



## EVALUATION OF COPD TREATMENT PATTERNS FOR PULMONOLOGISTS IN BULGARIA

K. Andreevska<sup>1\*</sup>, Zl. Dimitrova<sup>1</sup>, R.Kofinov<sup>2</sup>, V. Petkova<sup>3</sup>

<sup>1</sup> MU-Plovdiv, Bulgaria, Faculty of Pharmacy, Department of Pharmaceutical sciences'

<sup>2</sup> Pharmaceutical company Boehringer Ingelheim

<sup>3</sup> Department of Social Pharmacy, Faculty of Pharmacy, Medical University – Sofia, Bulgaria

### ABSTRACT

**Background.** International guidelines for Chronic Obstructive Pulmonary Disease (COPD) propose the most cost-effective management of the disease. However, the management of COPD differs between countries and between clinics within the same country. The aim of the study is to examine prescription trends for COPD by pulmonologists from different regions in Bulgaria and to study prescription adherence to international guidelines in order to identify the reasons for potential deviations.

**Methods.** A combined methodology is applied including documentary analysis for reviewing the normative basis for COPD treatment, sociological and mathematic-statistic methods

**Results.** The results suggest that compliance to international COPD management-guidelines do not showed a tendency to guideline adherence. Main omission in the treatment patterns is the group of long acting bronchodilators /LAAC and LABA/, which are the most important for the successful management of COPD

**Conclusions..** For the studied period the price of the therapy with LABA is very expensive and unaffordable for the COPD patients, because of their low incomes and the existing reimbursement restrictions In this case the pulmonologists prefer to prescribe LABA/ICS, even for the mild, moderate and severe COPD with no evidence repeating of exacerbations, because of their affordable price, although ICS are not recommended by the GOLD guidelines for these cases and often worse the symptoms. The xantines are recommended widely for all stages of COPD, because of their low price although they are not recommended because of their adverse drug reactions. This is a reason for the inadequate control of the disease in Bulgaria.

**Key words:** COPD, questionnaire, therapeutic schemes, national consensus

### INTRODUCTION

Chronic obstructive pulmonary disease (COPD) is a major global problem and its prevalence is increasing; yet under - or misdiagnosis is widespread, possibly due to clinical misinterpretation of symptoms, or lack of symptom reporting by patients. COPD in its early stages (stages I and II) is usually not recognized, diagnosed, or treated, and

therefore may not be included as a diagnosis in a patient's medical record. There is considerable evidence that management of COPD is generally not in accordance with current guidelines. Better dissemination of guidelines and their effective implementation in a variety of health care settings are urgently required (1). In 1998, in an effort to bring more attention to COPD, its management, and its prevention, a committed group of scientists encouraged the US National Heart, Lung, and Blood Institute and the World Health Organization to form the Global Initiative for Chronic Obstructive Lung Disease (GOLD). Among the important objectives of GOLD are to increase awareness of COPD and to help the millions of people who suffer from this disease and die prematurely from it or its

\*Correspondence to: Kalina Andreevska, MSc (pharmacy) Department of Pharmaceutical Sciences Faculty of Pharmacy, Medical University – Plovdiv, str.Vasil Aprilov 15.,Plovdiv-4000, BULGARIA, e-mail: andreevska@abv.bg

complications. The aim of GOLD is to give an information about all possibilities for COPD treatment /pharmacological and not pharmacological / and with the effort of experts to develop and implement COPD management guidelines that should be adapted to the local health practices (2). That is why there are guidelines developed for the different countries and widely used are GOLD, European Respiratory Society (ERS), The American Thoracic Society (ATS), and the British Thoracic Society (BTS) (3, 4). In our country a National consensus for COPD was developed (5). There is considerable evidence that management of COPD is generally not in accordance with current guidelines. Better dissemination of guidelines and their effective implementation in a variety of health care settings is urgently required (2). The next scheme show the GOLD recommendations for COPD treatment. (scheme 1) (2). These facts prompt us to analyze the treatment trends for COPD by pulmonologists from different regions in Bulgaria and to study treatment adherence to international guidelines.

