after the course of therapy as "good" (5.9 ± 0.2) (Table 6)

Table 6. Average values of the general condition of patients

Before treatment	After treatment
3,4 ± 0,2	5,9 ± 0,2

The CCQ questionnaire makes it possible to objectify symptoms both for 1 day and for the last week and to give them not only qualitative, but also clinical characteristics. The study showed that despite the remission of COPD, at the first visit to the doctor, the symptoms of the disease had a pronounced effect on the patient's life (the final score was 2.62 ± 0.21). After a 14-day course of therapy, patients noted an improvement in the quality of life and assessed symptoms as indolent (final score – 0.95 ± 0.24) (Table 7).

Table 7. Average patient symptom scores

Before treatment	After treatment
2,62 ± 0,21	0,95 ± 0,24

When assessing the CAT score, which reflects the degree of influence of COPD on the quality of life, the following results were obtained. Thus, in patients with COPD at the first visit, CAT was 25.3 ± 5.01 points, which indicated a pronounced effect of the disease on the quality of life, and by the 14th day of therapy – 17.1 ± 2.17 points, which indicated a moderate effect of disease symptoms on quality of life of patients with COPD.

The impact of COPD on quality of life is closely related to the occurrence of anxiety and depression. COPD is considered today as a systemic pathology with comorbid diseases [1], among which depressive disorders occupy an important place [4, 7]. People with COPD are at high risk of developing depression.

Thus, both the CCQ questionnaire and the CAT questionnaire demonstrated an improvement in the quality of life of patients with COPD (and hence the risk of developing anxiety and depression) during the 14-day tiotropium bromide/olodaterol therapy.

When examining oxygen saturation in capillary blood at the time of the patient's first visit to the pulmonologist, the following changes were revealed: saturation at rest was 97 ± 2.3%. At the same time, desaturation was noted in 4 patients (15%) up to 94 ± 0.8% in the 6MWT, which indicated the presence of chronic respiratory failure of the 1st degree. After a 2-week course of therapy, the same patients in 6MWT demonstrated normal findings of the studied parameter.

An analysis of observational studies has shown that exercise tolerance in COPD decreases already in the early stages of the disease. Previous physical inactivity or decrease in physical activity in COPD subsequently becomes an important predictor of hospitalization and mortality and may be a key factor in modifying the course of comorbidities. Thus, an increase in

exercise tolerance has a pronounced positive impact on the quality of life indicators [1].

In our study, we noted an increase in exercise tolerance. Thus, on the first day of the patients' visit, the distance covered in the 6MWT was 197.5 ± 13.8 m, and after the course of treatment, the distance covered by the patients increased to 244.3 ± 11.4 m, which is presented in Table 8.

Table 8. Distance covered in the 6MWT during treatment

Indicator	before treatment	after 14 days
Covered distance, m	197,5 ± 13,8	244,3 ± 11,4
Covered distance, % of due one	43 ± 2	57 ± 1

When comparing the distance covered within 6 minutes with the proper indicator, it was found that patients walked 43 ± 2% of the required distance before treatment, and after 14 days of treatment – 57 ± 1%.

When studying the ventilation function of the lungs of patients, it was found that the FEV1 indicator was 52.7 ± 2.6 (the maximum value was 65%, the minimum – 43%), while the TT was less than 0.7 and amounted to 0.54 ± 0.6. Thus, all patients were diagnosed with moderate or severe COPD. After a 14-day course of therapy, neither FEV1 nor TT changed significantly.

The BODE index has a greater predictive accuracy than FEV1 and TT. Based on the value of this index, the survival rate of patients with COPD can be predicted.

The BODE index in patients before treatment was 6.33 ± 0.64 points, and the probability of 4-year survival rate in the study group of patients was 40 ± 8.48%. During the 14-day therapy, the BODE index decreased and amounted to 5.67 ± 0.53 points, the probability of 4-year survival rate increased by 13.3%.

During treatment, all patients noted a decrease in the need for short-acting β2-agonists as "ambulances" during both day and night. Before treatment, 15 of 27 patients (55%) were taking SABA (short-acting β2-agonists). The number of doses of SABA per day before the treatment in these patients was 7.5 ± 1.97 (the minimum number of doses was 4, the maximum – 12). After a course of therapy with tiotropium bromide/olodaterol, the need for SABA was reduced to 1.3 ± 0.85.

CONCLUSION

When taking the drug of tiotropium bromide/olodaterol as a basic therapy for patients with stable COPD, there is a positive dynamics of some symptoms of the disease (normalization of oxygen saturation in capillary blood, reduction of dyspnea according to mMRC), a decrease in the need for short-acting β2-agonists as "first aid" in the daytime and at night), as well as an increase in exercise tolerance and the likelihood of 4-year survival rate. The above changes lead to an improvement in the quality of life of COPD patients according to the CCQ and CAT questionnaires.

