CHARLES UNIVERSITY IN PRAGUE
FACULTY OF PHARMACY IN HRADEC KRALOVE
Department of Social and Clinical Pharmacy

Diploma Thesis

ANALYSIS OF PHARMACOTHERAPY BY PATIENTS WITH DIAGNOSIS OF COPD

Supervisor
Prof. RNDr. Jiri Vlcek, CSc

May 2013

Marilena Kartali-Kaouni

"I declare that this thesis is my original copyrighted work. All literature and other resources I used while processing are listed in the bibliography and properly cited."

Hradec Kralove, 15/05/2013 Marilena Kartali-Kaouni

Abstract

Title: Analysis of Pharmacotherapy by patients with diagnosis of COPD
Student: Marilena Kartali-Kaouni

Tutor: *Prof. RNDr. Jiri Vlcek, CSc*

Department of Social and Clinical Pharmacy, Charles University in Prague, Faculty of Pharmacy in Hradec Kralove

Background: " Chronic Obstructive Pulmonary Disease (COPD) is characterized by airflow limitation that is not fully reversible. The airflow limitation is usually both progressive and associated with an abnormal inflammatory response of the lungs to noxious particles or gases". Tobacco smoking is the major risk factor in the development of COPD. COPD is a leading cause of morbidity and mortality worldwide.

Aim: 1st from the current literature to understand the nature of COPD and obtain information about the aetiopathogenesis of the disease, diagnosis options and summarize the current view of strategies for achieving the goals of treatment. 2nd in a pilot study to analyze drug therapy in COPD patients visiting a pharmacy in Greece.

Methods: 56 prescriptions with the diagnosis of COPD were collected during a period of 8 months from a Greek pharmacy. Information from the prescriptions with regard to COPD medications prescribed (active substances, trade names, strength, dosage scheme, pack size), patients characteristics (age and gender) and prescribing physicians characteristics (Specialty, Gender and Age) were analyzed.

Results: The COPD prevalence among the regular customers of the pharmacy was found to be 14,01% and being more common among men and older patients. 14% of those patients appear to suffer from COPD and Asthma at the same time. The pharmacological class of long-acting β2-agonists in combination device with inhaled corticosteroids (LABA/ICs) was the most frequently prescribed (34%) followed by the long-acting muscarinic antagonists which are represented only by Tiotropium Bromide (25%). Inhaled corticosteroids and LABA account for 18% and 10% respectively among the total medicines prescribed. Short-acting bronchodilators were used very rarely. Only 20% of the prescribed corticosteroids was in the oral form, the rest was given by inhalation. Antibiotics showed up with a very low frequency rate of 2%. The pharmacological class of combination LABA/ICs seems to be the most equally distributed among all age groups and the most frequently used among both genders.

81% of the prescribed medications were given the possibility of one month treatment by prescribing one package while the rest (19%) by two packages. 68% of the prescriptions were signed by pneumologists and 32% by general practitioners.

Conclusion: The pharmacological categories of LABA/ICs and LAMA were the most frequently prescribed. Pharmacotherapy found to fit with the recent COPD guidelines.

Limitations of this observational study were the lack of information regarding the clinical state of patients and marketing activities and campaigns of drug manufacturers. Also sample population of patients was small and not representative of the Greek population. The results of this pilot study suggest that it would be more appropriate to perform this study on a representative sample of Greek population.

Souhrn

Název: Analýza farmakoterapie u nemocných s diagnózou CHOPN

Student: Marilena Kartali-Kaouni

Školitel: *Prof. RNDr. Jiri Vlcek, CSc*

Katedra sociální a klinické farmacie, Univerzita Karlova v Praze, Farmaceutická fakulta v Hradci Králové

Úvod: Chronická obstrukční choroba plic (CHOPN) je charakterizovaná snížením schopnosti oxidace krve v plicích pro ireverzibilní pokles proudění vzduchu . Pokles prodění vzduchu v dýchacích cestách se během choroby zhoršuje a je spojeno se zánětlivými procesy. Kouření je základní rizikový faktor. CHOPN je jednou z hlavních příčin mortality

Cíl: 1/ Ze současné literatury získat nové informace o ethipatogenezi choroby a možnosti diagnostiky a sumarizovat současný pohled strategií umožňující dosáhnout cílů léčby; 2/ V pilotní studii analyzovat farmakoterapii u pacientů s CHOPN navštěvujíc jednu lékárnu v Řecku

Metoda: Bylo analyzováno 56 předpisů s diagnózou CHOPN, které byly vydány pacientů v jedné řecké lékárně během 8 měsíců. Z předpisů byly získány data o léčivech související s CHOPN (výrobní název, dávkové schéma, síla, velikost balení), o nemocných (věk a pohlaví) a o předepisujícím lékaři (věk, pohlaví a specializace).

Výsledky: Většina receptů pocházela od žen a starších pacientů. 14% pacientů z kohorty trpělo současně i astma bronchiále. Nejčastěji byly předepisovány dlouho účinkující betamimetika v kombinaci s inhalačními kortikoidy (LABA/ICs) (34%). Na druhém pořadí byly dlouho působicí parasympatolytika (LAMA) zastoupené pouze tiotropium bromidem (25%). Inhalační kortikoidy (ICs) tvořily mezi předepsanými léčivy 18%. Dlouze působící betamimetika (LABA) byly předepsány z 10%. Krátce působící betaminetika (SABA) byla předepisována zřídka.Pouze 20% z předepsaných kortikoidů bylo podáno systémově, zbytek byl podáván inhalačně. Antibiotika tvořila 2%. Kombinace LABA/IC byla předepisována všem věkovým skupinám a obou pohlavím. 81% předpisů umožnilo léčbu jednoměsíční léčbu při předepsání jednoho balení. pouze jednoho byla pro měsíční kůru dostatečné jedno balení. Zbytek léčivých přípravků (19%) potřeboval na měsíční kůru dvě balení. 68% receptů pocházelo od pneumologů.

Závěr: Nejvíce předepisovány jsou LABA/ICs a LAMA. Farmakoterapie odpovídá současným doporučením k léčbě CHOPN. Limitací této observační studie je, že neznáme klinický stav pacienta, řecká populace pacientů není reprezentativní a neznáme marketingové aktivity a kampaně výrobců léčiv. Výsledky naší pilotní studie ukazují, že by bylo vhodné provést tuto studii na reprezentativním vzorku řecké populace.

1. Introduction

The present study consists of two parts both related to Chronic Obstructive Pulmonary Disease, which was defined by the Global Initiative for Chronic Obstructive Lung Disease in as follows “Chronic Obstructive Pulmonary Disease (COPD) a common preventable and treatable disease, is characterized by persistent airflow limitation that is usually progressive and associated with an enhanced chronic inflammatory response in the airways and the lung to noxious particles or gases. Exacerbations and comorbidities contribute to the overall severity individual patients” (GOLD, 2013).

The goal of the theoretical part is to describe general features regarding the COPD. Namely it is important to understand the pathophysiology and aetiology of the disease, how it is diagnosed and how it can be prevented, what are the symptoms of the disease and what its complications. Also information about the available pharmacotherapy and patient care for those suffering from COPD will be analyzed.

The experimental part of this study has as aim the analysis of 56 prescriptions concern the medical treatment of COPD patients, that have been collected from a pharmacy in Greece with the assent of patients and pharmacy staff. The content of these medical orders is used to get some idea with regard to the most frequently administered drugs for COPD, their doses and dosage forms, the most frequently prescribed dosage schemes and number of packages. Also the role of some other factors like the age and gender of the patients as well as the age, gender and specialty of physicians will be analyzed.

All information together will provide a better understanding about the condition of Chronic Obstructive Pulmonary Disease and particularly about the ideal and most effective pharmacotherapy according to the conflation of literature evidence in theoretical part and statistical results in experimental part.

2. Literature review

During the period October 2012 – February 2013 literature research took place through the bibliographic databases as well as by the use of appropriate textbooks and reliable scientific organizations.

Literature search took place through the electronic databases of Pubmed, Micromedex, EBM review, Medline, Embase, WHO (World Health Organization), GOLD (the Global Initiative for Chronic Obstructive Lung Disease), American Thoracic Society are those used mostly for this work using keywords like: "COPD", "COPD drug therapy", "Chronic Obstructive Pulmonary Disease", 'Drugs for COPD", "COPD symptoms", "COPD complications", etc.

In addition the Greek National Formulary of Medicines (ΕΟΦ) which is the official Greek pharmaceutical guide was used as well as the British National Formulary (BNF).

Furthermore, the data that was selected for use in this paper was written in English and published during 2005-2013, this would offer the most recent data available regarding the management of Chronic Obstructive Pulmonary Disease.

2.1 Pathophysiology, Causes and Risk Factors of COPD

According to the National Institute for Health and Clinical Excellence COPD is defined as: "Chronic Obstructive Pulmonary Disease is characterized by airflow obstruction. The airflow obstruction is usually progressive, not fully reversible and does not change markedly over several months. The disease caused predominantly by smoking" (NICE, 2010).

Three are the main processes that take place in the organism of an individual leading to the pathogenesis of Chronic Obstructive Pulmonary Disease, these are inflammation, imbalance of proteinases and antiproteinases in the lungs, and oxidative stress.

The different kinds of pernicious inhalation exposure but mainly smoking contribute to the development of inflammatory response in the lungs. This type of inflammation is characterized as chronic and is different from that in bronchial

asthma. In lungs, high levels of neutrophils, macrophages and T-lymphocytes especially CD8+ are noticed. Also, during exacerbations, eosinipholis levels can be increased. Inflammatory cells then provoke the release of cytokines and inflammatory mediators e.g. leukotriene 4, interleukin-8 and tumor necrosis factor-a.

The imbalance between proteinases and antiproteinases in COPD patients, has not been known if it is the result of the production of proteinases in high levels or the decreased production of antiproteinases. Cigarette smoke facilitates oxidative stress which then causes a decrease in levels of antiproteinases.

Oxidative stress plays a role in the development of COPD because of the oxidation of a variety of biological cells which causes cell dystruction. Additionally, consequences of oxidative stress are damage to the intracellular matrix, inactivation of important antioxidants and enhancing gene expression (American Thoracic Society, COPD Guidelines, 2013).

All of the above pathological mechanisms are responsible for the following physiological disturbances:

- Mucus Hypersecretion and ciliary dysfunction – Enlarged mucus glands stimulate the mucus hypersecretion while ciliary dysfunction caused by the squamous metaplasia of epithelial cell. As it is stated by the American Thoracic Society, these are the first disturbances shown.
- Airflow limitation and Hyperinflation – The main side of airflow limitation is the smaller conducting airways which are less than 2mm in diameter and is the result of airway remodeling.
- Gas Exchange Abnormalities – These observed mainly in a severe stage of the disease and related to arterial Hypoxaemia. Abnormal distribution of ventilation and perfusion results in abnormal gaseous diffusion capacity.
- Pulmonary Hypertention (American Thoracic Society, COPD Guidelines, 2013).

As it has been concluded that tobacco smoking is the most important cause of COPD disease, active smokers compared to non-smokers have been found to have a significantly increased risk of COPD development. Generally smoking rate in men used to be higher than in women and as a result COPD used to be more common in

men. However in recent years COPD rate for women increased, affected by the increased smoking rates in women as well (Han, 2011).

Also it has been implied that passive smokers (particularly young people), namely those that are under the exposure of smoke from cigarettes especially in a close environment such as a cafeteria, bar or restaurant, are susceptible to specific alterations of the lung function and in increased risk to develop respiratory infections and lung diseases (Troosters et al, 2005).

However except for smoking, which is the main risk factor for COPD, there are other factors that contribute to the development of the disease. These can be dust, gases, exposure to chemicals at the working areas, fumes and other irritants as well as the a1-antitrypsin deficiency in individuals who have been observed to be at high risk of developing emphysema (Walker and Whittlessea, 2012). The air pollution also plays a role in causing lung distraction but it is a relatively small factor for the development of COPD disease (De Marco, 2011).

Although smoking appear to be the major factor responsible for COPD, this does not mean that all smokers will develop the disease, genetic factors also play a role as well as the age and gender of the individual, the occupation and the number of cigarettes smoked per day (GOLD, 2013)

2.2 Symptoms

Depending on whether the patient suffers mostly from emphysema or chronic bronchitis (both conditions are included under the term COPD), the symptoms can differ a bit.

Chronic Bronchitis is characterized by a persistent swelling and irritability of bronchi or bronchioles. As a result symptoms include: excess mucus production, wheezing, dyspnoea, productive cough (American Thoracic Society, 2013).

In emphysema, the air sacs of the lungs are damaged causing a difficulty for the individual to breath. Therefore the main symptom for those with emphysema is shortness of breath which can be so severe in some cases to be noted even at rest (Mayo Clinic, 2011). However the patient can also experience to some degree cough with sputum to be scanty and mucoid (Walker and Whittlesea, 2012).

2.2.1 Dyspnoea

Oxford medical dictionary defines dyspnoea as labored or difficult breathing. It has been deduced that dyspnea is the one most common and of high importance symptom that makes the individuals worry enough to visit their doctor and consequently leads to an early diagnosis. Because of the fact that COPD progresses slowly and the large reserve in lung function, there is a long period in which people who have smoked for years suddenly note breathlessness with physical activities that previously did not. At this stage reduced expiratory flow rates can be detected (Troosters et al, 2005).

It has been implied that COPD is strongly associated with reduced performance during exercise due to the symptom of dyspnoea which influences the capacity for activity.

In addition dyspnea is more common in patients with cardio-respiratory disorders and weak respiratory muscles than in healthy people. This is brought about by the extra effort required by the former to achieve the desired movement (Troosters et al, 2005).

2.2.2 Cough

Cough also called smoker's cough is very common and usually the initial symptom of the disease. It is caused as a reaction of the organism to clean airways and remove mucus, also appears to be persistent (American Thoracic Society, 2013). As a consequence cough is more often productive of mucus, however this is not necessary. It has been indicated that a history of frequent respiratory infections may be associated with increased cough, purulent sputum, and breathlessness (Eisner, 2008).

2.2.3 Wheezing

Usually it is described as a whistling sound heard during breathing. Sometimes the sound can be really strong and noticeable. Wheezing is caused by a narrowing or blockage of the airways. The combination of wheezing with dyspnea often leads to an incorrect diagnosis of asthma (Eisner, 2008).

2.2.4. Chest Tightness

Chest tightness is described as a feeling of pressure within the chest walls that makes automated breathing difficult. Sometimes, this tightness makes deep breathing painful causing respiration to be short and shallow. Chest tightness can be due to infection of the lungs and is often associated with COPD (Jadad, 2004).

2.2.5 Fatigue

Fatigue is a symptom that often is not recognized as a symptom of COPD, this is due to the emphasis given in the most established symptoms which are dyspnoea and cough (Leader, 2012). However it is a very uncomfortable symptom which is basically always co-exist with breathlessness. It is very important for the patient to learn how to keep active, this can improve the feeling of tiredness (American Thoracic Society, 2013)

2.2.6 Hemoptysis

Hemoptysis means coughing up blood from the respiratory tract and can be an indicator of severe lung and heart problems. Chronic bronchitis is the most common cause of hemoptysis but as long as this symptom exist, patients should contact their doctor in order to exclude more severe conditions like lung cancer. (Mayo Clinic, 2012).

2.2.7 Weight loss

Even though the majority of patients suffering from COPD are overweight or obese, weight loss can occur as a symptom in some cases (Kessler 2011). Usually patients of chronic bronchitis are overweight while patients with emphysema are quite thin (Walker and Whittlesea, 2012).

2.3 Diagnosis

The presence of symptoms like chronic cough (intermittent or/and productive), chronic sputum production, dyspnoea (persistent, progressive, worst during exercise) especially to those over the age of 40 who smoke or are at inhalational exposure to tobacco smoke, occupational dust or chemicals should alarm the individuals to visit their doctor as COPD would be very likely to exist (GOLD, 2013).

However these symptoms alone cannot confirm a diagnosis for chronic obstructive pulmonary disease, Spirometry has to be used for this. With the use of a spirometer the following values are measured:

- (FEV1) Forced Expiratory Volume in the first second of exhalation.
- (FVC) Forced Vital Capacity which is the volume of air inhaled and exhaled during a forced maximal expiration after complete inspiration.

COPD is confirmed when a patient, who has the symptoms mentioned above is also gets these values: FEV1 is less than 80% of that predicted for the patient and FEV1/FVC less than 0,7.

At the same time, as it has been inferred there is always a possibility of (false diagnosis) overdiagnosis in the elderly or underdiagnosis in the younger, this is brought about by the natural deterioration of the lung function with age. (Walker and Whittlesea, 2012).

In addition according to the results of spirometry, it can be seen the degree of airflow limitation and consequently diagnosed the severity of the disease. GOLD guideline provides a classification of the severity of COPD with reference to the FEV1 values. Namely,

- Mild if FEV1 > 80% predicted
- Moderate if FEV1 50-80% predicted
- Severe if FEV1 30-49% predicted
- Very severe if FEV1 < 30% predicted (GOLD, 2013)

2.4 Treatment

Every COPD patient requires a different approach depending on the stage of the disease and the response of each individual to the corresponding medical treatment, but in every case the first step for a COPD patient is to stop smoking as this will degrease the progression of the disease. Nicotine Replacement Therapy or the drug Bupropion could be quite helpful for the individuals if there is not present any contraindication (Walker and Whittlesea, 2012).

Nicotine Replacement therapy is available in five approved formulations which are: gums, transdermal, inhaler, nasal spray, lozenges. It is generally advised to discontinue gradually. Those with cardiac disease should be cautious but it is supported that it has not been reported any increase in cardiac events with use of nicotine replacement therapy.

Bupropion was used as an antidepressant and is a non-nicotine drug that has been shown to successfully facilitate quitting smoking particularly for those who have experienced a degree of depression. Treatment requires approximately 7 to 12 weeks at a dose of 150mg once daily or twice daily later on. Side effects include insomnia and dry mouth, while when used together with nicotine replacement therapy, blood pressured should be checked regularly (American Thoracic Society Guidelines, 2004).

World Health Organization implies the following goals for effective management of COPD (WHO, 2013):

- ✓ Prevent disease progression
- ✓ Relieve Symptoms
- ✓ Improve Exercise tolerance
- ✓ Improve Health Status
- ✓ Prevent and Treat Complications
- ✓ Prevent and Treat Exacerbations
- ✓ Reduce mortality

Approach to the pharmacological management of COPD and Pharmacological options for the management of COPD

<table>
<tr><th>I. Mild</th><th>II. Moderate</th><th>III. Severe</th><th>IV. Very Severe</th></tr>
<tr><td>FEV1/FVC<0,70
FEV1≥80%
Of predicted</td><td>FEV1/FVC<0,70
50%≤FEV1<80%
Of predicted</td><td>FEV1/FVC<0,70
30%≤ FEV1<50%
of predicted</td><td>FEV1/FVC<0,70
FEV1<30%
predicted or
FEV1<50%
predicted +
chronic
respiratory failure</td></tr>
<tr><td colspan="4">Active Reduction of risk factors: influenza, pneumococcal vaccination
Add short-acting bronchodilators when needed</td></tr>
<tr><td></td><td colspan="3">Add regular treatment with one or more long-acting bronchodilators when needed
Add Rehabilitation</td></tr>
<tr><td colspan="2"></td><td colspan="2">Add inhaled glucocorticosteroids if repeated exacerbations</td></tr>
<tr><td colspan="3"></td><td>Add Long-term Oxygen Therapy if Chronic Respiratory Failure.
Consider Surgical Treatment.</td></tr>
</table>

Figure .1. Table showing approach to pharmacological management of COPD (Russell et al, 2011).