## MATERIAL AND METHODS

The applied methods are:

- **Documentary analysis** which has been applied for reviewing the normative basis for COPD treatment.
  - GOLD, (2)
  - The American Thoracic Society (ATS), (3)
  - The British Thoracic Society (BTS) (4)
  - Bulgarian National consensus for COPD (5)
- **Statistic Methods which include:**
  - Descriptive methods and methods for assessment: generalized statistic characteristics of continuous variables average value, standard deviation, standard error of the average and 95% confident interval of the average; frequency analysis of categorical variables /nominal and ranking/ including absolute frequencies, proportional frequencies /%/ , cumulative proportional frequencies /%/ ; graphic images.
  - Methods for an assay of hypothesis: nonparametric methods; Kolmogorov Smirnov method and Shapiro-Wilk method; Mann-Whitney method ; chi-square test method or an accurate Fisher's exact test; Kruskal-Wallis Test comparison

The used critical level of significance is  $\alpha = 0.05$ . The relevant zero hypothesis is eliminated when **P-value** is a smaller  $\alpha$ . For the data processing of the study was used SPSS – SPSS for Windows 11.0.1.

- **Sociologic method** : A questionnaires Patient's COPD health status was developed and used including several sections: demographic characteristics; diagnosing COPD, severity; risk factors; pharmacotherapeutic schemes for COPD treatment and others. This specific instrument was translated into Bulgarian using conventional back translation procedure. The pulmonologists with a written agreement from COPD patients, interviewed them and together with the data from their ambulatory personal data fulfilled the questionnaires. 1210 questionnaires were collected. The reverse percentage is 100%.

## MATERIALS

The study is accomplished with 25 pulmonologists from 8 different towns in Bulgaria in the period May 2006- August 2008. 1210 COPD patients with following inclusion criteria: outpatients, men and women 40 years old or over and suffering from COPD (all stages) were included by an interview and by their medication history. Patients who refuse to participate according to the appraisal of the pulmonologists were excluded from this study.

## RESULTS

1210 questionnaires were analysed. The demographic characterization can be seen on **Table 1**. The distribution of COPD patients by sex is: men 58,4% and women 41,6%. The average age is  $66.38 \pm 10.69$  The COPD severeness, defined by a spirometric measure is also presented. The majority of the patients were in the moderate stage of COPD.

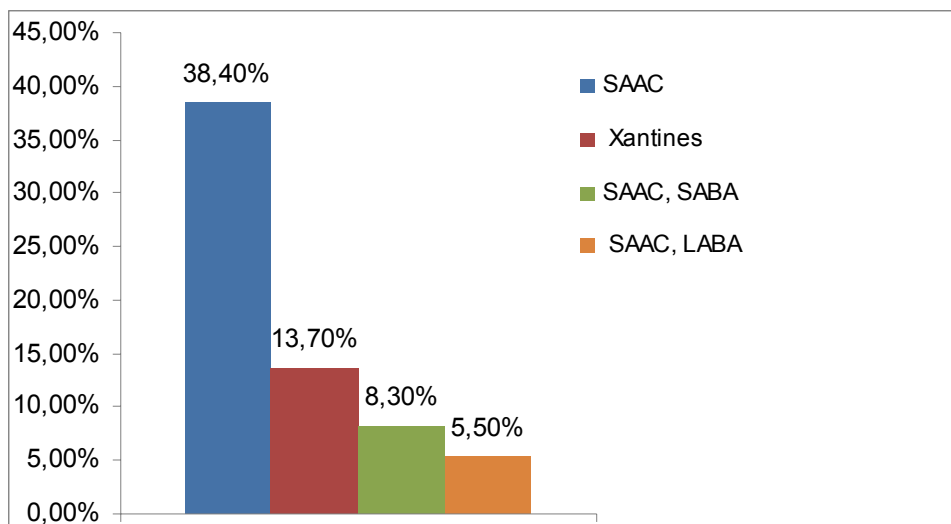
For the treatment of the mild COPD the most preferred are SAAC /38,4%/ followed by the use of Xanthines /13,7%/ , combination of SAAC and SABA /8,2%/ and other. (**Fig. 1**) The treatment is suitable for this stage of the disease and corresponds to the recommendations of GOLD and the Bulgarian National Consensus. For the moderate COPD the most prescribed are the SAAC /17,4%/ , the combination of three bronchodilators – SAAC, SABA and Xanthines /9,10%/ , followed by the used combination of LABA/ICS /8,3% /. As equal share / 6%/ of physicians prefer Xanthines or combination of Xanthines and SAAC, and other. (**Fig. 2**) For the treatment of the severe COPD the highest is the partition of the combined use of