Conflict of Interests. The authors declare that there is no conflict of interest.

REFERENCES

1. Aisanov ZR, Belotserkovskaya Yu.G., Avdeev S.N., Belevsky A.S. Modern Data on the Possibilities of Improving Exercise Tolerance and the Importance of Physical Activity in Patients with Chronic Obstructive Pulmonary Disease. *Pul'monologiya – Pulmonology*, 2019, no. 29 (2), pp. 207-215. DOI: 10.18093/0869-0189-2019-29-2-207-215.
2. Clinical Guidelines of the Russian Respiratory Society. COPD, 2018. Kontsevaya A.V., Mukaneeva D.K., Balanova Yu.A., Khudyakov M.B., Drapkina O.M. Economic Damage from Respiratory Diseases and Chronic Obstructive Pulmonary Disease in the Russian Federation in 2016. *Pul'monologiya – Pulmonology,* 2019, no. 29 (2), pp. 159-166. DOI:10.18093/0869-0189-2019-29-2-159-166
3. Kochetova E.V. CAT-Test in Patients with Chronic Obstructive Pulmonary Disease. *Tuberkuloz i bolezni logkikh – Tuberculosis and lung diseases*, 2017, vol. 95, no. 12, pp. 18-20. DOI: 10.21292/2075-1230-2017-95-12-18-20
4. Nizov A.A., Ermachkova A.N., Abrosimov V.N., Ponomareva I.B. Management of Patients with COPD: the Role of Disease Assessment in Real Clinical Practice. *Nauka molodykh (Eruditio Juvenium) – Science of the Young*, 2018, vol. 6, no. 3, pp. 429-438.
5. Agarwal A.K., Raja A., Brown B.D. Chronic Obstructive Pulmonary Disease (COPD). *StatPearls Publishing,* 2020, June 7.
6. Aisanov Z., Avdeev S., Arkhipov V. et al. Russian Guidelines for the Management of COPD: Algorithm of Pharmacologic Treatment. *Int. J. Chron. Obstruct. Pulmon. Dis*., 2018, pp. 183-187. DOI: 10.2147/ COPD.S153770
7. Ambrosino P. et al. Subclinical Carotid Atherosclerosis in Patients with Chronic Obstructive Pulmonary Disease: a Meta-Analysis of Literature Studies. *Ann Med*. 2017, no. 49 (6), pp. 513-524. DOI: 10.1080/07853890.2017.1311022
8. COPD. Available at: http://hobl-online.ru/.
9. Demeyer H., Donaire-Gonzalez D., Gimeno-Santos E. et al. Physical Activity is Associated with Attenuated Disease Progression in Chronic Obstructive Pulmonary Disease. *Med. Sci. Sports Exerc*., 2019, no. 51 (5), pp. 833-840. DOI: 10.1249/MSS. 0000000000001859.
10. Fiorentino G., Esquinas A.M., Annunziata A. Exercise and Chronic Obstructive Pulmonary Disease (COPD). *Adv Exp Med Biol*, 2020, pp. 355-368.
11. Global Initiative for Obstructive Lung Disease. Rocket Guide to COPD Diagnosis, Management and Prevention: A Guide for Health Care Professionals. 20 19 Report.
12. Global Strategy for the Diagnosis, Management and Prevention of COPD, Global Initiative for Chronic Obstructive Lung Disease (GOLD) 2018.
13. Gonçalves I., Guimarães M.J., van Zeller M., Menezes F., Moita J., Simão P. Clinical and Molecular Markers in COPD. GI DPOC-Grupo de Interesse na Doença Pulmonar Obstrutiva Crónica. *Pulmonology*, 2018, July-August, no. 24 (4), pp. 250-259. DOI: 10.1016/j.pulmoe.2018.02.005. Epub 2018 Jun 10.
14. Hillas G., Papaporfyriou A., Dimakou K., Papaioannou A.I. Pharmacological Treatment of Stable COPD: Need for a Simplified Approach. *Postgrad Med*, 2020 March, no. 132 (2), pp. 126-131.
15. Lareau S.C., Fahy B., Meek P., Wang A., Am J. Chronic Obstructive Pulmonary Disease (COPD). *Respir Crit Care Med*, 2019 Jan 1, no. 199 (1), pp.1-2.
16. Lipson D.A., Barnacle H., Birk R. et al. FULFIL Trial: Once-Daily Triple Therapy in Patients with Chronic Obstructive Pulmonary Disease. Am. J. *Respir. Crit. Care Med*., 2017, no. 196 (4), pp. 438-446. DOI: 10.1164/rccm.201703-04490C.
17. Maltais F., O'Donnell D., Gáldiz Iturri J. B. et al. Effect of 12 Weeks of Once-Daily Tiotropium/Olodaterol on Exercise Endurance during Constant Work-Rate Cycling and Endurance Shuttle Walking in Chronic Obstructive Pulmonary Discare. *Ther. Adv. Respir. Dis*., 2018, 12: 1753465818755091. DOI: 10. 1177/1753465818755091 .
18. Mirza S., Clay R.D., Koslow M.A., Scanlon P.D. COPD Guidelines: A Review of the 2018 GOLD Report. *Mayo Clin Proc*., 2018 October, no. 93 (10), pp. 1488-1502. DOI:10.1016/j.mayocp.2018.05.026.