Class	Agents	Mode of Action	Clinical Effects
LABA Long Acting β2-agonists	**Salmeterol** **Formoterol**	**Stimulates β2 adrenergic receptors in the airway smooth muscle. Cause increased levels of cAMP. Increase the rate of ciliary transport of mucus. Decrease mast cell degranulation.**	**Bronchodilation by relaxing smooth muscle and opening airways**
LAMA Long Acting Muscarinic Antagonists	**Tiotropium**	**Inhibit muscarinic receptors. Block the parasympathetic nervous system. Reduce viscous mucus secretions. Act on cholinergic tone, the only reversible mechanism of COPD.**	**Bronchodilation by reducing contraction. of airway smooth muscle. Reduce hyperinflation.**
Methylxanthi-nes (Phosphodiest-erase inhibitors)	**Theophylline**	**Phosphodiesterase Inhibition. Raised cAMP.**	**Limited use due to Safety profile.**
LABA-ICs Combinations	**Formoterol-Budesonide.** **Salmeterol-Fluticasone.**	**As above plus Inhaled Corticosteroids associated with anti-inflammatory effects**	**Reduce risk of exacerbation in patients with severe/very severe disease who experience repeated exacerbations.**
Short acting SABA-SAMA combinations	**Fenoterol/Ipratropium** **Salbutamol/Ipratropium**	**As above for long acting agents.**	**Only as rescue medication and not maintenance. May be associated with increased CV events.**

Figure .2. Table showing Pharmacological options for the management of COPD (Russell et al, 2011).

2.4.1.Bronchodilators (SABA –LABA – SAMA – LAMA)

There are two basic types of bronchodilators, the adrenoceptor agonists and the anticholinergic bronchodilators, both of them are further sub-classified into short-acting and long-acting. They are commonly used as a first line treatment in the management of COPD by causing relaxation of airway smooth muscle and reverse the airflow limitation caused by the disease (Katzung, 2007).

β-Agonists relax airway smooth muscle by stimulation of β2-adrenergic receptors and thus cause an increase in the intracellular messenger cyclic AMP that is responsible for the control of smooth muscle tone. Therefore β-agonists by activating β2-adrenergic receptors, they cause directly bronchodilation (Tashkin, 2010).

Anticholinergic agents are antagonists of muscarinic receptors, so they block muscarinic receptors from the neurotransmitter acetylcholine which released from cholinergic nerve endings in the airways. There are subtypes of muscarinic receptors, three of them M1, M2 and M3 are located in the smooth muscle of the airways. M3 receptors mediate the bronchoconstrictor response to cholinergic nerve stimulation and cholinergic agonists. Tiotropium bromide is the only selective agent for subtypes M1 and M3 receptors which provides sustained bronchodilation avoiding the bronchoconstriction caused by blockage of M2 receptors (Scullion, 2007). Also, it has been indicated that for those suffering from COPD, the parasympathetic airway muscle tone is the major reversible component and that inhaled antimuscarinic agents have the ability to reverse this tone, therefore they provide an extremely high bronchodilation effect (Walker and Whittlesea, 2012).

With regard to the short-acting bronchodilators, they are generally recommended for initial use as they provide rapid relief and the incidence of side effects is very rare (Walker and Whittlesea, 2012). The preferred route of administration is by inhalation because it is the same effective as the oral route and causes less side effects (BNF, 2007).

Commonly used short-acting β2-agonists are the salbutamol and terbutaline with a usual dose for inhalation to be 200µcg and 500µcg respectively and a duration of action 3-6 hours, they are typically prescribed to be used “as required”. Because of the present of β2 receptors in the myocardial tissue, there is a cardiovascular stimulation which contributes to side effects like tachycardia, arrhythmias and

palpitation. This is the reason for the administration of low doses (Walker and Whittlesea, 2012). Other possible but not very common side effects include tremor, hypotension, hypokalaemia, sleep disturbances, muscle cramps, peripheral vasodilation (ΕΟΦ, 2012).

Ipratropium bromide is a short-acting antimuscarinic agent, used in the aerosol form for short term relief. A typical dose is 20-40μcg 3-4 times daily (BNF, 2007). Although, antimuscarinic agents are very commonly used in COPD, they should be used in caution in patients having prostatic hyperplasia, bladder outflow obstruction and those susceptible to angle-closure glaucoma as the latter has been reported when used nebulised ipratropium. Other side effects are dry mouth, nausea, constipation, headache, tachycardia and atrial fibrillation (BNF, 2007).

In cases where breathlessness and exacerbation do not seem to fade, maintenance therapy with long-acting β2-adrenoceptor agonists (LABA) or long-acting antimuscarinic agents (LAMA) should be administered when FEV1>50%, alternatively when FEV1<50%, a combination of LABA with Inhaled corticosteroids or LABA with LAMA is better. In very severe cases, LABA with ICs and LAMA may be required (Walker and Whittlesea, 2012).

Also as it has been implied by GOLD, long-acting inhaled bronchodilators are recommended as first line maintenance treatment and preferred compared to the short-acting as they are more convenient and effective by producing prolonged symptom relief. In addition the use of long-acting bronchodilators has shown to decrease exacerbations and hospitalizations, leading to an improved health status (GOLD, 2013).

The most commonly used long-acting bronchodilators are the formoterol, salmeterol which are sympathomimetics and tiotropium bromide which is antimuscarinic. They usually have a duration of action of 12 hours and 24 hours for tiotropium and provide reduced exacerbation rates and increased exercise tolerance (GOLD, 2013). Specifically clinical trials comparing the effectiveness of long-acting tiotropium and short-acting ipratropium, implied that tiotropium was associated 40% less than ipratropium with severe exacerbations (Salpeter, 2007). However tiotropium in the form of nebulizer device Respimat has been shown to be related with increased risk of death in COPD patients taking 5μcg by this way. As it is stated there are

concerns that this form of medication may cause the delivery of higher concentration of tiotropium to the lungs and therefore more side effects (Sharafkhaneh et al, 2013).

In addition to those long-acting bronchodilators, indacaterol is the first ultra-long β2-acting agonist with a duration of action to be 24 hours meaning that can be administered only once daily. Studies have shown that indacaterol has an onset of action significantly faster than salmeterol, longer duration of action than formoterol and salmeterol and that indacaterol and formoterol have a higher intrinsic efficacy than salbutamol and salmeterol (Yorgancioglu, 2012). Also it has been indicated by studies that its use together with LAMA improves the health status and quality of life of COPD patients (Feldman, 2013).

According to a review comparing β-agonists and anticholinergic bronchodilators, even though both types are considered equally effective for the treatment of COPD, it is stated that β-agonists are twice more commonly present in prescriptions in the UK and Europe. However as it has been indicated, β-agonists are related with cardiovascular adverse effects and increase the risk of adverse cardiac events by over two-fold compared with placebo or even more in patients with COPD and concomitant heart disease. Also long-term use of β-agonists may cause significant tolerance regarding the respiratory effects whereas in clinical trials for anticholinergic agents, they have not been shown to cause any tolerance over their effects (Salpeter, 2007).

Additionally, it is stated that seven trials compared directly the two bronchodilators in COPD and the use of β-agonists was associated with a two-fold increased risk of hospitalizations and a five-fold increased risk of total mortality contrary to anticholinergics. Another four trials compared the use of combination of β-agonists and anticholinergics with anticholinerhics alone and as it is suggested it was not found a better effectiveness on long term clinical outcomes than using anticholinergics alone (Salpeter, 2007).

On the other hand, a study in which tiotropium 18μcg o.d. was compared to formoterol 12μcg b.i.d. and to both combined o.d. suggests that tiotropium provoked the greatest improvement in FEV1 during day time whilst during night both agents produced similar effects but the most significant efficacy showed up by the

combination of both where as it is stated rescue use of salbutamol was considerably lower compared to each agent alone (Van Noord et al, 2005).

Moreover as it has been stated that according to the Vogelmeier study (Vogelmeier et al, 2011), tiotropium 18µcg o.d. was found to cause a more significant delay of the first severe exacerbation compared to salmeterol 50µcg b.i.d. Also, the Briggs investigation (Briggs et al, 2005) suggests that tiotropium produces significant improvement of FEV1 compared to that of salmeterol. Despitely according to the Buhl study (Buhl et al, 2011), it was found by Yohannes that indacaterol 150µcg once daily was more effective in improving quality of life and a decrease in the symptom of dyspnoea compared to tiotropium 18µcg once daily but both treatment were well tolerated and adverse effects showed to be similar (Yohannes et al, 2013).

2.4.2 Inhaled corticosteroids

It has been implied that regular treatment with inhaled glucocorticoids cannot change noticeably the long-term decline in FEV1 but may influence the lung respiratory operation reducing the frequency of exacerbations and improving health status (Beers, 2006). As it has been indicated corticosteroids have a limited activity with regard to inflammation on patients with COPD due to the high steroid resistance that these patients appear to have (Barnes, 2004). However it is deduced that inhaled corticosteroids can be of value in the management of COPD particularly when the FEV1 is less than 50% of the predicted. Then regular treatment contributes to an improvement in exacerbations, symptoms, lung function and most important the quality of life (GOLD, 2013). Commonly used inhaled corticosteroids are beclomathasone dipropionate, budesonide, ciclesonide, mometasone furoate and fluticasone Propionate. Typical doses are beclomethasone dipropionate 400µcg twice daily as powder for inhalation, budesonide 100-800µcg dry powder inhaler twice daily and fluticasone propionate 100-500µcg dry powder inhaler twice daily. Adverse effects of inhaled corticosteroids may include osteoporosis, cataract formation, hoarse voice, increased risk of pneumonia, candidiasis of the mouth and throat (BNF, 2007). However according to the Global Initiative for Chronic Obstructive Lung Disease (GOLD, 2013), it is implied that in a long-study treatment of COPD patients

(who showed high prevalence of osteoporosis) with budesonide and another with fluticasone 500µcg twice daily, did not show any effect on the bone density.

As an outcome the use of inhaled corticosteroids in COPD is controversial but it can be said that combination of a long-acting β-agonist and an inhaled corticosteroid in a combination device has been concluded to be more effective than each drug as a monotherapy for stable chronic pulmonary conditions (Man, Sin, 2005).

2.4.3 Oral Corticosteroids

Generally long- term treatment with oral glucocorticosteroids is not recommended in the case of chronic obstructive pulmonary disease (GOLD 2006). Although, it has been stated that for those experiencing increased breathlessness, a short course of oral corticosteroids improves FEV1 value and minimize the incidence of hospitalization (Walker and Whittlesea, 2012). British National Formulary recommends prednisolone at a dose of 30mg daily for a period 7 to 14 days as an appropriate approach to COPD. All oral corticosteroids should be given as a single dose in the morning avoiding a disturbance to circadian cortisol secretion. In addition regular peak flow measurements help to optimize the dose, avoiding high doses that cannot offer any amelioration (BNF, 2007).

2.4.4 Mucolytics

Mucolytic agents provoke the breakdown of sputum in the airways so that can be easily coughed up. Consequently they can be helpful in conditions where chronic productive cough is present. The most common one is the N-Acetylcystein which is available in the form of tablets and for inhalation as a nebulizer. Usual dose is 200mg twice daily. Other mucolytics are erdosteine, bromheksin, carbocysteine and guiafenesin. Nausea, rashes, breathing spasms and diarrhea can be the side effects (American Thoracic Society, 2013). However according to the GOLD guidelines the use of mucolytic has low beneficial results (GOLD, 2006).

2.4.5 Phosphodiesterase-4 inhibitors

It has been reported that Phospodiesterase-4 inhibitors like roflumilast have been indicated in patients with severe COPD to reduce exacerbations when treated in combination with oral corticosteroids. The same applies when roflumilast is used with long- acting bronchodilators (Chong, 2011).

Generally is given as an oral therapy for COPD disease and asthma conditions (Boswell-Smith, Page, 2006). Roflumilast as a drug has a wide range of anti-inflammatory properties and by these should be a potential contributor in the treatment of many inflammatory diseases. This drug seems to increase the cellular levels of cAMP, condition which causes the inhibition of the vascular trafficking and the entire molecular signaling, reducing the excretion of chemokines from the inflammatory cells (Christie, 2005, Kwak et al 2005).

As it has been concluded when roflumilast was compared with an inhaled beclomethasone dipropionate in a study, oral use of 500μcg of roflumilast once daily compared to the inhaled dose of 400μcg of beclomethasone dipropionate twice daily, the former was found to provide better results by improving pulmonary function (improved values of FEV1 and FVC) (Bousquet et al, 2006).

With regard to the pharmacokinetic properties, roflumilast is partly metabolized by cytochrome P450 (CYP) 34A (Nassr et al, 2006).

2.4.6 Cilomilast

The drug cilomilast is being developed for the treatment of COPD, it is a second-generation PDE 4 inhibitor that as it is stated seem to be a major anti-inflammatory drug by causing much less nausea and gastric acid secretion. The action of the drug on physiological pH, limiting its penetration into the CNS (Martina et al, 2006).

2.4.7 Ibudilast

Ibudilast (3-isobutyryl-2-isopropylpyrazolo [1,5-a] pyridine) is a nonselective drug PDE inhibitor which preferentially inhibits PDE 3A, PDE 4, PDE 10, and PDE 11 that are acting to the bronchus. It is suggested that this agent could be useful in the management of respiratory conditions as well as a range of neurological

conditions, which are linked in molecular and cellular level increasing the cellular cyclic nucleotide concentrations (Brown, 2007).

2.4.8 BAY 19-8004 (Lirimilast)

Lirimilast is a selective inhibitor of phosphodiesterase-4. It is implied that according to some scientific results after treatment with BAY 19-8004 at a dose of 5 mg once per day, it was observed reduction of inflammation in patients with COPD. Also in a study which examined eleven patients with COPD (FEV1-60% predicted, all smokers) and 7 patients with asthma (FEV1-70% predicted, all non-smokers) seems that FEV1 was improved after 1 week of treatment. (Grootendorst et al, 2003)

2.4.9 Aclidinium

Aclidinium is an inhaled long-acting muscarinic antagonist, which currently is at an early stage of clinical development, having authorized in Europe just in July 2012. However the available clinical studies have shown a potent bronchodilator. Additionally, it is indicated that preclinical studies showing decrease in the presence of the common adverse effects of this drug category like dry mouth and constipation (NICE, 2013).

2.4.10. Theophylline

Theophylline is a methylxanthine drug and is a weak bronchodilator which appears to have a role in COPD therapy. It has been suggested that theophylline at concentrations less than 10mg/L produces also anti-inflammatory effect on COPD patients, this dose is below the dose usually required for bronchodilatory effect to be achieved. It is stated that as a bronchodilator does not predominate over LABA and LAMA, however is shown to help in reducing symptoms like dyspnoea and wheezing and having a potential to improve the corticosteroid resistance in COPD patients. Generally its use is suggested in more severe cases and preferably with the co-use of long-acting β2-agonists (Barnes, 2005).

Theophylline should be prescribed with care, as its clearance affected by a variety of factors, one of which is tobacco smoking. It exists as Aminophyline in parenteral form but oral forms are also available. Side effects of Theophylline

include: tachycardia, palpitation, nausea, gastro-intestinal disturbances, headache, CNS stimulation, insomnia, arrhythmias (BNF, 2007)

2.4.11 Antibiotics

Antibiotics are only recommended for the treatment of infectious exacerbations and other bacterial infections (Butorac-Petanjek et al, 2010).

2.4.12 Oxygen Therapy

Long-term oxygen therapy has been shown to improve survival and lower morbidity in patients with COPD. It should be said that the decision for long-term therapy should be made only in stable patients (Davidson, 2011). It is indicated that patients should receive long-term oxygen therapy if they have the following values: PaO2 is 55-59mmHg, Sa,Co2% is 88-89% and have signs of pulmonary hypertension, Cor pulmonale, erythrocytosis, eodema from a right heart failure (American Thoracic Society, COPD Guidelines, 2013).

2.4.13 The surgery

For those patients suffering from very severe form of chronic obstructive pulmonary disease who have not seen any type of improvement using the appropriate medication or combination of medications, the surgery may be a useful therapeutic option. However a major surgery like that requires a very healthy candidate which is usually not the case for COPD patients. There are three types of surgery for COPD, these are:

- Lung Transplantation
- Lung Volume-Reduction Surgery
- Bullectomy

In Lung Transplantation, the lung is removed and replaced with another healthy one which have been offered by a donor.

In Lung Volume-Reduction Surgery, a high percentage of damaged lung tissue is removed by joining the rest together.

In Bullectomy, giant air pockets and surrounding lung tissue are removed (New York Times, Guide, 2012).

2.5 Difficulties in COPD treatment

- ✓ Patients do not will to quit smoking
- ✓ Difficulty in correct use of inhaler, usually leading to the administration of under dose than the one required
- ✓ Overuse of symptom relief medications
- ✓ Low compliance with treatment schedule
- ✓ Lack of exercise
- ✓ Behavioral problems
- ✓ Lack of education concerning the COPD
- ✓ Patient's unwilling to long oxygen therapy at home

(Rand, 2005)

2.6 Prevention

2.6.1 Cigarette Smoking

Controlling smoking behavior is the most important protecting method at all stages of the disease progression. Physicians can play an important role by setting a smoke-free dietary program and health care settings and by supporting social and antismoking tries. Smoking inhibition should be in high priority for all patients with COPD because is the main case which is exacerbating the symptoms. The Lung function may not improve after smoking cessation, but the accelerated loss of operational indignity due to smoking will be slower which is useful for the patients. The advice of physicians is important and effective in reducing the symptoms progression (Papadopoulos, 2011).

2.6.2 Preventing Influenza and Pneumonia

Patients with COPD are usually in a higher risk to lung infections. The influenza or other lung bacterial infection can be prevented or minimized in severity by immunization or chemoprophylaxis. Single dose of pneumococcal vaccine should be given as well as annual influenza vaccination. It has been shown that by this way,

hospitalizations due to chronic lung disease are minimized (Walker and Whittlesea, 2012).

2.6.3 Pulmonary Rehabilitation

It has been concluded that pulmonary rehabilitation is very important established preventive health strategy which may improve the usual therapy for people with chronic lung disease in order to control the symptoms and restrict the medical and economic linkage of the disease. The most famous and usable programs including the appropriate education, the respiratory and chest physiotherapy and the exercise training. As with other rehabilitation programs, the main target is to make the patient to be active in an independent way of action function. This could be achieved by helping patients become more knowledgeable about their disease, and less dependent on their family.

The most important benefits and goals of the pulmonary rehabilitation are the improved exercise tolerance without any medical support and the reduction of the hospitalizations. The improvement of the quality of life is crucial for these patients with a decline in respiratory symptoms, an increase in exercise tolerance and ability to perform physical activities, with less exacerbation of anxiety and depression (Beauchamp, 2011).

2.7 Complications

COPD affects an estimated of 340 millions of population worldwide and according to the World Health Organization, it is predicted to be the third leading cause of death in 2020. COPD is very complex condition that can be accompanied by a lot and serious comorbidites.

The main complications of COPD include pulmonary hypertension, heart failure, pneumothorax, respiratory failure, increased risk of pneumonia, obstructive sleep apnea, anemia, osteoporosis, lung cancer, diabetes, depression and others.