SAAC, SABA, Xanthines and LABA/ICS /12,30%/, followed by the combined use of SABA and Xanthines / 9,4%/, the combined use of LABA/ICS, Xanthines and SAAC /8,8%/, the single use of SAAC/7,6%/ and other. **(Fig. 3)** For the treatment of the very severe COPD the highest is the relative partition of the simultaneous use of SABA and Xanthines /13 %/, followed by the combined

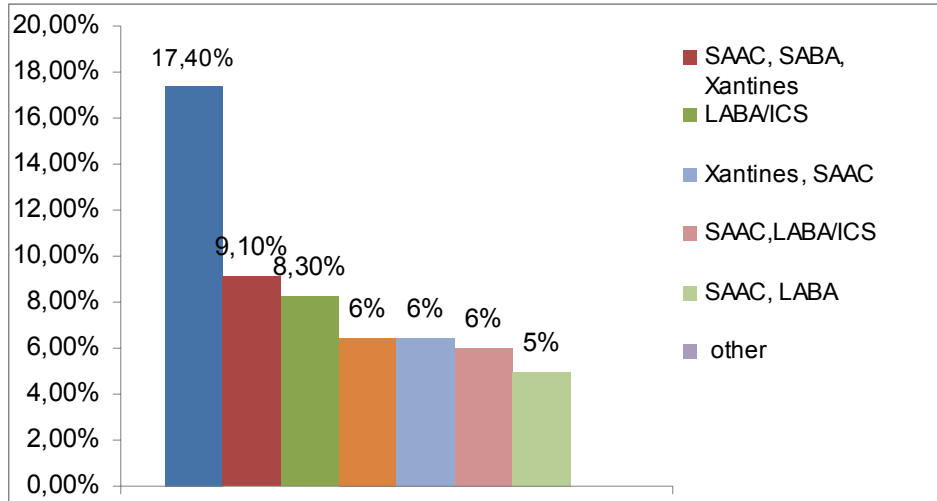
use of SAAC and LABA/ICS /9,1%/, the same is the relative partition /9,1%/ of the combined use of SAAC, LABA/ICS and SABA and other. **(Fig. 4)** According to the results in the preferred therapeutic schemes for the treatment of severe and very severe COPD, long acting bronchodilators are not detected again although they are strongly recommended.

**Table 1.** Main characteristics of the population sample.

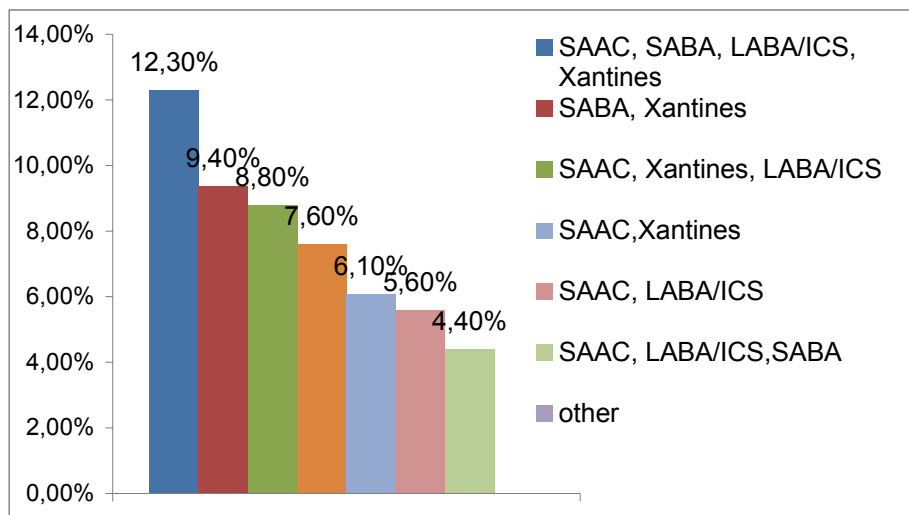
Demographics	n=1210
Age	66,38±10,69
Sex	
Female	504
Male	706
Female/male ratio	0.71
Cigarette smoker (%)	
never	43,0%
exsmoker	32,1%
still	24,9%
Severity of COPD (according to FEV <sub>1</sub> )	
Mild intermittent (%)	12,1%
Moderate persistent (%)	52,7%
Severe persistent (%)	28,3%
Very severe (%)	6,4%