19. Pizarro C., Skowasch D. Exacerbation of COPD: Treatment and Follow-Up. *MMW Fortschr Med.,* 2019 December, no. 161 (21-22), pp. 37-39.
20. Poh T.Y., Mac Aogáin M., Chan A.K., Yii A.C., Yong V.F., Tiew P.Y., Koh M.S., Chotirmall S.H. Understanding COPD-Overlap Syndromes. *Expert Rev Respir Med*., 2017 April, no. 11 (4), pp. 285-298. DOI: 10.1080/17476348.2017.1305895.
21. Rabe K.F., Hurst J.R., Suissa S. Cardiovascular Disease and COPD: Dangerous Liaisons*? Eur Respir Rev.*, 2018 October 3, no. 27 (149):180057. DOI: 10.1183/16000617.0057-2018. Print 2018 Sep 30.
22. Sidhaye V.K., Nishida K., Martinez F.J. Precision Medicine in COPD: Where Are We and Where Do We Need to Go? *Eur Respir Rev.,* 2018 August 1, no. 27 (149):180022.
23. Singh D., Corradi M., Spinola M. et al. Triple Therapy in COPD: New Evidence with the Extrafine Fixed Combination of Beclomethasone Dipropionate, Formoterol Fumarate, and Glycopyrronium Bromide. *Int. J. Chron. Obstruct. Pulmon. Dis.*, 2017:12: 2917-2928. DOI: 10.2147/COPD.S146822
24. Soriano J.B., Polverino F., Cosio B.G., Eur Respir J. What is Early COPD and Why Is It Important? *European Respiratory Journal*, 2018 December 6, no. 52 (6):1801448. DOI: 10.1183/13993003.01448-2018. Print 2018 Dec.
25. Studnicka M., Horner A., Sator L., Buist A.S., Lamprecht B; BOLD Collaborative Research Group. COPD: Should Diagnosis Match Physiology? *Chest,* 2020 February, no. 157 (2), pp. 473-475.
26. Troosters T., Maltais F., Leidy N. et al. Effect of Bronchodilation, Exercise Training, and Behavior Modification on Symptoms and Physical Activity in Chronic Obstructive Pulmonary Disease. *Am. J. Respir. Crit. Care Med*., 2018, no. 198 (8), pp. 1021-1032. DOI: 10.1164/rccm.201706-12880C.
27. Trueman D., Woodcock F., Hancock E. Estimating the Economic Burden of Respiratory Illness in the UK. *British Lung Foundation*, 2017. Available at: https://www.blf.org.uk/policy/economic-burden.
28. Tworek D., Antczak A. Eosinophilic COPD – a Distinct Phenotype of the Disease*. Adv Respir Med*., 2017, no. 85 (5), pp. 271-276.
29. Worth H., Buhl R., Criée C. P. et al. GOLD 2017 Treatment the Treatment Pathways in 'Real Life': An Analysis of the DACCORD Observational Study. *Respir: Med.,* 2017, no. 131, pp. 77-84. DOI: 10.1016/j.rmed.2017.08.
30. Wouters E.F.M., Wouters B.B.R.E.F., Augustin I.M.L., Houben-Wilke S., Vanfleteren L.E.G.W., Franssen F.M.E. Personalised Pulmonary Rehabilitation in COPD. *Eur Respir Rev*., 2018 March 28, no. 27 (147):170125. DOI:10.1183/16000617.0125-2017. Print 2018 Mar.
31. Zewari S., Vos P., van den Elshout F., Dekhuijzen R., Heijdra Y. Obesity in COPD: Revealed and Unrevealed Issues. COPD. 2017 December, no. 14 (6), pp. 663-673.