2.7.1 Pulmonary hypertension and Cor Pulmonale

It has been demonstrated that pulmonary arterial hypertension is probably the most usual comorbidity across the patients suffering from chronic pulmonary diseases which is linked to high incidence of excacerbations and mortality. Pulmonary hypertension arises from the increase pressure in the pulmonary circulation as a result of obstruction of the airways. It is suggested that hypoxia, loss of capillaries and inflammation in severe cases of COPD play a role in the development of pulmonary hypertension. Cor Pulmonale is a secondary to pulmonary hypertension condition which is the result of right ventricular hypertrophy and dilation causing right heart failure (Chaouat et al, 2008).

It has been referred a 1–3% of patients with severe pulmonary arterial hypertension arise from the airways impairment at the patients. In addition to that it has been stated that some studies showed 50% of patients with very severe COPD who undergo lung volume reduction surgery or lung transplantation develop a severe condition of pulmonary arterial hypertension (Thabut et al, 2005).

2.7.2 Respiratory Failure

The presence of severe hypoxia and hypercapnia in COPD patients facilitates the development of acute respiratory failure to those patients. The condition can lead to heart rhythm abnormalities and other life-threatening conditions (New York Times Health Guide, 2012).

As it has been implied during the progression of COPD disease, the exercise capacity of the respiratory system decreases and when this happens to a large degree influences the quality of life of the patient dramatically. The patient experiences significant decrease physical activity and may not be able to exercise even a little. (O' Donnell et al, 2007).

During exercise, the COPD patients increase the high intra-thoracic pressures due to their action of increasing the respiratory need and demands by the dynamic hyperinflation (O' Donnell et al, 2007).

2.7.3 Pneumothorax

Pneumothorax is defined as: “air in the pleural cavity. Any breach of the lung surface or chest wall allows air to enter the pleural cavity, causing the lung to collapse. In tension pneumothorax a breach in the lung surface acts as a valve, admitting air into the pleural cavity when the patient breaths in but preventing its escape when he breaths out. This air must be let out by surgical incision” (Oxford Medical Dictionary, 2007).

Secondary pneumothorax (pneumothorax as a complication of an underlying lung disease) usually results from acute exacerbations in COPD patients. COPD is considered as the most common cause of secondary pneumothorax with about 50-70% of cases to be due to COPD. As it is implied, severity of the disease is closely related to the likelihood of an individual to develop secondary pneumothorax (Light, 2012).

2.7.4 Osteoporosis

As it has been inferred, COPD patients are at high risk of osteoporosis and this is because of the age, the limited exercise, smoking, use of corticosteroids, loss of appetite and low BMI (Chatila et al, 2008)

It has been implied that more than half of patients with COPD who took part to the large TORCH (Towards a Revolution in COPD Health) trial (with 6,000 patients) had osteoporosis or osteopenia as determined by dual-energy radiograph absorptiometry. In addition in a cross-sectional study which was referent to the main prevalence of osteoporosis was 75% in patients with Global Initiative for Chronic Obstructive Lung Disease stage IV concerning that the osteoporotic and bone broke prevalence is high for males and even higher for females. (Vrieze et al, 2007, Jorgensen et al, 2007).

COPD itself may be a risk factor for osteoporosis and this may be related to systemic inflammation. Using computed tomography to determine bone density of thoracic vertebrae, there is a significant correlation between CT-measured emphysema and bone density, supporting the view that osteoporosis is related to emphysema and maybe to COPD especially in patients with severe pulmonary operation reduction (Ohara et al, 2008).

2.7.5 Pneumonia

Patients suffering from COPD are much more capable of developing lung infections like Pneumonia which can be life-threatening. In addition the use of inhaled corticosteroids among these patients have been shown to increase the risk of pneumonia.

COPD patients who have also pneumonia are very difficult to treat as they show decreased immune function and the presence of inflammation in the lungs do not help healing.

Also because both conditions have similar symptoms (sever cough, difficulty in breathing, wheezing, mucus production), sometimes in COPD patients, pneumonia is under diagnosed.

Usually pneumonia can cause exacerbations where breathing becomes really hard and Oxygen levels reduced dramatically. In this case Oxygen therapy appears to be necessary until pneumonia is faded. The most common cause of pneumonia is the bacteria Streptococcus Pneumoniae, so a course of antibiotic therapy is required (Schreiber, 2011).

2.7.6 Lung cancer

It has been deduced that patients with COPD are three to four times more likely to develop lung cancer than smokers with normal lung function. As a consequence lung cancer is indicated to be a common cause of death in COPD patients, especially those to a late stage of the disease (Turner et al, 2007).

2.7.7 Depression

Patients with COPD are frequently isolated and unable to participate to activities or socialize themselves. As a consequence, anxiety and depression are very common in patients with COPD more than the healthy persons and could be more prevalent than in other cases of patients with chronic diseases. Anxiety and depression symptoms may be confused with symptoms of COPD, so these psychiatric problems are often undiagnosed and untreated in clinical practice. It has been indicated that depressive symptoms that are clinically relevant occur approximately

in 10 to 80% of all patients while specifically COPD patients show a predisposition towards depression to be 19–42% (Yohannes et al, 2006, Hill et al, 2008).

2.7.8 Diabetes

It has been suggested that a lot of published studies show that there is an increased prevalence of diabetes disease among COPD patients, even in patients with mild disease. The relationship between diabetes and COPD is not known yet. However because asthma patients do not have an increased risk of diabetes, it has been assumed that the different pattern of inflammation in COPD compared to that of asthma as well as the systemic inflammation which is more representative in COPD patients may be related to the development of diabetes. In addition the proinflammatory cytokines which produced in COPD disease, including TNF-a and IL-6 may also contribute by affecting the insulin resistance which is provoked by the blockage of the molecular signaling pathway on insulin receptors and therefore increase the risk of type2 diabetes (N'dumele et al, 2006).

2.7.9 Sleep Apnoea

As it is suggested the general epidemiological studies have shown that more than 20% of patients with obstructive sleep apnoea also have COPD. Additionally 10% of patients with COPD have obstructive sleep apnoea independent of disease severity and progression of each pulmonary operation. These brought about a connection between the two pathological conditions (Alam et al, 2007).

Sleep Apnoea is defined as " a serious condition in which airflow from the nose and mouth to the lungs is restricted during sleep. It is defined by the presence of more than five episodes of apnoea per hour of sleep associated with significant daytime sleepiness. Snoring is a feature of the condition but is not universal" (Oxford Medical Dictionary, 2007).

2.7.10 Anemia

As it has been indicated there are recent studies which have shown that there is a high prevalence of anemia in COPD patients. Anemic COPD patients have been appeared to have elevated levels of erythropoietin, this could be the result of

erythropoietin resistance. COPD inflammation mechanisms have been found to contribute to erythropoietin resistance (Chatila et al, 2008).

Treatment with erythropoietin does not appear to be helpful, giving preference to blood transfusion (Similowski et al, 2006).

3. Experimental part

3.1 Introduction-Second Part

The aim of experimental part of this study was to collect from one selected pharmacy located in Greece, a sample of approximately 60 prescriptions which have been used for the pharmacotherapy of patients diagnosed with COPD.

Having gathered all the information present on the COPD prescriptions which includes the different kinds of prescribed COPD medicines, dosage schemes, formulations, number of packs, age and gender of patients and physicians characteristics, it would be essential to conclude to some results that could be further analyzed.

3.2 Methodology

The first step was the collection of prescriptions with the diagnose of COPD dispensed in one pharmacy. This was proceed from October 2011 to May 2012 with the consent of patients and medical staff. It was managed to collect a sample of 56 prescriptions for the treatment of COPD.

Here it should be mentioned that the standard patients of this specific pharmacy are 364 per month and from these, 51 patients are suffering from COPD. This means that 5 of the prescriptions in the sample are from patients who are not known at the moment to be regular customers of this pharmacy.

The only criterion for the selection of these prescriptions was to be prescriptions indicate that the patient is diagnosed with COPD and only repeated prescriptions were excluded. So the information that was needed to collect from these prescriptions for the realization of this study was:

- ✓ COPD medications prescribed
- ✓ Medications prescribed for other respiratory condition coexisting with COPD
- ✓ Strength of medications
- ✓ Drug formulations prescribed
- ✓ Dosage scheme
- ✓ Number of packages prescribed

- ✓ Patients characteristics (age and gender)
- ✓ Physicians characteristics (specialty, gender and age)

Statistical results obtained, showing the number of patients visiting the pharmacy and specifically the ratio of those treated for COPD, characteristics of patients treated for COPD (age, gender), characteristics of physicians (number, specialty, age and gender), frequency of commonly administered medications (as trade names and as active substances) associated with the treatment of chronic obstructive pulmonary disease, frequency of pharmacological classes among the total number of medicines prescribed, frequency of specific dosage schemes, number of packages prescribed and types of formulation, frequency of medications not indicated for COPD but other conditions that may exist as well. In addition more detailed analysis concerning frequency of pharmacological classes among the four different age groups (30-45, 46-56, 57-66 and 67+ which is the retirement age for men in Greece) and among gender took place.

3.3 Results

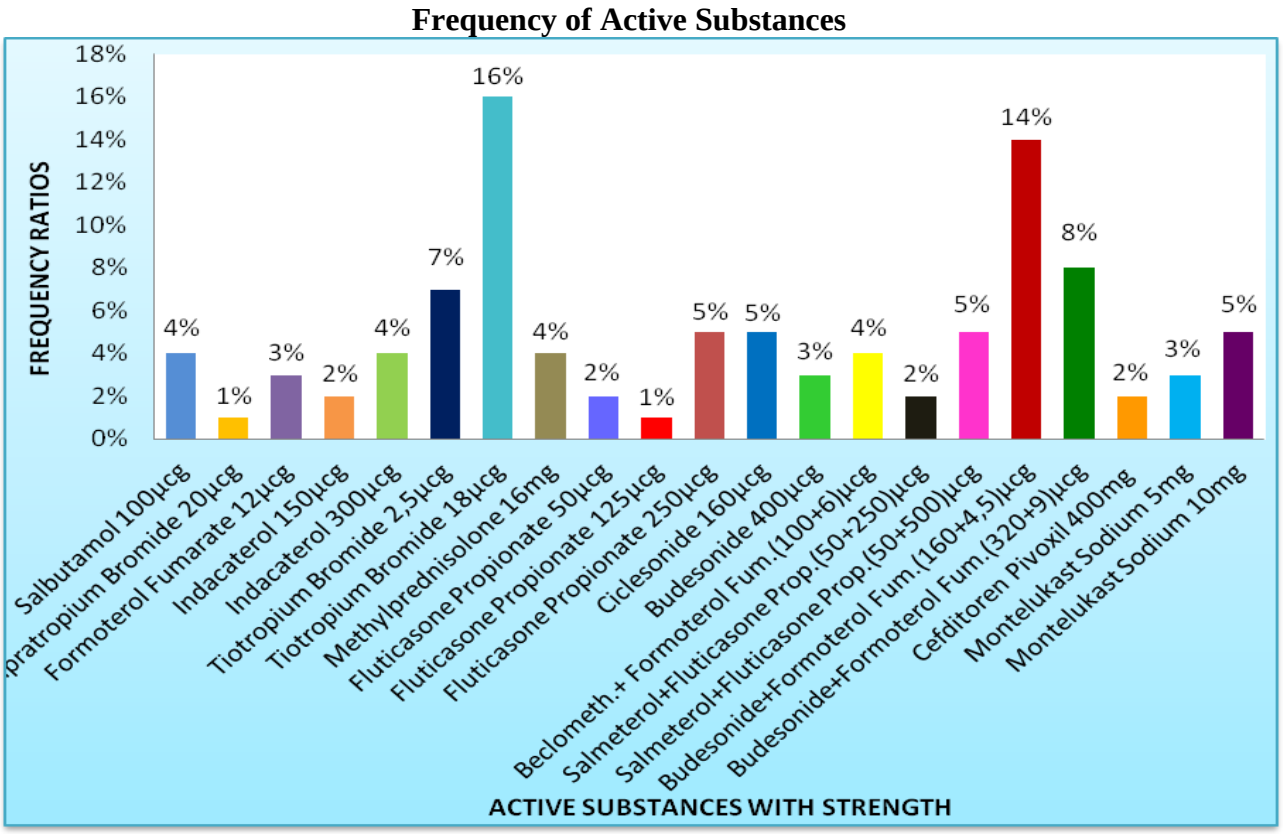
The results of the analysis described above concerning the frequency and the nature of the prescriptions collected, are represented in the tables and charts following.

From the total of 364 standard patients per month who are visiting the pharmacy in which the study took place, 51 of them are patients of Chronic Obstructive Pulmonary Disease and their prescriptions were used. Another 5 prescriptions for COPD treatment were used which however are not known at the moment to belong to regular patients of this pharmacy.

Therefore as it is shown below the frequency of COPD condition among the standard patients of the pharmacy and relatively to the total number of them, has been calculated to be 14,01%

Prevalence of COPD Patients in the Pharmacy	
Total No of Patients in Pharmacy	364
COPD Patients	51
% of COPD Patients	14,01%

Figure .8. Table showing the frequency of COPD condition among the ill patients of the pharmacy of this study



* Beclomethasone Dipropionate + Formoterol Fumarate (100+6)µcg
* Salmeterol Xinafoate + Fluticasone Propionate (50+250)µcg and (50+500)µcg
* Budesonide + Formoterol Fumarate (320+9)µcg

Figure .13. Bar Chart shows the frequency ratios of active substances with strength according to the COPD prescriptions used in this study where 100% is the total number of active substances.

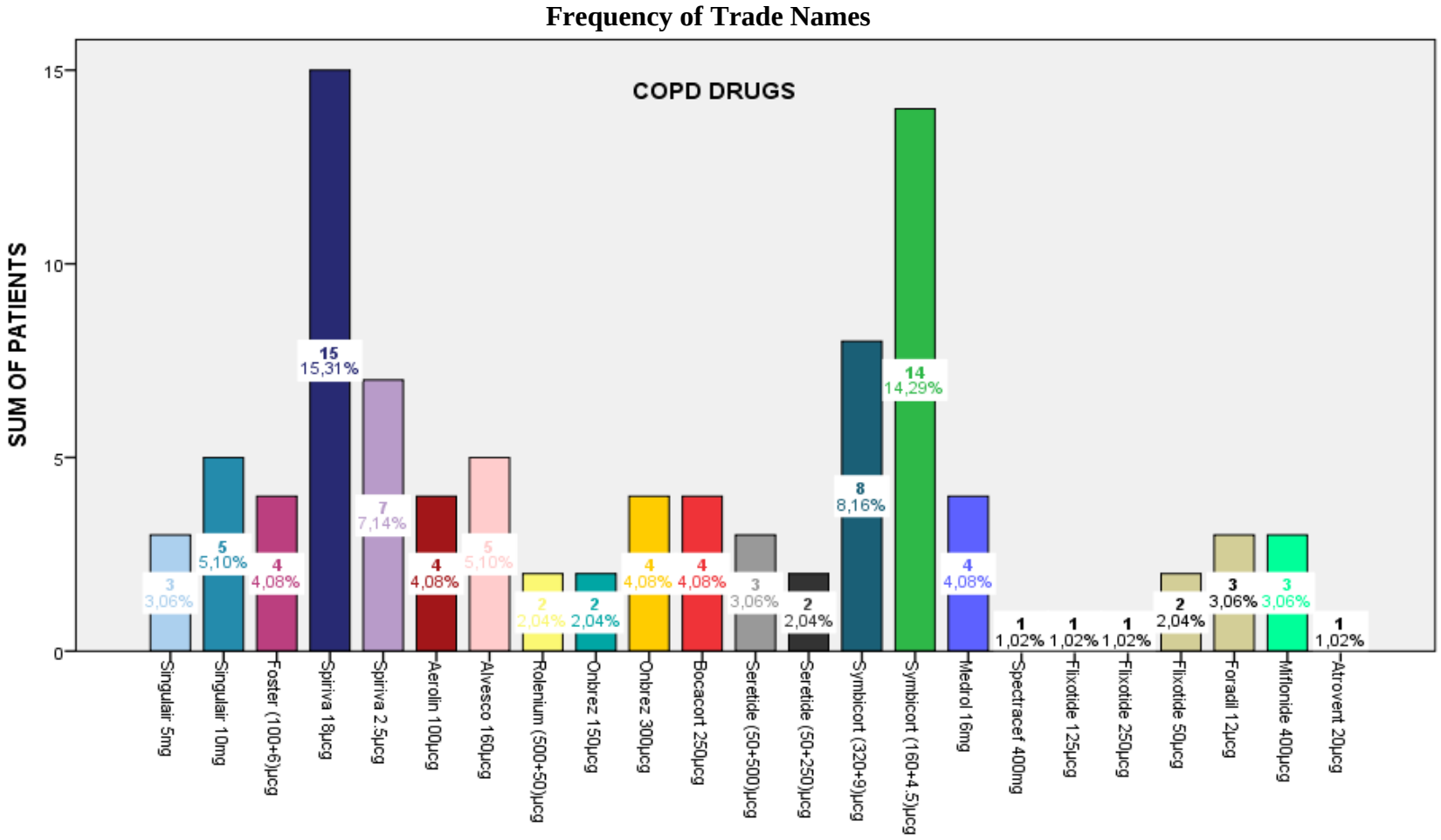


Figure.3. Bar chart showing frequency ratios of trade names including strength, present in the sample of prescriptions in this study where 100% is the total number of trade names of drugs.

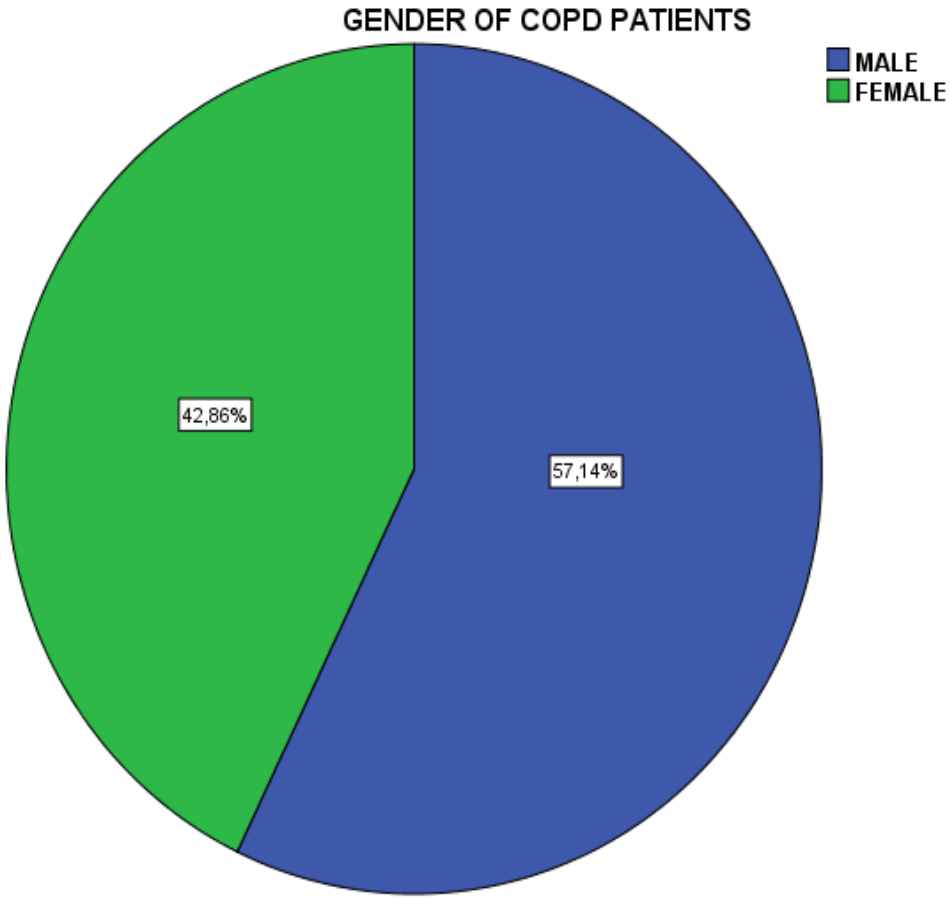


Figure.4. Pie chart showing the distribution of COPD patients in genders according to the sample of prescriptions where 100% is the total number of patients.