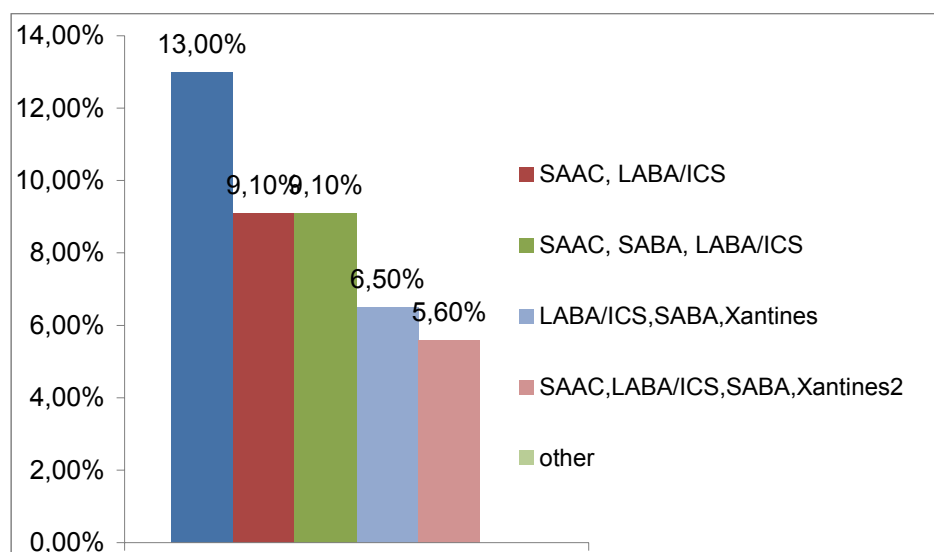
**Fig. 1.** Preferred drug therapies for the mild COPD treatment



**Fig. 2** Preferred drug therapies for the moderate COPD treatment



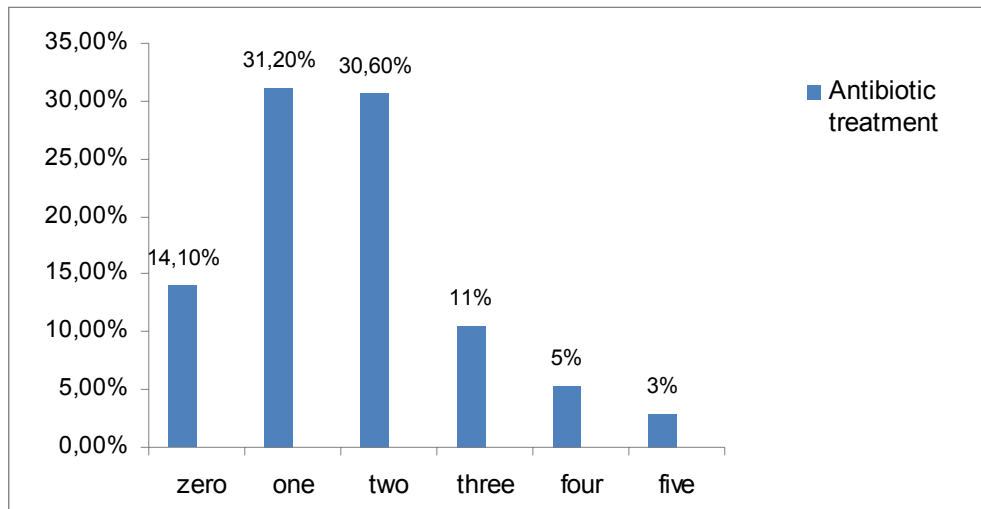
**Fig. 3** Preferred drug therapies for the severe COPD treatment