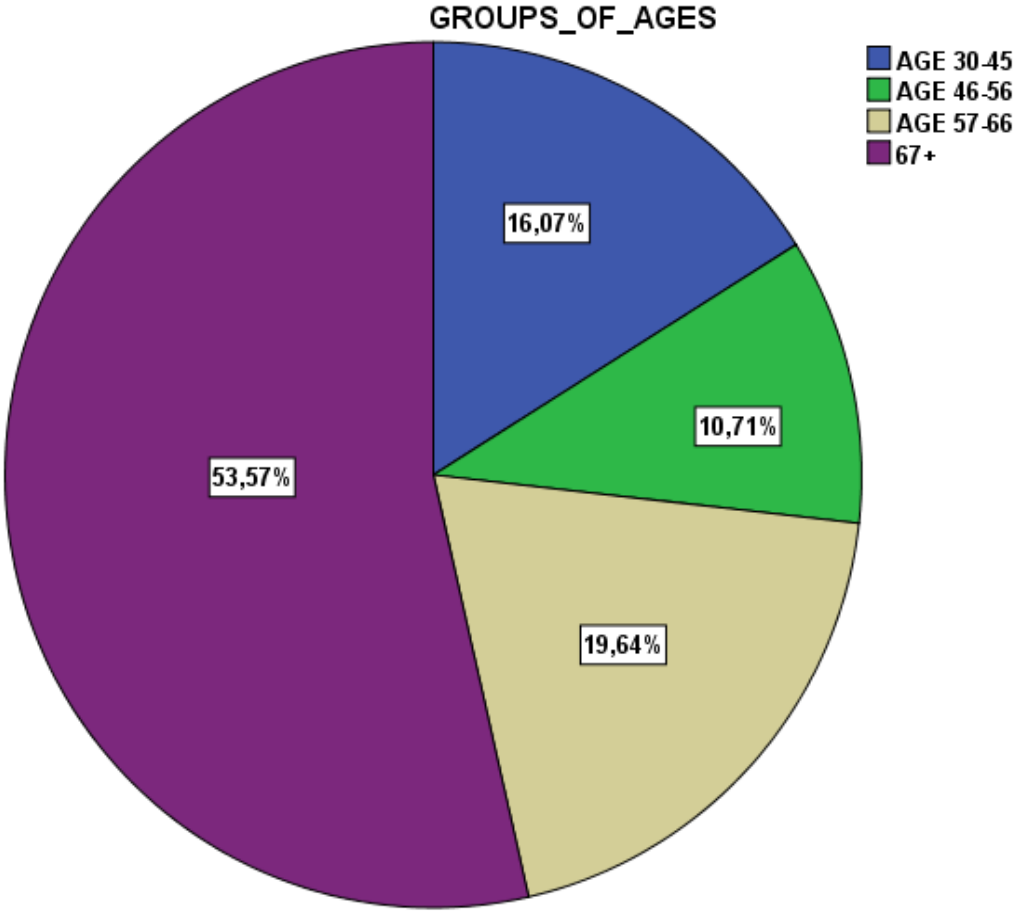


Figure.5. Pie chart showing the distribution COPD patients in age groups according to the sample of prescriptions where 100% is the total number of patients.

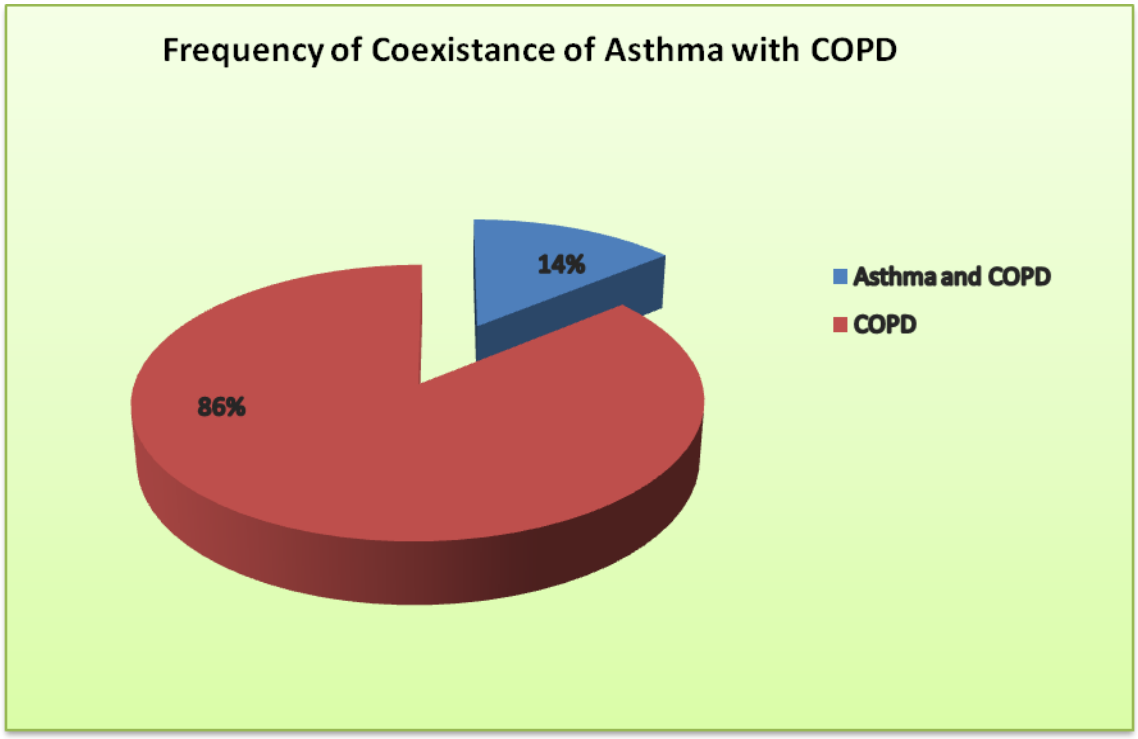


Figure .17. Pie Chart showing the percentage of patients suffering from Asthma and COPD in this study where 100% is the total number of patients.

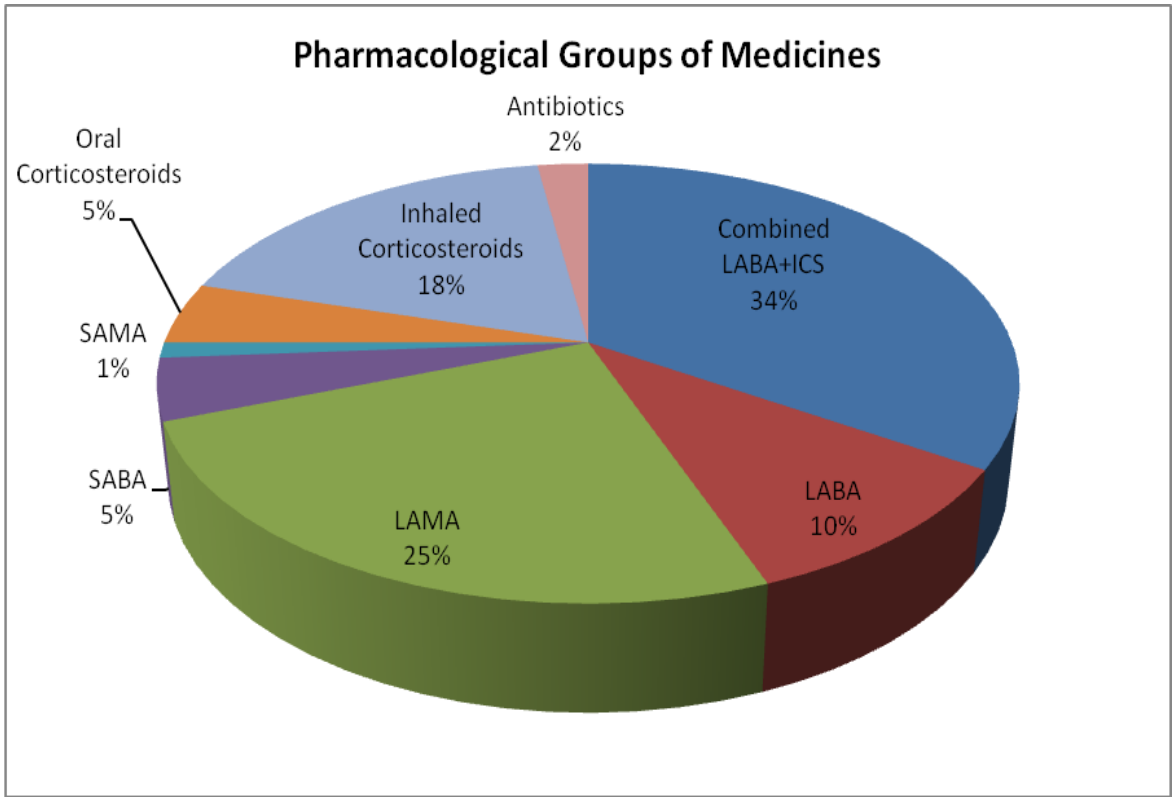
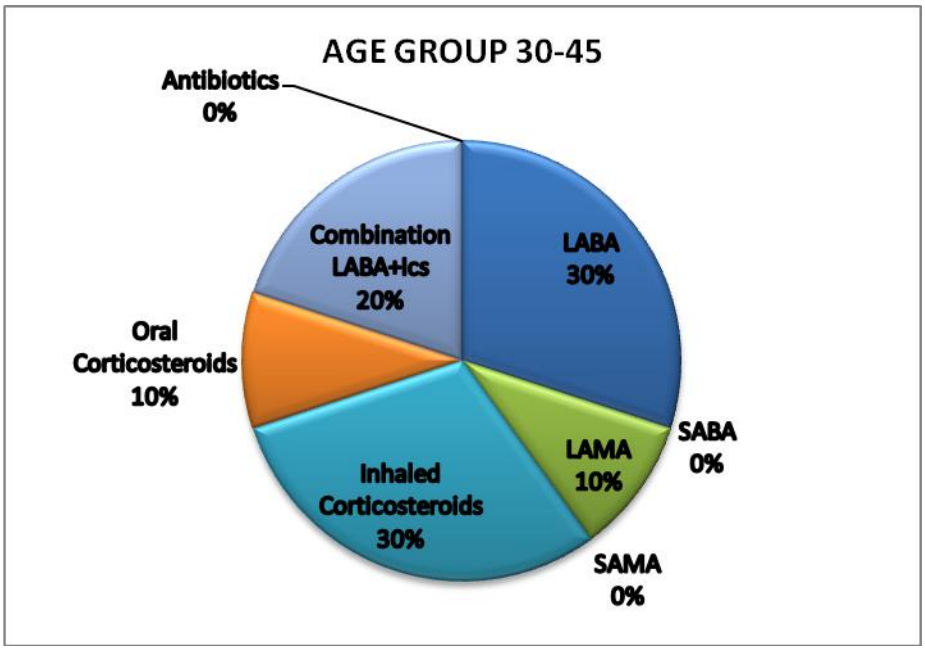


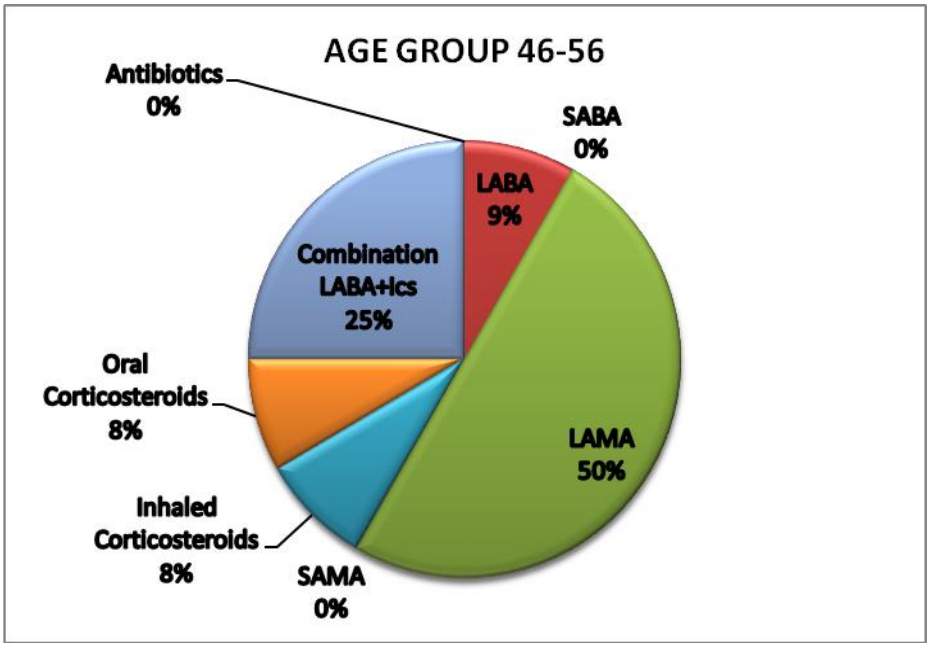
Figure .9. Pie Chart showing frequency ratios of COPD medicines according to their pharmacological class present in the sample of prescriptions used in this study where 100% is the total number of active substances.

Distribution of Different Pharmacological Categories among Age Groups

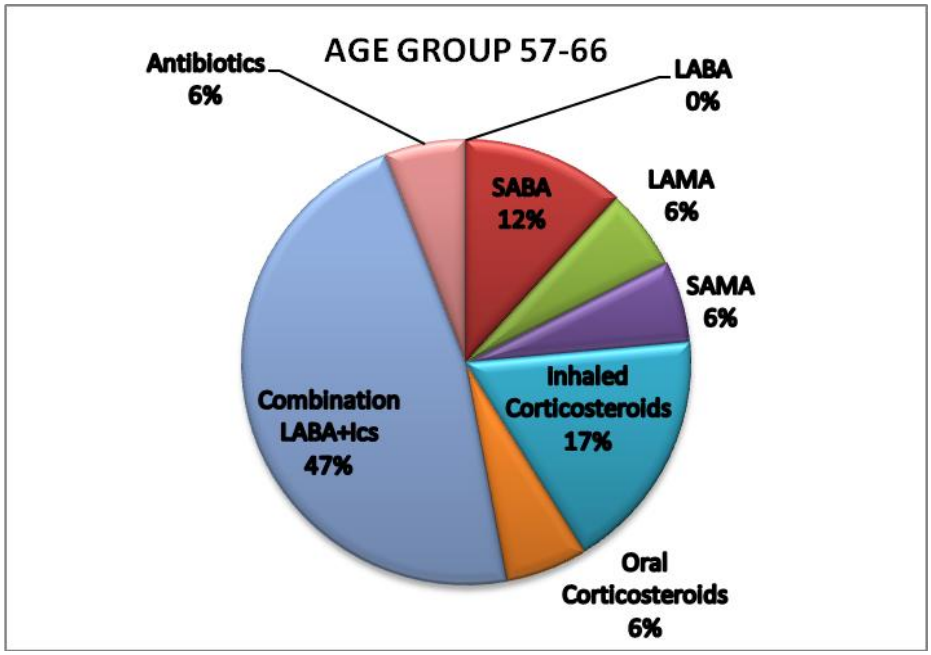
(A)



(B)



(C)



(D)

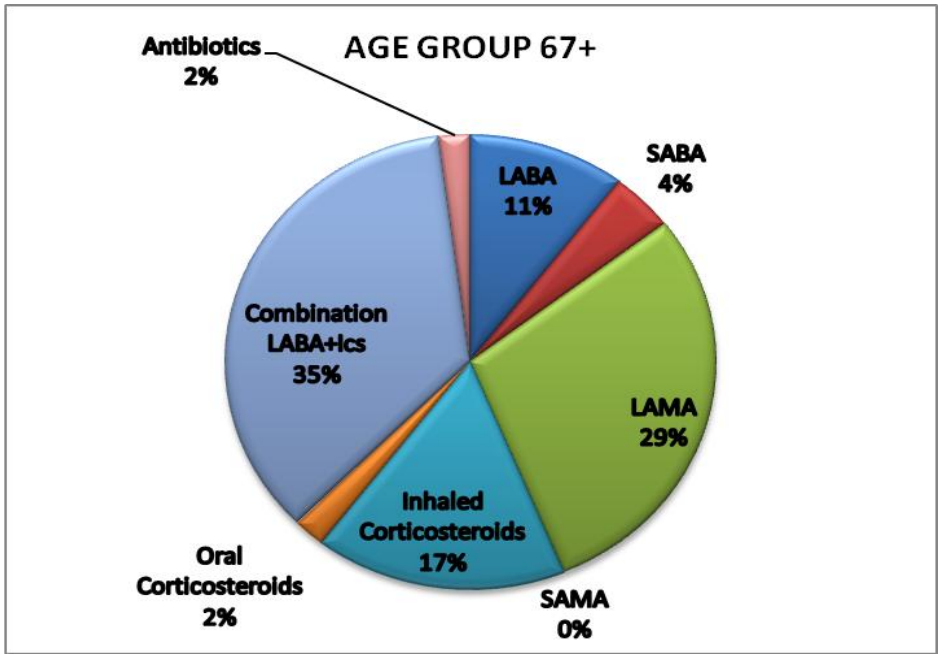


Figure .12. Pie Charts (A), (B), (C) and (D) showing frequency ratios of pharmacological categories among the four different age groups of patients where 100% is the total number of active substances used by the corresponding age group.