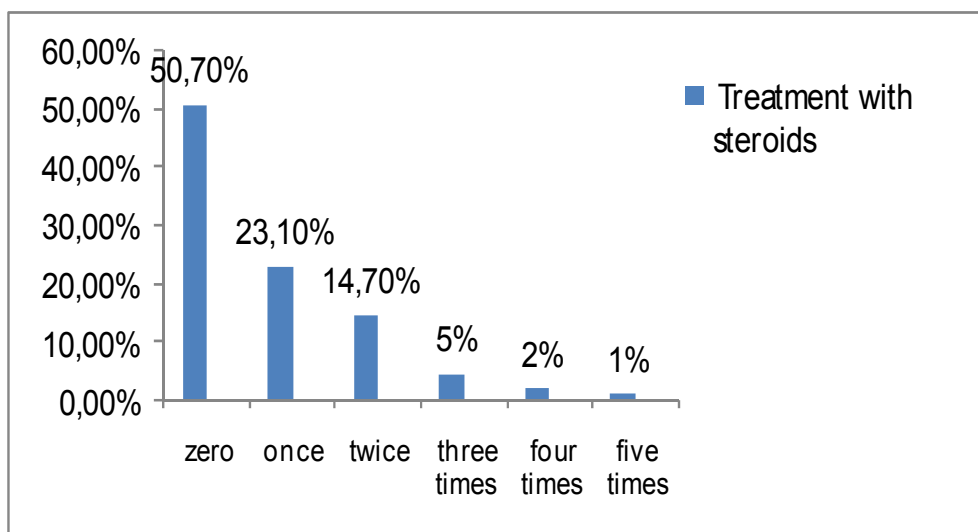
**Fig. 4** Preferred drug therapies for the very severe COPD treatment

The data analysis shows that antibiotic has been added to the treatment therapy in 85,9% of COPD patients and this is a sign for a worsening of the disease (**Fig. 5**). Treatment with inhaled steroids for this period has been provided to 40,3% of patients. The high

percentage of steroid use is an indicator for an event of exacerbations. (**Fig.6**) The treatment of COPD with the prices of the drugs are analyzed (**Table 2**). It can be seen that the cheapest alternatives are: Xanthines and short acting  $\beta$ -agonists.



**Fig. 5** Treatment with antibiotics for the last year of the studied period



**Fig. 6** Treatment with steroids for the last year of the studied period

## DISCUSSION

According to the GOLD guidelines and Bulgarian National Consensus bronchodilator medications are central to the symptomatic management of COPD. They are given on an as-needed basis or on a regular basis to prevent or reduce symptoms and exacerbations. The principal bronchodilator treatments are  $\beta_2$ -agonists, anticholinergics, and methylxanthines used as mono therapy or in combination (2, 7)

According to the results of our study the accepted international and national recommendations for the treatment of moderate COPD are not strictly followed in Bulgaria mainly because these classes long acting bronchodilators /LAAC and LABA/ are not widely prescribed in Bulgaria, because of their high price (8). Regular treatment with long-acting bronchodilators is more effective and convenient than treatment with short-acting bronchodilators. Treatment with a long-

acting inhaled anticholinergic drug /Tiotropium/reduces the rate of COPD exacerbations and improves the effectiveness of pulmonary rehabilitation (2). According to our study the physicians in Bulgaria prescribe LABA/ICS for moderate COPD although ICS use can worsen the COPD patient health status

and can led to exacerbations. The addition of regular treatment with inhaled glucocorticosteroids to bronchodilator treatment is appropriate only for symptomatic COPD patients with an FEV<sub>1</sub> < 50% predicted (Stage III: Severe COPD and Stage IV: Very Severe COPD) and repeated exacerbations (2).

**Table 2.** Drug treatment of COPD and asthma and levels of reimbursement (September 2006-2007)

drug	Drug form		price (retail)	reimbursement	patient's price	"Patient Program" Acsees
	dosis	package	BGN	BGN	BGN	BGN
Seretide	50/250	60	104.91	61.1	43.3	16.44
Symbicort	4,5/160	60	57.53	40.2	17.2	
Symbicort	4,5/160	120	114.86	80.3	34.5	
Serevent	25 mcg	60	31.69	0	31.69	
Salbutamol	100 mcg	200	7.47	0	<b>7.47</b>	
Atrovent	20 mcg	200	14.04	0	14.04	11.31
Flixotide	250 mcg	60	46.64	0	46.64	
Becloforte	250 mcg	200	28.00	0	28.00	
Pulmicort	200 mcg	100	40.37	12.9	24.4	
Ventolin	100 mcg	200	9.56	8.0	<b>5.5</b>	
Spiriva	18 mcg	30	106.33	40.4	65.9	
Theophylline	300mg	50	2.99	2.24	<b>0.75.</b>	

This study of COPD patients, covers the 8<sup>th</sup> Bulgarian regions that are most influenced with COPD for the last 5 years. It is shown that the Bulgarian National consensus for COPD is not revised on one hand and the pulmonologists do not follow it or GOLD because of the insufficient reimbursement status of the COPD drugs. For this reason they prescribe mostly the cheapest alternative (ex. Xanthines). On the other hand this study is representative and covers only a 2 years period of study.

## CONCLUSIONS

Analyzing the preferred drug therapies for the treatment of COPD it can be summarized that Bulgarian physicians are not strictly following the approved and accepted treatment recommendations of the National consensus and GOLD. Main omission in treatment is the group of long acting bronchodilators /LAAC and LABA/. The main reason is the high price of them, reimbursement restrictions and the

low social status of COPD patients. For all stages of the disease, the treatment schemes include two or three short- and long-acting bronchodilators. According to GOLD, regular treatment with long-acting bronchodilators is more effective and convenient than treatment with short-acting bronchodilators. Xanthines are widely used because of their low price although they have adverse drug reactions and are not prescribed in the western countries at all. Combination of LABA/ICS has been used sometimes even for the moderate COPD against the existing recommendations because of better reimbursement and an affordable price. Probably this inadequate treatment may lead to repeated exacerbations of the disease and may cause serious negative impacts on patients' quality of life, lung function, and socioeconomic costs. The National Health Insurance System and Ministry of Health should undertake prompt measures for additional reimbursement of long acting

bronchodilators , mainly of long acting antiholinergics /Tiotropium/ which are strongly recommended for a maintenance COPD treatment of the Global Initiative for Lung Disease (GOLD) (2).

#### REFERENCES

1. Rabe K et al GOLD 2007 Am J Respir Crit Care Med 2007; 176: 532–555
2. Global Initiative for Chronic Obstructive Lung Disease. Global strategy for the diagnosis, management and prevention of chronic obstructive lung disease. NHLBI/WHO workshop report. Bethesda, National Heart, Lung and Blood Institute. 2001; NIH Publication No. 2701:1-100 (updated 2009)
3. American Thoracic Society. Standards for the diagnosis and care of patients with chronic obstructive pulmonary disease. *ANDREEVSKA K., et al.*  
Am J Respir Crit Care Med 1995;152(5 Pt 2):S77-S121
4. British Thoracic Society. Guidelines for the management of chronic obstructive pulmonary disease. Thorax 1997;52(Suppl 5): S1-S28.
5. COPD – National consensus for Bulgaria, Bulgarian Respiratory Society, Sofia, 2002 (available in Bulgarian)
6. Fromer L, Cooper CB. A review of the GOLD guidelines for the diagnosis and treatment of patients with COPD. Int J Clin Pract. 2008 Aug;62(8):1219-36. Epub 2008 Jun 28.
7. Ramsey SD. Suboptimal medical therapy in COPD: exploring the causes and consequences. Chest 2000;117(2 Suppl):33S-37S.9.
8. Spisak\_Lekarstva\_2008 (<http://www.nhif.bg/>).