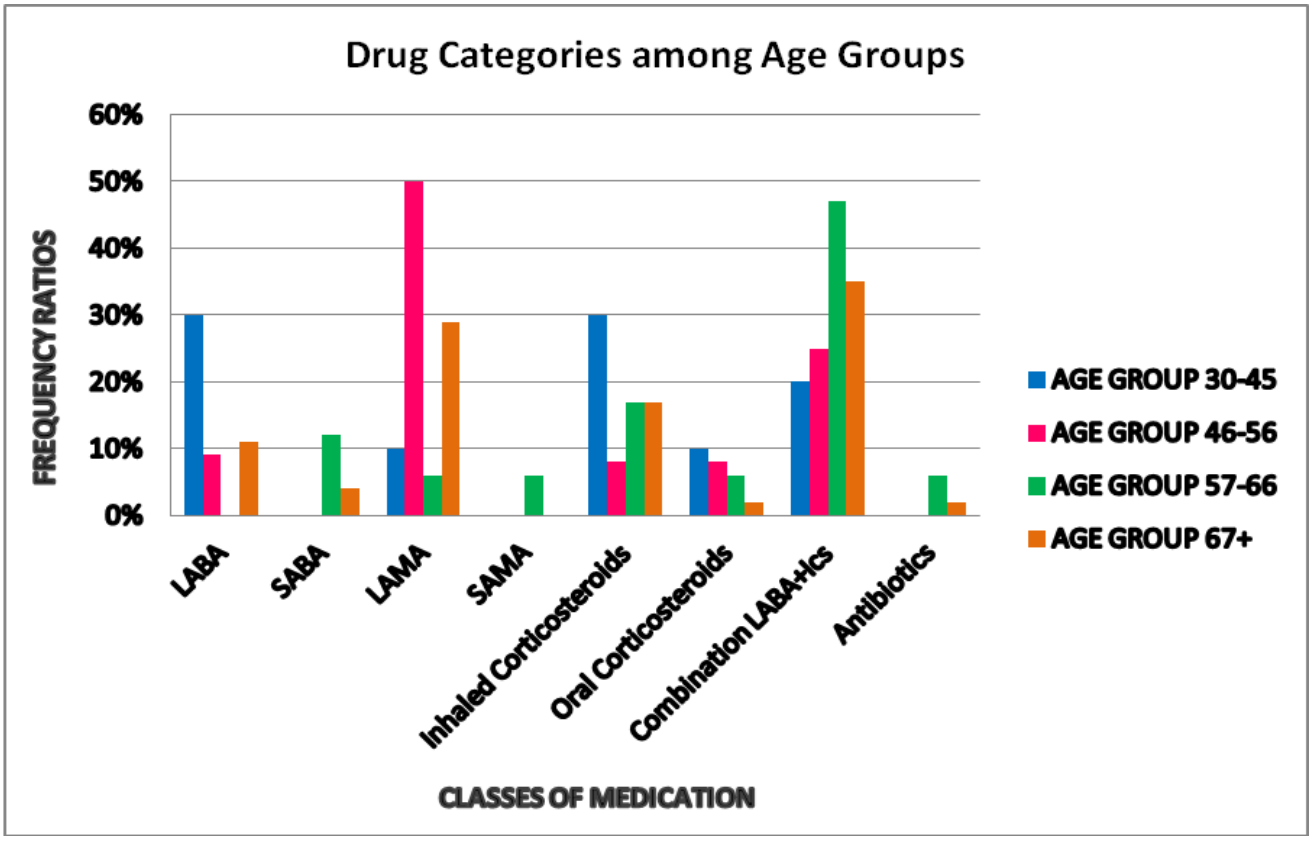


Figure .14. Overall Bar Chart representing the frequency of pharmacological classes of drugs among the four different age groups where 100% is the total number of active substances used by the corresponding age group.

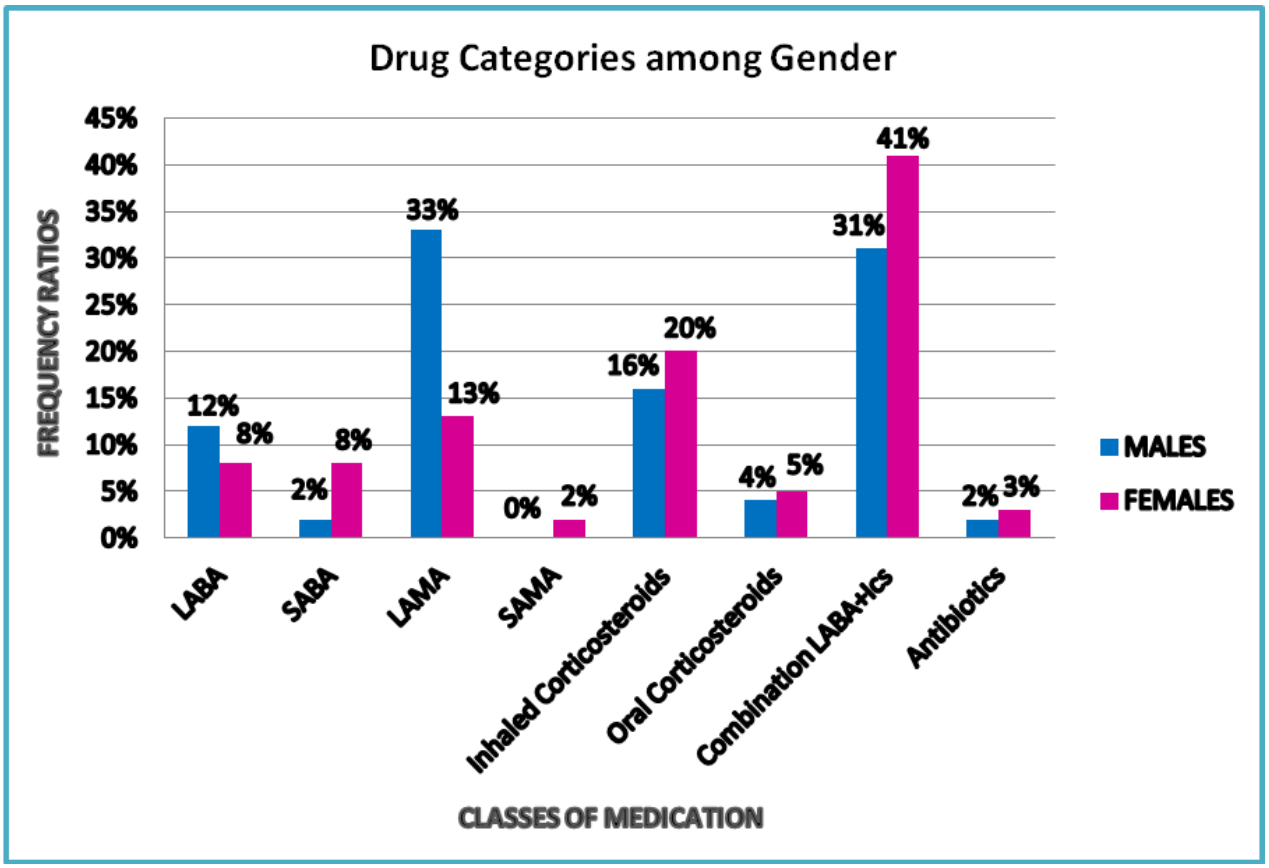


Figure .15. Bar Chart showing the frequency ratios of different pharmacological categories among the two genders where 100% is the total number of active substances used by each gender.

Route of Administration for Chronic COPD

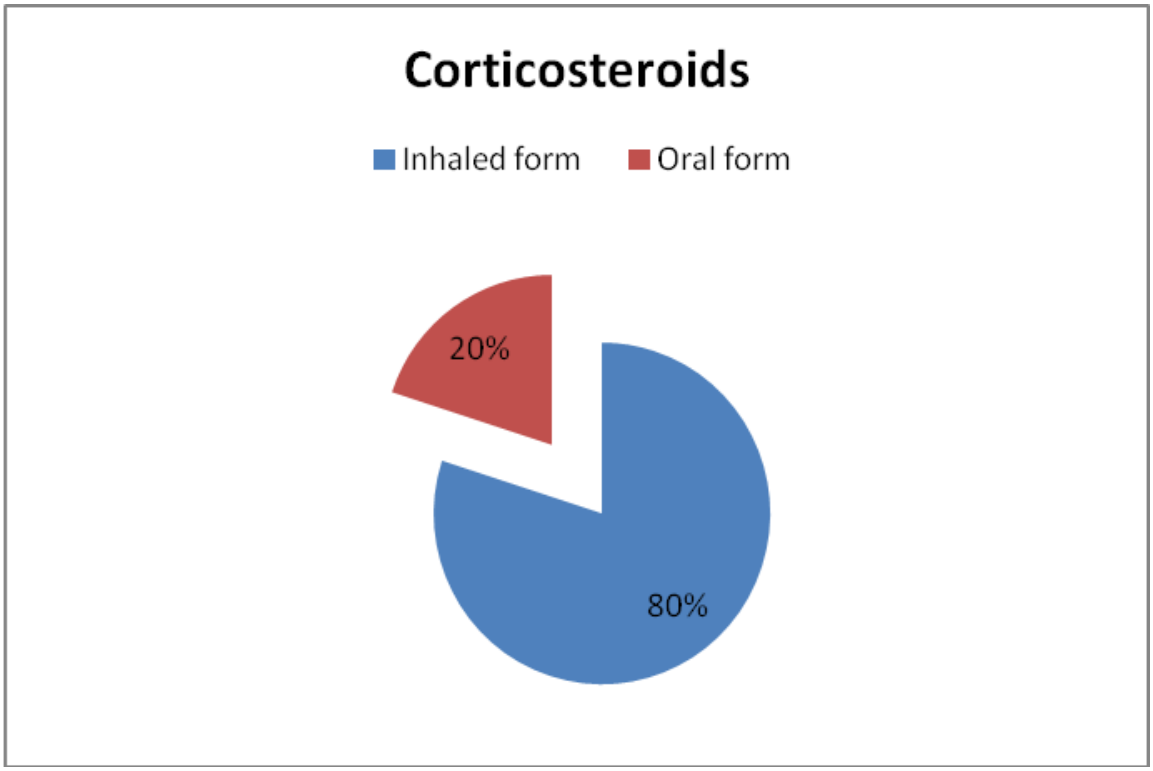
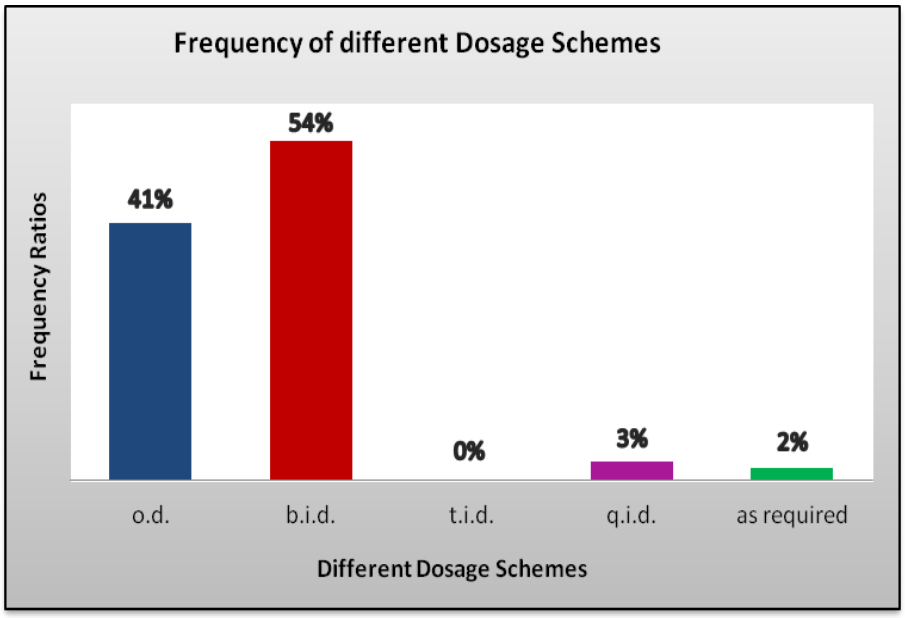


Figure .10. Pie Chart showing the frequency ratio of route of administration among the pharmacological class of corticosteroids in the prescriptions where 100% is total number of prescribed corticosteroids.

Statistical Features on Prescriptions

(A)



(B)

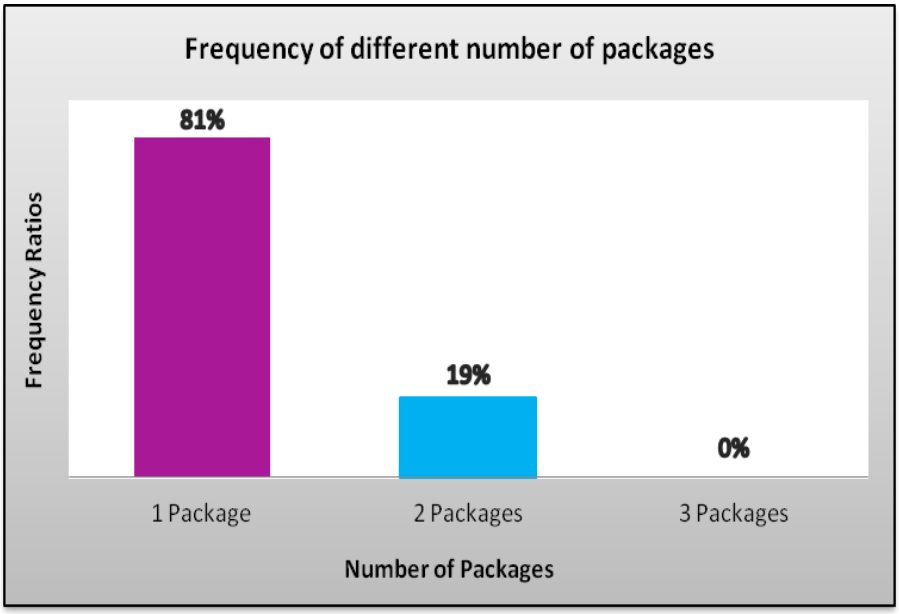
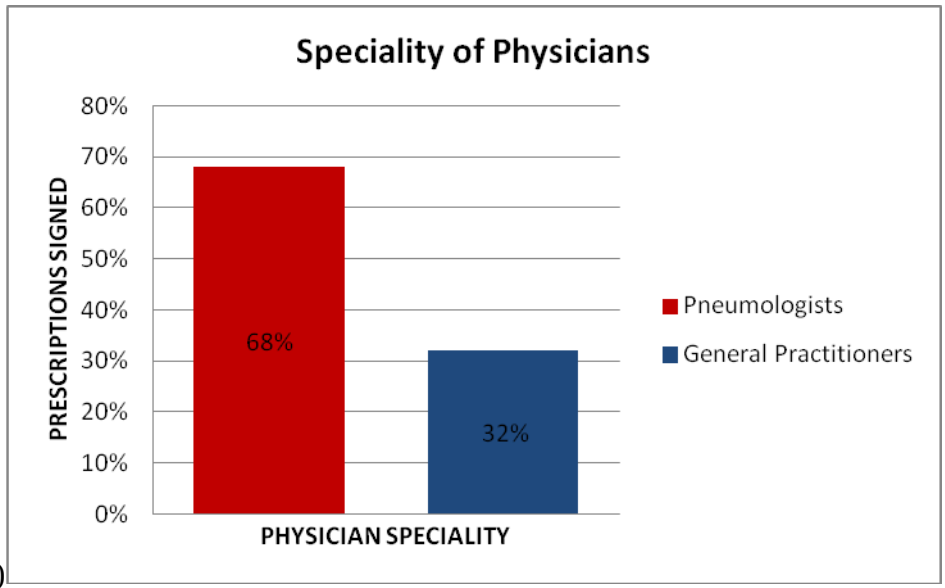


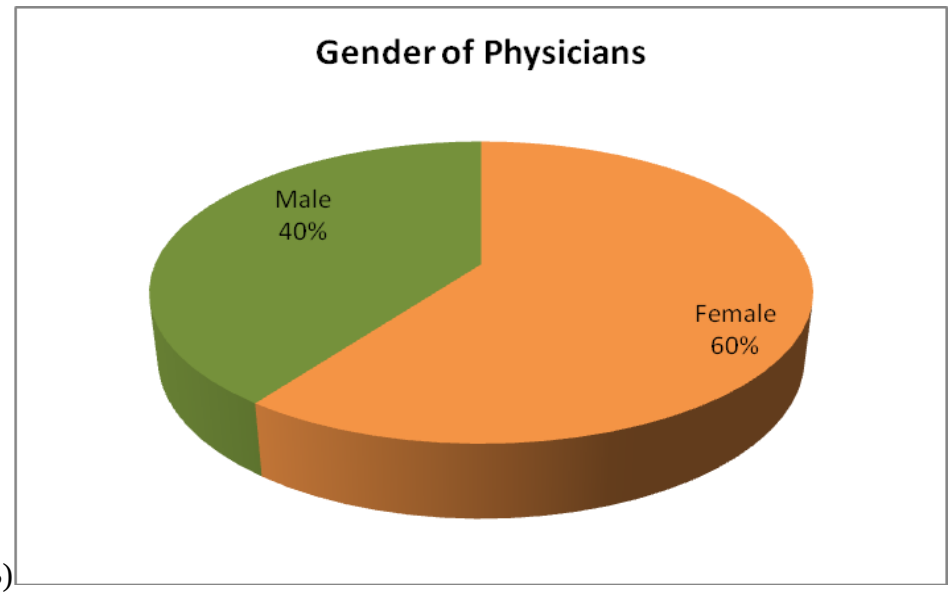
Figure .16. Bar Charts showing the most frequently prescribed (A) dosage schemes and (B) number of packages according to the sample of prescriptions used in this study where for (A) and (B) 100% is total number of trade names.

Characteristics of Physicians

(A)



(B)



Specialty	*Gender*	*Age*
Pneumologist	Female	51
Pneumologist	Female	49
Pneumologist	Male	54
General Practitioner	Female	47
General Practitioner	Male	56

Figure .11. Bar Chart (A) represents No of medical orders signed by each doctor specialty where 100% is total number of prescriptions. Pie Chart (B) shows distribution of physicians according their gender where 100% is total number of physicians and table shows all physicians characteristics.

Active Substances

Drug Name	Active Ingredients	Pharmacological Class
Singulair	montelukast sodium	leukotriene inhibitor
Foster	beclomethasone dipropionate+ formoterol fumarate	corticosteroid+ long-acting β2-agonist
Spiriva	tiotropium bromide	long-acting anticholinergic agent
Alvesco	ciclesonide	corticosteroid
Aerolin	salbutamol	short-acting β2-agonist
Rolenium	Salmeterol xinafoate+ fluticasone propionate	long-acting β2-agonist+ corticosteroid
Onbrez	indacaterol	long-acting β2-agonist
Bocacort	fluticasone propionate	corticosteroid
Seretide	salmeterol xinafoate+ fluticasone propionate	long-acting β2-agonist+ corticosteroid
Symbicort	budesonide+ formoterol fumarate	corticosteroid+ long-acting β2-agonist
Medrol	methylprednisolone	corticosteroid
Spectracef	cefditoren pivoxil	3rd generation cephalosporine antibiotic
Flixotide	fluticasone propionate	corticosteroid
Foradil	formoterol fumarate	long-acting β2-agonist
Miflonide	budesonide	corticosteroid
Atrovent	ipratropium bromide	short-acting anticholinergic agent

Figure.7. Table showing the active ingredients and drug category of each medicine.

All patients referred smoking history with the majority of them to have not been able to quit even after they have been diagnosed with COPD and experienced a lot of uncomfortable symptoms as well as the necessity to use medications.

The examined data (Figure 11 A.) have shown that quite more than half of the prescriptions were signed by pneumologists (68%) whereas the rest by general practitioners (32%). Also from figure 11 B. it can be seen that 60% of the physicians are females and 40% males with age (figure 11 C.) to be between the range of 47 for the youngest to 56 for the older. Figure 11 C shows in detail the characteristics of each one of the five in total physicians and it can be seen that 2 out of the 3 in total pneumologists are women while general practitioners appear to be equally distributed by being present one male and one female. Furthermore it can be noted that all three female physicians appear to be younger in age (47, 49, 51) than the two male physicians (54, 56) .

With regard to the characteristics of patients, frequency ratios according to the age of the patients is shown in figure 5. It is clear from the graph that patients were classified into four age groups: 30-45, 46-56, 57-66 and 67+. As it can be observed the vast majority of patients are at the age of 67 and over, accounting for more than half of the total number of patients with the considerably high percent of 53,6%. Patients aged between 46-56 appear to be the least common age group with 10,7% whereas younger people (30-45 years old) show a higher prevalence of COPD by gathering 16,1% of the total COPD patients. At the age group of 56-66 years old belongs the rest of the patients which accounts for 19,6%. The average age of patients in this study, was found to be 64 years old.

Pie chart in figure 4 shows the frequency ratio with regard to the gender of the patients to whom the examined sample of prescriptions apply. As it is demonstrated the number of male patients is rather high compared to females with 57% for the former and 42,9% for the latter, suggesting that chronic obstructive pulmonary disease is more common in men than in women.

As for the pharmacological classes of medications that have been seen in the sample of prescriptions, pie chart in figure 9 shows the statistical results. So as it is indicated the most frequently prescribed type of medication is the combined

LABA+ICs in one device having 34% of the total number of active substances prescribed. The pharmacological classes of long-acting muscarinic antagonists and inhaled corticosteroids accounted for 25% and 18% respectively. On the other hand oral corticosteroids appear have a considerably lower frequency with 5%, which is the same to the frequency of short-acting β2-agonists as well. However it can be seen that long-acting β2-agonists accounted for 10% which is exactly twice the frequency of their short-acting formulation. The two least frequently prescribed classes appear to be antibiotics and short-acting muscarinic-antagonists with 2% for the former and just 1% for the latter.

Pie Charts A,B,C and D in figure 12 show the frequency of pharmacological classes among the four age groups. Each Pie Chart represents another age group while Bar Chart in figure 14 includes the same information but in a condensed form.

As it can be seen long-acting β2-agonists (LABA) medicines were more frequently prescribed in the patients of age group 30-45 with 30%. Age groups 46-56 and 67+ have very similar frequency in this class of medicines with 9% and 11% respectively while the age group 57-66 appears not to have used LABA at all with 0%. In addition, figure 14 implies that short-acting β2-agonists (SABA) were used only by older patients belong to the age groups of 57-66 and 67+. Figure 12 C and D show in detail that for age group 57-66, SABA accounted for 12% while for age group 67+ only 4%.

Furthermore bar chart in figure 14 shows that long-acting muscarinic antagonists (LAMA) have been used by patients of all age groups with the significantly high rate of 50% among the age group 46-56 (figure 12 B.) They were prescribed for 29% of the patients older than 67 (figure 12 D.) whereas patients of age groups 30-45 (10%) and 57-66 (6%) appear to use less frequently this class of drugs. Contrary, from bar chart (figure 14) it can be seen that short-acting antimuscarinic agents have been used only by patients aged 57-66 and not very frequently (6%).

Bar Chart in figure 14 suggests that corticosteroids (oral and inhaled) as well as LABA+ICs (in combination device) are the most equally distributed among all age groups.

Inhaled corticosteroids as well as oral corticosteroids appear to be more common in younger patients of the age group 30-45 having a frequency ratio of 30% for the former and 10% for the latter (figure 12 A.). Inhaled corticosteroids show the exact same frequency in use (17%) among the age groups of 56-66 and 67+ but in age group of 45-55, the frequency is less than half with 8% (figure 14).

Oral corticosteroids appear to have been prescribed in similar frequencies among the age groups of 30-45, 46-56 and 57-66 (figure 14) but mostly in the younger people aged 30-45 with 10% frequency ratio (figure 12 A.). In the age groups of 46-56 and 57-66, frequency is slightly lower for the former group with 8% and even lower for the latter group with 6% (figure 12 B. and C.). In older people belonging to the age group of 67+, use of oral corticosteroids shows a significantly lower frequency accounted for only 2% (figure 12 D.).

Combination of LABA+ICs in one device shows the highest frequency (47%) on patients of the age group 57-66 (figure 12 C.) and the lowest (20%) among the patients of age group 30-45 (figure 12 A.). In between, older people 67+ also appear to use quite frequently LABA+ICs by showing a frequency ratio of 35% (figure 12 D.) whilst for those aged 46-56 the frequency in use is lower with 25% (figure 12 B.).

Bar Chart in figure 14 implies that antibiotics have been used rarely and only by patients of older ages. Namely they show a frequency of 6% among those aged 57-66 and 2% among patients older than 67 years old (figure 12 C. and D.).

Bar Chart in figure 15 demonstrates the frequency in use of each pharmacological class among the two genders of the patients. As it can be seen for females, the most commonly prescribed medication is by far the combination LABA+ICs which accounts for 41%. This means that 41% of the women patients have been using this type of medication. Males also appear to have a quite high frequency in use of LABA+ICs with 31% but they show just a little bit more in the use of LAMA with 33%. LAMA does not appear to be a common choice for females, who show a frequency in use 13% which is less than half of that of males. However female patients appear to be the only users of the short-acting form of this type of medication. Namely SAMA have been prescribed to 2% of the women patients but to none of the males. As it is shown, similar story in the case of LABA which are

preferred by males having a frequency in use 12% while 8% by females. Again the short-acting form (SABA) gets higher rate in use among women with 8% and only 2% for men.

Additionally from bar chart (figure 15) it seems that both types of corticosteroids are more frequently prescribed in women than in men. Generally, inhaled corticosteroids show a significantly higher frequency in use among both genders compared to oral corticosteroids. The inhaled form shows a frequency ratio of 20% among women while for men the figure is a bit lower with 16%. In contrast as it is demonstrated by the bar chart, use of oral corticosteroids is considerably lower with frequency ratios to be 5% for women and 4% for men.

Antibiotics appear to have very low frequency in use among both genders with only 3% for females and 2% for males.

Pie Chart in figure 17 indicates the frequency of asthma and COPD coexistence. As it can be seen asthma have been shown to be a coexisting condition in 14% of the COPD patients.

Figure 13 represents the frequency of prescribed medicines according to their active substances and strength. It can be easily seen that tiotropium bromide 18μcg is the most frequently prescribed medicine present in the sample of medical orders with 16% while ipratropium bromide 20μcg and fluticasone propionate 125μcg are the least common with just 1% for each. In addition tiotropium bromide with strength 2,5μcg is seen to be in 7% of the prescriptions which is less than half of the percent of tiotropium bromide in the strength of 18μcg.

The combination medicine of budesonide+formoterol fumarate (160+4,5)μcg accounts for the second highest percent which is 14% whereas the same combination in the strength of (320+9)μcg scores only 8%.

The corticosteroids ciclesonide 160μcg and fluticasone propionate 250μcg, the combination medicine salmeterol+fluticasone propionate (50+500)μcg, and the leukotriene Inhibitor montelukast sodium 10mg, all of them appear to have the same frequency by getting 5% each one. However salmeterol+fluticasone propionate in the strength of (50+250)μcg and montelukast sodium of 5mg appear to be less common than their higher strength versions with 2% and 3% respectively.

Considerably low frequency seems to have also the corticosteroid budesonide 400μcg and the LABA formoterol fumarate 12μcg with 3% whilst even lower the percent (2%) for the corticosteroid fluticasone propionate 50μcg, the antibiotic cefditoren pivoxil 400mg and the LABA indacaterol 150μcg. On the other hand indacaterol 300μcg appears to be twice more frequent than it is in the strength of 150μcg accounted for 4%. As it is shown in figure13, same frequency (4%) have the following medicines: the SABA salbutamol 100μcg, the corticosteroid methylprednisolone 16mg and the combination medicine of beclomethasone dipropionate+formoterol fumarate (100+6)μcg.

Figure 3 represents the same as figure 13 but according to their trade names and not as active substances. However by looking in Figure 7, it is indicated the correlation between trade names and active substances.

Oral preparations were present only as corticosteroids and to a significantly low proportion, namely 20% of the total number of corticosteroids prescribed were oral preparations (Figure 10).

Figure 16 A. demonstrates the frequency of different dosage schemes indicated on the available sample of prescriptions. It is obvious that the simplest instructions like “once daily” (o.d.) and “twice daily” (b.i.d.) are also the most common. As it can be seen 41% of the medications were signed with direction o.d. and 54% for b.i.d. However “three times daily” (t.i.d.) does not seem to be preferred as there is no medication with this indication for use, while “four times daily” (q.i.d.) even with a very low frequency rate (3%) is present. Furthermore 2% of the prescriptions indicate the use of medication with the instructions to be used “as required”.

In addition to these, the number of packages of a medication in medical orders prescribed was also examined. From figure 16 B. it can be seen that for the vast majority of medications, it was prescribed only one pack. Specifically for the 81% of the total number of medicines present in the sample of medical orders of this study, it was indicated the dispensing of one package of the appropriate product. There is also a 19% of prescriptions where two packages are required to be dispensed. Directions asking for three packages or more were absent in the examined sample of prescriptions.

4. Discussion

The selected pharmacy in Greece in which the study took place, is a relatively small pharmacy located in the Greek island of Crete and specifically in the Old Town of Rethymnon. This means that mostly the customers of this pharmacy are people who are living in Old Town and therefore it is easy for them to visit this pharmacy. However, random patients are often especially during summer and this is because Old Town is a place where all tourists and visitors of the town are going to visit. Generally Greek patients usually prefer the pharmacy of their neighborhood as they have easy access any time but many of them may prefer a pharmacy which is very close to their doctor, by this way they can get their medications immediately after visiting their physicians. However there is no evidence to prove such a Greek behavior and this is only a deduction from pharmacist experience.

Back to the pharmacy of this study, as it has been referred earlier the total number of standard patients of this pharmacy is 365 per month which on one hand is a relatively low proportion as the population of the town is approximately 33.000. On the other hand, if it is taken into account the dramatically increase on the number of pharmacies which is approximately 60 and that a lot of extra random patients and tourists visit this pharmacy through the year, it could be said that the number is satisfactory.

In Greece, prescriptions have a space line next to the sign “Diagnosis” which is required to be filled by the physician with the corresponding condition. In the selected pharmacy 51 out of the 365 medical orders per month indicate the diagnosis of COPD and 8 of those 51 were also indicating asthma at the same time. This gives a COPD prevalence among the regular patients of this pharmacy to be 14%.

COPD prevalence 14%, at first may not sound a significantly high frequency ratio, however 14% prevalence is quite noticeable and of concern. Unfortunately, it was not managed to determine the prevalence of COPD in Greece in more recent years but according to a study in 2004 with scope to determine the COPD prevalence in Greece, it was found the following figures: Athens 6%, urban areas 10,1%, semi-urban 8,5% and rural areas 9,1% (Tzanakis et al, 2004). As it can be seen the COPD prevalence of this study is quite higher than all of the above mentioned.

However this study is very limited and there are many factors that may influence the results. For example the selected pharmacy of this study is very close to two of the pneumologists who have been seen in the examined prescriptions and obviously this fact influences the number of COPD patients of this pharmacy.

In addition, as it has been mentioned before, in this study 56 prescriptions with the diagnosis of COPD were analyzed but because only 51 of them are known to belong to regular customers of the selected pharmacy, only those 51 were taken into account for the calculation of COPD frequency ratio among the patients of the pharmacy. However this may not be right, as it is not known if those extra 5 prescriptions belong to some random visitors, tourists, etc or to new patients of this pharmacy who have recently diagnosed with COPD. So these 5 prescriptions can be new COPD cases which if were included in the calculation, would give a higher COPD prevalence among the patients of the pharmacy.

COPD prevalence among the total population of the town is not a figure that can be calculated. We are unable to set a denominator as the sample of this study is very limited and there is a large number of COPD patients (which is not known) who visit other pharmacies of the town, therefore such a calculation would not provide us a reliable result regarding the frequency of COPD in the population of the town.

This is a pilot study and therefore it is very limited. There are no information concerning the medical history of the patients, co-existing diseases, for how long the patient suffers and what is the severity of it or contraindications. In addition the period of eight months that took to collect the sample is very short to observe an accomplished approach in therapy of COPD and the fact that only one pharmacy has been used as a source of prescriptions does not allow us to use the results as representative of the COPD management in Greece or even in Crete were the study took place. Therefore the results of this study allow us only to observe the medications which appear to be most commonly prescribed in the selected sample of prescriptions in Greece.

Medications prescribed in Greece are valid for one week. In other words from the date that a prescription is signed by the physician, pharmacist has the right to dispense the prescribed medication only within one week, after that period of time,

orders are assumed to be invalid and patients need to contact their doctor again for a new prescription. Also the amount of medicines prescribed need to be enough for the patients to cover their needs for one month. Same medications are not permitted to be prescribed more than once in the same month, therefore the number of packages prescribed must be proportional to the corresponding dosage scheme of the patient so that can last for one month.

This regulation in Greece, asking the patient to visit physician every month for a new prescription could be characterized inconvenient for the patient as the period of one month is very short and the patient is forced to do this procedure very often. On the other hand it could be said that the advantage of this regularly visit to the physician is that the clinical state of patient and the process of the disease are under tight surveillance, providing a better control of the condition of the patient.

In addition to the diagnosis, medications with dosage scheme, dosage form and number of packages, prescriptions include other information concerning the patient and physician. Complete name, gender and date of birth of the patient are necessary to be filled on the prescription. Physician's stamp provides the name and specialty of the doctor while their age can be found by looking on a special number named "AMKA of the doctor". By reading this number, the first six digits denote the date of birth of physician.

In this study all COPD prescriptions that were used, have been signed by five different physicians, three of them being specialized for respiratory conditions (pneumologists) and the other two general practitioners (figure .11.). The vast majority of the prescriptions (68%) have been signed by pneumologists, showing that patients prefer to visit specialized doctors than General Practitioners (figure .11.). Two of the pneumologists and one general practitioner are women, giving rise to the female gender among the total number of physicians as well as among the specialized of them. The age range is between 47-56 which should be considered young aged physicians.

According to a study exploring the impact of doctor's characteristics on patients, it is implied that younger and female doctors were found to have a better personal manner, technical skills, explanation skills and are considered more reliable

on their diagnosis, advice and suggested treatment by the patients (Shah et al, 2006). Even though the results of this study comply with the above mentioned evidence, it is obvious that the number of physicians is very low and these results regarding physicians characteristics cannot be used for any definite conclusion. As it is mentioned before Greek patients usually choose their doctor and pharmacist based on the location that is more convenient for them to have access. Therefore, this could be an explanation of the limited variability among the physicians present.

According to the results of this study, more than half (53,6%) of the total number of COPD patients were found to be older than 67 years old and the rest of the patients were distributed among the three other age groups(30-45, 46-56, 57-66). This is an expected result as it has been concluded by several studies that prevalence of COPD increases with age and especially for those over 65 years old, the risk increases by five-fold compared to those aged less than 40 years old (Raherison et al, 2009). Therefore our results fit with these results but there is lack of information concerning denominator number of citizens. COPD is an age dependent disease and this may be due to duration of smoking, usually resulting in ventilatory impairment (Walker and Whittlesea, 2012). Also because COPD develops slowly, individuals older than 40 years are more commonly diagnosed (WHO Fact Sheet No 315, 2012). However this study suggests a higher frequency ratio of COPD among the age group of 30-45 (16,1 %) compared to those aged 46-56 (10,7%). This could be the result of other risk factors that contribute to COPD development like occupation, genetic factors, air pollution, airway hyper-responsiveness and allergy or high tobacco exposure from early age (Walker and Whittlesea, 2012).

Figure 4 from results suggests that in this study, COPD is more common in males (57,1%) than in females (42,9%). Generally this fact used to be true due to the higher incidence of tobacco smoking in men but nowadays the number of women smoking tobacco especially in developed countries has increased noticeably, suggesting that both genders are almost equally affected by COPD (WHO Fact Sheet No 315, 2012). Hence, even though the evidence implying the COPD incidence equality between the two genders, in this study it can be seen that the older standpoint predominates.

In this study, as it has been shown before in results, the extremely high ratio of 80% of the prescriptions indicate the dispensing of 1 package. This is concomitant of the fact that most of the pharmaceutical products contain the required number of doses (relative to the corresponding strength) for one month treatment according to the standard dosage scheme for each medication, which is recommended by the National Greek Formulary of Medicines. For example if a medication in capsule form is to be used once daily, normally the box of the product will contain two blisters, each of which will have 14 capsules. However there are cases where the product does not contain the necessary amount for one month or the physician implies a different course of treatment with higher dose than the usual and therefore more packages of a medication may be required. This is shown in this study by the requirement of two packages in 19% of the prescriptions. For example Flixotide 50μcg/60 doses as a powder inhaler contains 60 blisters, the prescribed dose was 100μcg twice daily which means 120 doses are required and therefore 2 packages have been prescribed.

Observation of prescribed rate of active substances suggests tiotropium bromide and budesonide+formoterol fumarate (Symbicort) to be the most favorable prescribed medicines for those diagnosed with COPD. Tiotropium bromide with strength of 18μcg is the most frequently used one while Symbicort (160+4.5)μcg is the second with percentages of 16% and 14% respectively. The same drugs but in different strength are shown to be the third and fourth most often prescribed drugs with Symbicort (320+9)μcg to score the percentage of 8% whereas tiotropium bromide 2,5μcg slightly less with 7%.

Tiotropium bromide is an anticholinergic agent and specifically a long acting antimuscarinic broncodilator. On the contrary, Symbicort contains a combination of the active ingredients budesonide which is a corticosteroid and formoterol fumarate which is a long-acting β2 agonist, this type of combination device is very common in severe conditions of COPD where persistent breathlessness exist.

The recommended daily dose as it stated by ΕΟΦ (ΕΟΦ, 2012) for tiotropium bromide is usually 18μcg once daily using Handihaler device or 5 μcg using Respimat and for Symbicort turbohaler is (160+4.5)μcg twice daily or (320+9)μcg once daily which comes in agreement with the prescribed doses in this sample. Here

it should be mentioned that most of the prescriptions which indicate the use of tiotropium bromide and/or Symbicort were signed by specialized doctors for respiratory conditions called pneumologists, applying that these drugs are preferred by the specialized physicians in this study.

A high number of clinical trials have been studied the effects of tiotropium bromide in COPD, indicating that tiotropium bromide can improve lung function and exercise capacity as well as reduce lung hyperinflation and COPD exacerbations. However the use of tiotropium bromide in nebulizer device Respimat is of concern as there are speculations that this device delivers increased concentration of active substance in the lungs (Sharafkhaneh et al, 2013).

In contrast to tiotropium bromide which has been used by nearly one quarter of the total number of patients, ipatropium bromide which belongs to the short-acting antimuscarinic agents and can be seen under the trade name Atrovent, has been prescribed to a single patient at the dose of 40μcg four times daily as an aerosol inhaler. Ipatropium bromide provides short-term relief and can be used 3-4 times daily at a dose of 20-40μcg (BNF, 2007).

Clinical trials comparing the effectiveness of long-acting tiotropium and short-acting ipratropium, implied that tiotropium was associated 40% less than ipratropium with severe exacerbations (Salpeter, 2007).

Generally inhaled anticholinergic agents are considered to be the first choice bronchodilation therapy for mentainance management of stable COPD and this is because they have the ability to reverse the vagal tone which is the only reversible component of airflow limitation in COPD (Restrepo, 2007), therefore the high frequency ratio in use of the pharmacological class of LAMA with 25% was expected.

Long-acting β2-agonist with corticosteroids in combination devices are very common as maintenance therapy for COPD especially when FEV1 is less than 50% of the predicted (Walker and Whittlesea, 2012). Although the examined sample of prescriptions is small, this fact is illustrated by the results of the study. Symbicort (budesonide+formoterol fumarate) which has been annotated already, Foster, Rolenium and Seretide all belong to this type of medication and in total account for

the 34% of the prescribed medicines which is the highest frequency rate among the pharmacological groups.

Seretide and Rolenium both contain the same combination of the LABA salmeterol xinafoate and the corticosteroid fluticasone propionate. Even though Seretide is available in the form of discus and aerosol inhalers, only discus have been dispensed during this study. 2,04% of those at the strength of (50+250)μcg and 3,06% with strength (50+500)μcg twice daily. Rolenium was also prescribed at the strength of (50+500)μcg which is considered a more common choice for the management of COPD with ratio frequency 2,04%. By looking only the active substances in figure 13, it can be seen that salmeterol xinafoate+fluticasone propionate has been prescribed more in the strength of (50+500)μcg with 5% rather than in (50+250)μcg with 2% (ΕΟΦ, 2012).

Foster consists of a different combination of LABA and corticosteroid which is formoterol fumarate dihydrate and beclomethasone dipropionate, it exists only at the dose of (100+6)μcg and in the form of inhaler. Bar Chart shows that 4 patients out of the 56 were prescribed this medication as part of the COPD treatment (ΕΟΦ, 2012).

As it has been seen, in this study the most popular drugs among combinations of LABA+ICs are the budesonide+formoterol fumarate and fluticasone+salmeterol xinafoate. These combination therapies have been compared in a few small studies about their efficacy to lung delivery and the resolution of lung respiratory disability, concluding that budesonide+formoterol fumarate has a faster onset bronchodilator effect and reversible airway obstruction than fluticasone+salmeterol xinafoate in COPD patients (Lindberg et al 2007). However, according to Mensing (Mensing et al, 2007) a comparison between those two combinations is not easy as long term head to head comparisons in COPD patients are not available but generally it is implied that there is some evidence giving preference to combination therapy than using each component separately when both components are required (Mensing and Aalbers, 2007).

Although the use of bronchodilators for COPD is broadly accepted, the role of inhaled corticosteroids is less known even if their use increases nowadays. Available published results of a large number of clinical studies have demonstrated clinical

benefits after using the inhaled corticosteroids in COPD, including the important symptoms relief, improved lung function and most importantly the reduction in frequency and severity of exacerbations in severe COPD. Furthermore, it has been shown that the usage of the inhaled corticosteroids may reduce the rate of mortality and morbidity related to COPD (Decramer and Selroos, 2005, Russell et al, 2011).

Additionally, it has been implied that inhaled corticosteroids may reduce the progression of the disease in patients with COPD. Even though several scientific studies could not show alterations in the degree of FEV1 between treatment with inhaled corticosteroids and placebo drugs, it is indicated that there are few studies which have already prove that inhaled corticosteroids improve the FEV1 in a very important way (Decramer and Selroos, 2005, Russell et al 2011).

However because inhaled corticosteroids have been reported by several trials that are related with increased risk of pneumonia in COPD, their addition in COPD pharmacotherapy of a patient should be considered carefully by balancing the exacerbations benefit and long term risk of pneumonia (Singh, Loke, 2010).

Alvesco, Bocacort, Flixotide and Miflonide are all medicines that belong to the drug class of inhaled corticosteroids which accounts for 18% of the prescribed medicines and as it can be seen from the charts above, all of them have been prescribed as part of COPD management to a number of patients of the study, some of them more often and some other less.

Generally, it has been suggested that inhaled corticosteroids show long-term benefits in patients with moderate to severe disease who are having exacerbations and usually they are used together with LABA or LAMA (Walker Whittlesea, 2012). In this study, inhaled corticosteroids have been prescribed in all cases in combination with a bronchodilator.

Alvesco is a trade name for the corticosteroid ciclesonide and according to ΕΟΦ (the Greek national formulary of medicines, 2012), the dose should be 160μcg by aerosol inhalation daily as a single dose or reduced to 80μcg if control maintained. As is shown in figure 13, ciclesonide 160μcg accounted for 5% of the medications prescribed while there is no prescription to indicate ciclesonide in the dose of 80μcg.

Fluticasone propionate is the active ingredient (corticosteroid) of Bocacort and Flixotide, as a result both of these medicines have exactly the same pharmacological action. By looking the bar chart in figure 3, it is seen that Bocacort is present with frequency ratio to be 4,1% and with strength 250μcg whereas Flixotide is sub classified into three different strengths which are 50μcg, 125μcg and 250μcg accounted for 2%, 1% and 1% respectively. Hence, it can be assumed that in our study fluticasone propionate at the strength of 250μcg, is more favorable under the trade name of Bocacort compared to the Flixotide. The prescribed dosage schemes comply with the recommended dose of fluticasone propionate which is 100-250μcg or even 500μcg (if required) twice daily in the form of dry powder or aerosol inhalation (ΕΟΦ, 2012).

The rate of consumption of particular trade names when these contain the same active substance depends on physician's experience, level of reimbursement, patient preference and marketing activities on particular industry or wholesalers. Reimbursement level of both of the above mentioned products is the same and we are not able to monitor the rest of particular factors.

In addition the inhaled corticosteroid Miflonide, which contains as active ingredient the budesonide has been administered to three of the patients having a percent of 3,1%. Budesonide is available in the form inhaled capsules with strength 200μcg or 400μcg. In our sample only the latter strength was used which is the recommended dose to be taken twice daily for those suffering from COPD disease (ΕΟΦ, 2012). From the data available, it is known that two of the patients received budesonide together with formoterol fumarate which is a long-acting β2-agonist while in the third prescription, budesonide was combined with tiotropium bromide (LAMA).

Even though systemic inflammation is a big issue in COPD causing a lot of symptoms and reduces the quality of life, it has been concluded by studies that the use of systemic corticosteroids does not show long term benefits in stable COPD. In contrast it is suggested that their use is related with toxicity, osteoporosis, hypertension, glucose intolerance and myopathy. Especially in patients older than 65 years, it is suggested to increase mortality rate (Falk et al, 2008). Unfortunately as it

has been mentioned before, there is no available information regarding the comorbidities of the patients and therefore we are not able to make an extensive analysis of their use in this study.

It should be noted that the use of oral and inhaled corticosteroids concomitantly or the use of more than one inhaled corticosteroid by patients was not found and therefore the frequencies which have been calculated based on the total number of corticosteroids prescribed, are equal to the frequencies among the number of patients using corticosteroids.

The use of oral corticosteroids in our cohort study is low and this may be due to their increased risks. It is obvious that prescribing of oral corticosteroid was very low with only 20% of the patients using corticosteroids to have been prescribed the oral form and the major 80% left to use the inhaled form. Especially among the elderly group (67+) oral corticosteroids account for the really low frequency rate of 2% while among the younger age group 30-45, their use was more frequent but still low with 10%. Generally corticosteroids are not first choice in COPD (Falk et al, 2008) and as it can be seen in our cohort study, inhaled form is prioritized due to the lower risk of adverse drug reactions.

However their use for COPD exacerbations has been found to offer improved pulmonary function and dyspnoea, decrease in relapse of the treatment of exacerbations and length of hospitalizations. According to a study on patients with COPD exacerbations, the administration of 0,5mg/kg of methylprednisolone intravenously improved bronchodilator FEV1significantly compared to placebo (Falk et al, 2008).

The majority of COPD exacerbations are managed in hospital and this data of information was not available as well. Methylprednisolone is the only oral corticosteroid present in our sample and it is found under the trade name Medrol. Medrol tablets with strength 16mg have been prescribed to four of the patients to be taken every morning. The dose of 16mg daily is inside the recommended dose limits which is between 4mg-48mg daily (ΕΟΦ, 2012).

Therefore, according to the available COPD guidelines and evidence reviews it can be assumed that those patients who have been prescribed the oral corticosteroid

methylprednisolone, suffer with severe COPD and are experiencing severe exacerbations.

Long-acting β2-agonists are considered a very important pharmacological class for the management of COPD, improving symptoms and health status of the patients or even stimulate a reduction in CODP exacerbations. Also studies suggest that their long term use is not associated with increased rate in mortality or exacerbations and only slightly with adverse events like palpitations or skeletal muscle tremors (Decramer et al, 2013). However other studies support that β-agonists are related with cardiovascular adverse effects and increase the risk of adverse cardiac events by over two-fold compared with placebo or even more in patients with COPD and concomitant heart disease (Salpeter, 2007).

In our study LABA were most frequently used among the younger age group 30-45 and much less in the others. The increased risk of cardiovascular events that is suggested, may be the reason for mostly prescribing these drugs among younger people who are considered less susceptible of heart problems.

Indacaterol and formoterol fumarate are the only long-acting β2-agonists present in our study and account for 10% of the total prescribed medicines with indacaterol to have been prescribed more than formoterol fumarate. Both medications are in the form of dry powder for inhalation. Formoterol fumarate (Foradil) is available with strength 12μcg whereas for indacaterol (Onbrez), there are two options with dose of 150μcg or 300μcg (ΕΟΦ, 2012). Data indicates that indacaterol 300μcg was twice as common as indacaterol 150μcg (4% and 2% respectively) and formoterol fumarate has a frequency of 3%..

It is important to note that indacaterol is one more medicine that seems to be preferred in our cohort by specialized doctors as there are in total six orders referring to Onbrez and all of them have been signed by pneumologists. Unfortunately, it was not managed to find what is the consumption of indacaterol in Greece in order to comprehend if it generally a drug of choice in Greece. The advantage of indacaterol compared to formoterol fumarate, is that it is the first ultra-long-acting beta-agonist that can be taken once every day as it has a 24- hours activity (Naline et al 2007, Sturton et al 2008), this increases drug compliance by particular patients, also

because of the improved cardiovascular safety profile over the rest of LABA and its specificity in use for COPD rather than asthma (Battram et al 2006). In contrast, Foradil which is the a trade name for formoterol fumarate is used for asthma and COPD and has a duration of action of 12- hours, as a result should be taken twice daily (ΕΟΦ, 2012).

Of course the preference for indacaterol could be based as for others medicines on drug marketing, physician's experience, being recommended and reimbursement reasons which are not known.

As it has been mentioned above the pharmacological categories of LABA as well as LAMA are of high importance as bronchodilators for COPD. By a number of studies, it is indicated that combination treatment of those two different bronchodilators can provoke significant improvement in lung function in COPD patients compared to the use of each drug alone (Singh et al 2008, Welte et al 2009, Cazzola,Tashkin, 2009). Consequently the modern approach of the ideal drug therapy is focused on the development of drugs that are based on the combination therapy of both muscarinic antagonists and β2-agonists in a single molecule. An advantage of this combination therapy known as MABA is the benefit of delivering in every region of the lung (Steinfeld et al, 2011).

Only 4,1% from the medicines prescribed was the drug salbutamol. Aerolin is a trade name for salbutamol which belongs to the class of medicines called short-acting β2-agonists (SABA). Short-acting β2-agonists are very commonly used as inhalers and 'as required' by patients suffering from COPD disease as they provide symptom relief, they can improve exercise tolerance and are not known to cause a lot of side effects (Walker and Whittlesea, 2012). SABA appear to have a very low frequency rate of 5% during the period of the study.

Salbutamol of 100μcg as aerosol inhaler was the only SABA in our prescriptions and followed with the instructions of four times daily or "as required". Also the data from the prescriptions shows that all patients who received salbutamol, received a LABA as well. Generally during treatment with LABA, the add on therapy of a SABA medication is recommended when airflow obstruction increases suddenly

to provide rapid and effective control of symptoms and airway obstruction (La Piana et al, 2011).

SABA have been used mostly by females who are older than 57 years old. The same appears to apply for the pharmacological class of SAMA which have the same indication in use as SABA. Thus it could be deduced that in our sample females aged 57 and over, are experiencing more often sudden worsening of symptoms and therefore require the use of a short-acting bronchodilator as a rescue medicine. Generally, studies on the difference of COPD among gender, have concluded that women experience more severe symptoms and overall worse health status than men (Han et al, 2007).

Furthermore, cefditoren pivoxil (Spectracef) is a medicine that can be seen in two of the prescriptions, having a frequency ratio of 2%. Cefditoren pivoxil belongs to the 3rd generation cephalosporin antibiotics. It is indicated for the treatment of pharyngitis, tonsillitis and uncomplicated skin disorders at a dose of 200mg. However in this study, patients received Spectracef tablets at a dose of 400mg which is the approved dose for chronic bronchitis therapy (ΕΟΦ, 2012). Both prescriptions implied the use of cefditoren pivoxil 400mg with Symbicort (160+4,5)μcg (budesonide+formoterol fumarate).

A course of antibiotics in COPD is usually required when patients experience severe acute exacerbations. As it has been indicated, use of antibiotics among elderly is limited and according to a study among COPD patients with age over 65 with exacerbations, only half of them received antibiotics. It is suggested that their use is more commonly among COPD patients experiencing exacerbations who also co suffer from other diseases like diabetes and heart failure (Akgun et al, 2012). The results of this study suggest that antibiotics have been used by patients older than 56 years and of both genders but again because our cohort is too small, it cannot been considered as a fact. However it could assumed that those patients have been experiencing COPD exacerbations, but if they suffer from any other comorbidity, is an assumption that cannot be made as there is not enough information available with regard to the clinical state of patients.

Furthermore, it should be noted that the drug montelukast sodium has been prescribed quite often to the patients of the study with frequency ratio in use 5% for montelukast 10mg while in strength of 5mg one was a bit less common with 3%. Montelukast sodium is a leukotriene inhibitor which is used orally for the control of asthma usually in combination with inhaled corticosteroids (BNF, 2007), hence it seems to be an inappropriate choice for the treatment of COPD. However, according to the data available it has to be reported that the diagnosis for those patients, stated COPD and asthma so it can be explained the administration of montelukast sodium together with other medications like inhaled corticosteroids, LABA and anticholinergic agents. EOF recommends that an adult dose should be 10mg every night which is the prescribed dose in all of the prescriptions (ΕΟΦ, 2012). In three medical order montelukast sodium of 5mg has been prescribed but directions implied two tablets to be taken every night which means 10mg daily.

It is very interesting to note that all of the prescriptions in our study with the diagnosis "COPD and Asthma" included the montelukast sodium as part of the treatment. This is very surprising because montelukast sodium is not generally used as first choice drug in the treatment of asthma. It is considered as an effective alternative to low dose ICs, (which is the recommended first line treatment in mild-moderate asthma control) as monotherapy or as add on therapy when patients are not controlled or satisfied with ICs treatment. However a high number of studies in recent years, have demonstrated the effectiveness, the good safety profile as well as the higher compliance of montelukast sodium compared to ICs due to the inhalation technique twice daily of the latter. In addition it has been implied that montelukast sodium is particularly effective for some specific asthma phenotypes, with one of them to be "asthma in smokers" which can be said that is closely related to the cases present in this study and therefore this may be a reason for the high frequency rate of montelukast sodium (Paggiaro and Bacci, 2011, Mclvor et al, 2009).

On the other hand, according to all international guidelines the ICs are still considered more effective than leukotriene inhibitors in monotherapy and montelukast sodium is positioned in second choice (Paggiaro and Bacci, 2011). Hence it is still inquisitive why all prescriptions with the diagnosis of "COPD and

Asthma" referred to montelukast sodium. An assumption that could be the case, is that may there were more prescriptions for patients with COPD and asthma in our sample but they were not indicated by physician because the treatment is very common or may there are reasons regarding the reimbursement that influence the decision of physician not to sign both conditions. However all of this is hypothetical and in any case it should not be considered as datum.

The frequency of patients with COPD and asthma in our cohort is shown to be 14% of the total COPD patients. It is suggested that according to a study, 17% to 19% of patients with obstructive airway diseases had more than one condition or overlap (Kim and Rhee, 2010). Hence in our study the frequency is shown to be lower than those results.

As it has been stated by epidemiological studies, a large proportion of older people suffering from COPD experience the overlap syndrome of asthma-COPD. Asthma-COPD syndrome is related mainly with the elderly with smoking history who are experiencing asthmatic features to their COPD. Although asthma and COPD are two different diseases, distinguishing them is not always possible due to symptoms overlap. Even the differentiation between asthma-COPD overlap and asthma and COPD coexistence is hard due to lack of information on guidelines and as a result a course of treatment which would cover both conditions is often prescribed (Zeki et al, 2011).

Inhaled corticosteroids and long-acting β2-agonists play an important role in the management of asthma bronchial, therefore it could be assumed that their relatively high frequency in use in this study is partially owed to those patients diagnosed with asthma and COPD. However this cannot be confirmed as they are generally used for both conditions.

Medical orders imply that every single one of the 56 in total COPD patients has been prescribed at least one medication in the inhalation form suggesting that patients regardless gender or age group have to use an inhalation device. Correct use of inhalation devices is very important, however even patients who are not suffer from COPD may not be able to use them correctly and especially among the elderly. This leads to patient incompliance with treatment that usually results to under

treatment. In addition according to an adherence study on older people, it was indicated that a high percent of patients did not comply with treatment because of the increased cost of inhalation device (Akgun et al, 2012)

Therefore as it can be seen there are a lot of problems with regard to patients no adherence related to the inhalation route of administration. However inhalation is the main form of medications used in COPD and this is because inhalation form has the advantage of being as effective as the oral form with much less side effects (Walker and Whittlesea, 2012).

Finally, an evaluation-criticism of this study would be appropriate to be noted. Only 56 prescription were gathered in the current study that took place during a period of eight months which is a very small sample as well as a very short period of time for obtaining accomplished results. A major disadvantage of this study was the lack of detailed information concerning each patient and their pharmacotherapy individually. For instance details regarding the medical history or the existence of comorbidies were absent, and therefore we were not have the ability to evaluate factors influencing the use of drugs like contraindications, adverse events or drug-drug interactions. Moreover, clinical state of patients, for how long a patient suffers and severity of COPD are very important factors on the choice of appropriate medical treatment. Hence, not knowing these information does not allow us to understand the scope and meaning of prescribed pharmacotherapies but only observe them. As a result of the above mentioned limits of the study, it can be concluded that the aim of this study namely the analysis of pharmacotherapy of COPD in Greece was not reached. A more extensive study is required with the collection of as more as possible information related to patient medical state and disease and also the contribution of more pharmacies from different places through Greece providing a broadly spectrum approach to the COPD pharmacotherapy in Greece.

5. Conclusion

COPD is a long term lung disease which is considered as a leading cause of mortality and morbidity with smoking to be the major risk factor for its development.

To conclude, according to the results of this study, COPD found to have a prevalence of 14% among the ill patients who are visiting the selected pharmacy regularly. The disease was found to be more common in men and elderly than in women and younger people. In addition among the COPD patients of the study, a 14% of them was diagnosed with COPD and asthma as well.

The pharmacological classes of LABA/ICs and LAMA appear to be the most frequently prescribed. Generally the pharmacological categories of SABA, SAMA, oral corticosteroids and antibiotics are shown to have considerably lower frequency in use compared to LABA, LAMA, LABA/ICs and inhaled corticosteroids. Combination medicines of LABA/ICs appear to be the most equally distributed in frequency of use among all age groups.

A more extensive study with information regarding the patients clinical state, advertising campaigns of pharmaceutical companies and a representative sample of Greek population would provide a better understanding of the prescribed pharmacotherapies.

6. Abbreviations

COPD – Chronic Obstructive Pulmonary Disease

SABA – Short acting β2-agonists

LABA – Long acting β2-agonists

SAMA – Short acting muscarinic antagonists

LAMA – Long acting muscarinic antagonists

ICs – Inhaled corticosteroids

o.d. – Once daily

b.i.d. – Twice daily

t.i.d. – Three times daily

q.i.d. – Four times daily

VC – Vital Capacity

FVC – Forced Vital Capacity

FEV1 – Forced Expiratory Volume in the first second of exhalation

RV – Residual Volume

BNF – British National Formulary

ΕΟΦ – Greek National Formulary for Medicines

GOLD – Global Initiative for Chronic Obstructive Lung Disease

ΑΜΚΑ – Social Security Number

TORCH – Towards a Revolution in COPD Health

CNS – Central Nervous System

BMI – Body Mass Index

TNF – Tumor Necrosis Factor

cAMP – Cyclic Adenosine Monophospate

PDE – Phosphodiesterase

IL-6 – Interleukin 6

PAO2 – Partial Pressure of Oxygen in arterial blood

7. References

Aaron SD, Vandemheen KL, Fergusson D et al for the Canadian Thoracic Society/Canadian Clinical Research Consortium: Tiotropium in combination with placebo, salmeterol, or fluticasone-salmeterol for treatment of chronic obstructive pulmonary disease: a randomized trial. Ann Intern Med 2007; 146:545-55.

Akgun K, Crothers K, Pisani M et al, A Bio Sci Med Sci, 2012; 67A(3): 276-291.

Alam I, Lewis K, Stephens JW et al, Obesity, metabolic syndrome and sleep apnoea: all pro-inflammatory states. Obes Rev 2007; 8: 119–127.

American Thoracic Society, COPD Guidelines For Health Professionals, Management of Stable COPD, Long Term Oxygen Therapy, 2013, available from: http://www.thoracic.org/clinical/copd-guidelines/for-health-professionals/management-of-stable-copd/long-term-oxygen-therapy/home-oxygen-therapy.php

American Thoracic Society, Pathology – Pathophysiology of COPD, 2013, available from: http://www.thoracic.org/clinical/copd-guidelines/for-health-professionals/pathology-pathogenesis-and-pathophysiology/pathogenesis.php

American Thoracic Society, Standards for the diagnosis and management of patients with COPD, European Respiratory Society, 2004, available from: http://www.thoracic.org/clinical/copd-guidelines/resources/copddoc.pdf

Barnes PJ, Corticosteroid Resistance in airway disease, Proc Am Thorac Soc, 2004; (1): 264-268.

Barnes PJ, Theophylline in Chronic Obstructive Pulmonary Disease, Proceedings of the American Thoracic Society, 2005; 2(4): 334-339.

Battram, C. et al. In vitro and in vivo pharmacological characterization of 5-[(R)-2-(5,6-diethyl-indan-2-ylamino)-1-hydroxyethyl]-8-hydroxy-1H-quinolin-2-one (indacaterol), a novel inhaled b2 adrenoceptor agonist with a 24-h duration of action. J. Pharmacol. Exp. Ther, 2006; 317: 762–770.

Beauchamp MK, Janaudis-Ferreira T, Goldstein RS et al, Optimal duration of pulmonary rehabilitation for individuals with chronic obstructive pulmonary disease - a systematic review. Chron Respir Dis. 2011; 8(2):129-40.

Beers M, The Merck Manual of Diagnosis and Therapy, Chronic Obstructive Pulmonary Disease, 18th Edition, Merck Research Laboratories, 2006; 400-420.

BNF, British National Formulary, 53, British Medical Association, Royal Pharmaceutical Society of Great Britain, BMJ Publishing Group Ltd, 2007; 143-176.

Boswell-Smith V, Page CP, Roflumilast: a phosphodiesterase-4 inhibitor for the treatment of respiratory disease, Expert Opin Investig Drugs, 2006; 15:1105–13.

Bousquet J, Aubier M, Sastre J et al. Comparison of roflumilast, an oral anti-infl ammatory, with beclomethasone dipropionate in the treatment of persistent asthma. Allergy, 2006; 61:72–8.

Briggs DD Jr, Covelli H, Lapidus R et al, Improved daytime spirometric efficacy of tiotropium compared with salmeterol in patients with COPD, Pulm Pharmacol Ther, 2005; 18(6): 397-404

Brown W, Treating COPD with PDE 4 Inhibitors, Int J Chron Obstruct Pulmon Dis, 2007; 2(4): 517-533.

Buhl R, Dunn LJ, Disdier C et al, Blinded 12-week comparison of once-daily indacaterol and tiotropium in COPD, Eur Respir J, 2011; 38(4): 797-803.

Butorac-Petanjek B, Parnham MJ, Popovic-Grle S, Antibiotic therapy for exacerbations of chronic obstructive pulmonary disease (COPD), J Chemother. 2010; 22(5): 291-7.

Cazzola M, Tashkin DP, Combination of formoterol and tiotropium in the treatment of COPD: effects on lung function, 2009; 6: 404–415.

Chaouat A, Naeije R, Weitzenblum E, Pulmonary Hypertension in COPD, 2008, available from http://erj.ersjournals.com/content/32/5/1371.short

Chatila W, Tomashow B, Minai O et al, Comorbidities in Chronic Obstructive Pulmonary Disease, Pro Am Thorac Soc. 2008; 1 5(4): 549-555

Chong J, Poole P, Leung B et al, Phosphodiesterase 4 inhibitors for chronic obstructive pulmonary disease. Cochrane Database Syst Rev. 2011; 11:(5).

Christie P, Roflumilast: a selective phosphodiesterase 4 inhibitor. Drugs Today. 2005; 41:667–75.

Davidson PM, Johnson MJ, Update on the role of palliative oxygen, Curr Opin Support Palliat Care. 2011; 5(2):87-91.

De Marco R, Accordini S, Marcon A et al, Risk factors for chronic obstructive pulmonary disease in a European cohort of young adults, Am J Respir Crit Care Med, 2011; 183(7): 891-7.

Decramer M, Hanania N, Lotvall J et al, The safety of long-acting β2-agonists in the treatment of stable chronic obstructive pulmonary disease, Int J Chron Obstruct Pulmon Dis, 2013; 8: 53-64.

Decramer M, Selroos O. Asthma and COPD: differences and similarities With special reference to the usefulness of budesonide/formoterol in a single inhaler (Symbicort) in both diseases. Ltd Int J Clin Pract, 2005; 59(4): 385–398.

Eisner MD, Blanc PD, Yelin EH et al, COPD as a systemic disease: impact on physical functional limitations, Am J Med, 2008; 121(9):789.

Falk J, Minai O, Mosenifar Z, Inhaled and systemic corticosteroids in Chronic Ostructive Pulmonary Disease, Proc Am Thorac Soc, 2008; 5(4): 506-512.

Feldman GJ, Improving the quality of life in patients with Chronic Obstructive Pulmonary Disease: Focus on Indacaterol, 2013; 8: 89-96.

GOLD, Global Initiative for Chronic Obstructive Lung Disease, Global strategy for the diagnosis, management, and prevention of chronic obstructive pulmonary disease: Executive summary, 2006, available from: http://www.goldcopd.org/Guidelines/guideline-2006-revision%3a-executive-summary%2c-global-strategy-for-the-diagnosis%2c-management%2c-and-prevention-of-copd.html

GOLD, Global Initiative for Chronic Obstructive Lung Disease, Global strategy for the diagnosis, management, and prevention of chronic obstructive pulmonary disease, 2013, available from: http://www.goldcopd.org/guidelines-global-strategy-for-diagnosis-management.html

Grootendorst DC, Gauw SA, Benschop N et al, Efficacy of the novel phosphodiesterase-4 inhibitor BAY 19-8004 on lung function and airway inflammation in asthma and chronic obstructive pulmonary disease (COPD), Pulm Pharmacor Ther, 2003; 16: 341- 7.

Han M, Postma D, Mannino D et al, Am J Respir Crit Care Med, 2007; 15;176(12): 1179-1184.

Han MK, Update in chronic obstructive pulmonary disease in 2010, Am J Respir Crit Care Med, 2011; 15;183(10):1311-5

Hill K, Geist R, Goldstein RS et al, Anxiety and depression in end-stage COPD. Eur Respir J 2008; 31: 667–677.

Jadad A, Rizo C, Cubillos P et al, Measuring symptom response to pharmacological interventions in patients with COPD: a review of instruments used in clinical trials, Curr Med Res Opin, 2004 ;20(12):1993-2005.

Jorgensen NR, Schwarz P, Holme I et al The prevalence of osteoporosis in patients with chronic obstructive pulmonary disease: a cross sectional study, Respir Med, 2007; 101: 177–185.

Katzung B.G, Basic and Clinical Pharmacology, 10th Edition, The McGraw-Hill Companies, 2007; 319-335.

Kessler R, Partridge MR, Miravitlles M et al, Symptom variability in patients with severe COPD: a pan-European cross-sectional study. Eur Respir J, 2011;37(2): 264.

Kim SR, Rhee YK, Overlap between Asthma and COPD: Where two diseases converge, Allergy Asthma Immunol Res, 2010; 2(4): 209-214.

Kwak HJ, Song JS, No ZS, et al. The inhibitory effects of roflumilast on lipopolysaccharide-induced nitric oxide production in RAW264.7 cells are mediated by heme oxygenase-1 and its product carbon monoxide. Inflamm Res, 2005; 54: 508–13.

La Piana GE, Corda L, Bertella E et al, Dose-response curve to salbutamol during acute and chronic treatment with formoterol in COPD, Int J Chron Obstruct Pulmon Dis, 2011; 6: 399-405.

Leader D RN, About.com Guide, COPD Symptoms, Understanding COPD Symptoms: The First Step in Managing COPD, 2012, available from: http://copd.about.com/od/signsandsymtpomsofcopd/tp/COPD-Symptoms-.htm

Light RW, UpToDate, Secondary spontaneous pneumothorax in adults, Wolters Kluwer Health, 2012, available from: http://www.uptodate.com/contents/secondary-spontaneous-pneumothorax-in-adults

Lindberg A, Szalai Z, Pullerits T et al, Fast onset of effect of budesonide/formoterol versus salmeterol/fluticasone and salbutamol in patients with chronic obstructive pulmonary disease and reversible airway obstruction. Respirology, 2007;12(5): 732–739.

Man SF, Sin DD, Inhaled Corticosteroids in Chronic Obstructive Pulmonary Disease: Is there a clinical Benefit?, 2005; 65 (5): 579-91.

Martina SD, Ismail MS, Vesta KS, Cilomilast: orally active selective phosphodiesterase-4 inhibitor for treatment of chronic obstructive pulmonary disease and Pharmacotherapy, 2006; 40:1822–8.

Mayo Clinic, Coughing up blood, 2012, available from: http://www.mayoclinic.com/health/coughing-up-blood/MY01064/METHOD=print

Mayo Clinic, Emphysema, 2011, available from: http://www.mayoclinic.com/health/emphysema/DS00296/DSECTION=symptoms

Mclvor RA, Kaplan A, Koch K et al, Montelukast as an alternative to low-dose inhaled corticosteroids in the management of mild asthma (the SIMPLE trial): An open-label effectiveness trial, Can Respir J, 2009; 16: 11A-16A.

Mensing M, Aalbers R, Comparison and optimal use of fixed combinations in the management of COPD, Int J Chron Obstuct Pulmon Dis, 2007; 2(2): 107-116.

N'dumele CE, Pradhan AD, Ridker PM, Interrelationships between inflammation, C-reactive protein and insulin resistance. J Cardiometab Syndr 2006; 1: 190–196.

Naline E, Trifilieff A, Fairhurst RA et al, Effect of indacaterol, a novel long acting b2-agonist, on isolated human bronchi, Eur Respir J, 2007; 29: 575–581.

Nassr N, Lahu G, von Richter O et al, Lack of a pharmacokinetic interaction between steady-state roflumilast and single-dose midazolam in healthy subjects, Br J Clinical Pharmacology, 2006; 29: 14-20.

New York Times, Guide, COPD complications, 2012, available from: http://health.nytimes.com/health/guides/disease/chronic-obstructive-pulmonary-disease/complications.html

New York Times, Health Guide, 2012, available from: http://health.nytimes.com/health/guides/disease/chronic-obstructive-pulmonary-disease/surgical-procedures.html

NICE, National Institute for Health and Care Excellence, Chronic Obstructive Pulmonary Disease: Aclidinium Bromide, 2013, available from: http://publications.nice.org.uk/esnm8-chronic-obstructive-pulmonary-disease-aclidinium-bromide-esnm8

NICE, National Institute for Health and Clinical Excellence, Chronic Obstructive Pulmonary Disease: Management of chronic obstructive pulmonary disease in adults in primary and secondary care. London: National Clinical Guideline Centre, 2010, available from: http://guidance.nice.org.uk/CG101/Guidance/pdf/English

O'Donnell DE, Laveneziana P, Dyspnoea and activity limitation in COPD: mechanical factors, COPD, 2007; 4: 225–36

Ohara T, Hirai T, Muro S et al, Relationship between pulmonary emphysema and osteoporosis assessed by CT in patients with COPD, Chest, 2008; 134: 1244–1249.

Oxford Medical Dictionary, Fourth Edition, Oxford University Press, 2007.

Paggiaro P, Bacci E, Montelukast in Asthma: A review of its efficacy and place in therapy, Ther Adv Chronic Dis, 2011; 2(1): 47-58.

Papadopoulos G, Vardavas CI, Limperi M et al, Smoking cessation can improve quality of life among COPD patients: validation of the clinical COPD questionnaire into Greek, BMC Pub Med, 2011; 11:13

Qaseem A, Snow V, Shekelle P et al, Diagnosis and management of stable chronic obstructive pulmonary disease: a clinical practice guideline from the American College of Physicians, Clinical Efficacy Assessment Subcommittee of the American College of Physicians. Ann Intern Med, 2007; 147(9): 633

Raherison C, Girodet PO, Institute of Public Health, Epidemiology and Development, University of Bordeaux 2, European Respiratory Review, Epidemiology of COPD, 2009; 18(114): 213-221.

Rand CS, Johns Hopkins School of Medicine, European Respiratory Review, Patient adherence with COPD therapy, 2005; 14(96): 97-101.

Restrepo RD, Use of inhaled anticholinergic agents in obstructive airway disease, Respir Care, 2007; 52(7): 833-51.

Russell R, Anzueto A, Weisman I, Optimizing management of chronic obstructive pulmonary disease in the upcoming decade, Inter J Chron Obstruc Pulmon Dis, 2011; 6: 47-61.

Salpeter S, Bronchodilators in COPD: Impact of β-agonists and anticholinergics on severe exacerbations and mortality, 2007; 2(1): 11-18.

Schreiber R, MD, Guide to Managing COPD, an American Lung Association in New York Expert, 2011, available from: http://www.everydayhealth.com/health-report/chronic-obstructive-pulmonary-disease/pneumonia-copd-blog.aspx

Scullion JE, The development of anticholinergics in the management of COPD, 2007; 2(1): 33-40.

Shah R, Oqden J, What's in a face? The role of doctor ethnicity, age and gender in the formation of patient's judgments: an experimental study, Patient Educ Couns, 2006; 60(2): 136-41

Sharafkhaneh A, Majid H, Gross NJ, Safety and Tolerability of inhalational anticholinergics in COPD, 2013; 5: 49-55.

Similowski T, Agusti A, MacNee W et al, The potential impact of anaemia of chronic disease in COPD. Eur Respir J, 2006; 27: 390–396.

Singh D, Brooks J, Hagan G, Cahn A, O'Connor BJ: Superiority of "triple" therapy with salmeterol/fluticasone propionate and tiotropium bromide versus individual components in moderate to severe COPD. Thorax, 2008; 63:592-8.

Singh S and Loke YK, An overview of the benefits and drawbacks of inhaled corticosteroids in chronic obstructive pulmonary disease, Int J Chron Obstruct Pulmon Dis, 2010; 5: 189-195.

Steinfeld T et al. THRX-198321 is a bifunctional muscarinic receptor antagonist and b2-adrenoceptor agonist (MABA) that binds in a bimodal and multivalent manner. Mol. Pharmacol, 2011; 79, 389–399.

Sturton RG, Trifilieff A, Nicholson AG et al. Pharmacological characterization of indacaterol, a novel once daily inhaled b2 adrenoceptor agonist, on small airways in human and rat precision-cut lung slices. J Pharmacol Exp Ther, 2008; 324, 70–75.

Tashkin D, Fabbri LM, Long-acting beta-agonists in the management of chronic obstructive pulmonary disease: current and future agents, 2010; 11(1): 149.

Tashkin DP, Rennard SI, Martin P, et al. Efficacy and safety of budesonide and formoterol in one pressurized metered-dose inhaler in patients with moderate to very severe chronic obstructive pulmonary disease: results of a 6-month randomized clinical trial, Drugs, 2008; 68(14):1975–2000.

Thabut G, Dauriat G, Stern JB et al, Pulmonary hemodynamics in advanced COPD candidates for lung volume reduction surgery or lung transplantation. Chest, 2005; 127: 1531–1536.

Troosters T, Casaburi R, Gosslink R et al, Pulmonary Rehabilitation in chronic obstructive pulmonary disease. Am J Respir Crit Care Med, 2005; 172:19–38.

Turner MC, Chen Y, Krewski D et al, Chronic obstructive pulmonary disease is associated with lung cancer mortality in a prospective study of never smokers. Am J Respir Crit Care Med, 2007; 176: 285–290.

Tzanakis N, Anagnostopoulou U, Filaditaki V et al, COPD group of the Hellenic Thoracic Society, Chest, 2004; 125(3): 892-900.

Van Noord JA, Aumann JL, Janssens E et al, Comparison of Tiotropium once daily, Formoterol twice daily and both combined once daily in patients with COPD, 2005; 26(2): 214-22.

Vogelmeier C, Hederer B, Glaab T et al, Tiotropium versus salmeterol for the prevention of exacerbation of COPD, N Engl J Med, 2011; 364(12): 1093-1103.

Vrieze A, de Greef MH, Wijkstra PJ et al, Low bone mineral density in COPD patients related to worse lung function, low weight and decreased fat-free mass. Osteoporosis Int, 2007; 18: 1197–1202.

Walker R and Whittlesea C, Clinical Pharmacy and Therapeutics, 5th Edition, Elsevier Ltd, 2012; 26: 431-442.

Welte T, Optimising treatment for COPD – new strategies for combination therapy. Int J Clin Pract, August, 2009; 63(8): 1136–1149.

WHO, World Health Organization, Chronic Respiratory Diseases, Chronic Obstructive Pulmonary Disease, 2013, available from: http://www.who.int/respiratory/copd/management/en/

WHO, World Health Organization, Media Centre, Chronic Obstructive Pulmonary Disease (COPD), Fact Sheet No 315, 2012, available from: http://www.who.int/mediacentre/factsheets/fs315/en/index.html

Yohannes A, Connolly MJ, Hanania N, Ten years of tiotropium: clinical impact and patient prospective, Int J Chron Obstruct Pulmon Dis, 2013; 8: 117-125.

Yohannes AM, Baldwin RC, Connolly MJ, Depression and anxiety in elderly patients with chronic obstructive pulmonary disease. Age Ageing, 2006; 35: 457–459.

Yorgancioglu A, Indacaterol in chronic obstructive pulmonary disease: an update for clinicians, 2012; 3(1): 25-36.

Zeki A, Schivo M, Chan A et al, The Asthma-COPD overlap syndrome: A common clinical problem in the elderly, J Allergy, 2011; 861-926.

ΕΟΦ, Εθνικος Οργανισμος Φαρμακων – National Formulary of medicines in Greece, 2012, available from: www.eof.gr