

**AN OPEN LABELLED, RANDOMISED, PROSPECTIVE STUDY  
COMPARING THE EFFICACY AND SAFETY OF DOXOFYLLINE WITH  
THEOPHYLLINE IN COPD PATIENTS**

*DISSERTATION SUBMITTED TO*

**THE TAMILNADU DR.M.G.R MEDICAL UNIVERSITY  
IN PARTIAL FULFILLMENT FOR THE AWARD OF THE DEGREE OF  
DOCTOR OF MEDICINE  
IN  
PHARMACOLOGY**



**DEPARTMENT OF PHARMACOLOGY  
TIRUNELVELI MEDICAL COLLEGE  
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## **CERTIFICATE**

This is to certify that the dissertation entitled “**AN OPEN LABELLED, RANDOMISED, PROSPECTIVE STUDY COMPARING THE EFFICACY AND SAFETY OF DOXOFYLLINE WITH THEOPHYLLINE IN COPD PATIENTS**” presented herein by **DR.K.VINOTH** is an original work done by him in the Department of Pharmacology, Tirunelveli Medical College, Tirunelveli for the award of the Degree of Doctor of Medicine in Pharmacology during the academic period of 2015-2018.

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## **DECLARATION**

I solemnly declare that the dissertation titled “**AN OPEN LABELLED, RANDOMISED, PROSPECTIVE STUDY COMPARING THE EFFICACY AND SAFETY OF DOXOFYLLINE WITH THEOPHYLLINE IN COPD PATIENTS**” is done by me in the Department of Pharmacology , Tirunelveli Medical College, Tirunelveli.

The dissertation is submitted to The Tamilnadu Dr.M.G.R.Medical University in partial fulfillment for the award of the degree of Doctor of Medicine in Pharmacology.

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# CONTENTS

SL. NO.	TOPIC	PAGE NO.
1.	INTRODUCTION	1
2.	REVIEW OF LITERATURE	4
3.	AIM OF THE STUDY	69
4.	MATERIALS AND METHODS	70
5.	RESULTS	76
6.	DISCUSSION	91
7.	CONCLUSION	99
8.	REFERENCES	
9.	APPENDIX I - CONSENT FORM	
10.	APPENDIX II - PROFORMA	
11.	APPENDIX III - MASTER CHART	

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## CERTIFICATE OF REGISTRATION & APPROVAL OF THE TIREC

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PROTOCOL TITLE: AN OPEN LABELLED, RANDOMISED, PROSPECTIVE STUDY COMPARING THE EFFICACY AND SAFETY OF DOXOFYLLINE WITH THEOPHYLLINE IN COPD PATIENTS.

PRINCIPAL INVESTIGATOR: Dr.K. VINOTH, MBBS.,

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Dear, Dr. K. Vinoth, MBBS., The Tirunelveli Medical College Institutional Ethics Committee (TIREC) reviewed and discussed your application during the IEC meeting held on 05.08.2016.

### THE FOLLOWING DOCUMENTS WERE REVIEWED AND APPROVED

1. TIREC Application Form
2. Study Protocol
3. Department Research Committee Approval
4. Patient Information Document and Consent Form in English and Vernacular Language
5. Investigator's Brochure
6. Proposed Methods for Patient Accrual Proposed
7. Curriculum Vitae of the Principal Investigator
8. Insurance /Compensation Policy
9. Investigator's Agreement with Sponsor
10. Investigator's Undertaking
11. DCGI/DGFT approval
12. Clinical Trial Agreement (CTA)
13. Memorandum of Understanding (MOU)/Material Transfer Agreement (MTA)
14. Clinical Trials Registry-India (CTRI) Registration

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1. The approval is valid for a period of 2 year /s or duration of project whichever is later
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3. A written request should be submitted 3weeks before for renewal / extension of the validity
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## **CERTIFICATE - II**

**This is certify that this dissertation work title “AN OPEN LABELLED, RANDOMISED,PROSPECTIVE STUDY COMPARING THE EFFICACY AND SAFETY OF DOXOFYLLINE WITH THEOPHYLLINE IN COPD PATIENTS”** of the candidate **Dr.K.VINOTH** with registration Number **201516202** for the award of **M.D.** Degree in the branch of **PHARMACOLOGY .** I personally verified the urkund.com website for the purpose of plagiarism check. I found that the uploaded thesis file contains from introduction to conclusion page and result shows **1 percentage** of plagiarism in the dissertation.

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Message: An open-label, randomized, prospective study comparing the efficacy and safety of doxofylline with [theophylline](#) in COPD patients with [FEV1](#) < 80% of predicted. The global initiative for chronic obstructive pulmonary disease (GOLD) defines COPD as a disease state characterized by airflow limitation that is not fully reversible. The chronic airflow limitation characteristic of COPD is caused by a mixture of small airway disease (obstructive bronchiolitis) and parenchymal destruction (emphysema), the relative contributions vary from person to person. The goals of drug therapy are not only to improve lung function, but also to improve the quality of life, exercise capacity, and to prevent exacerbations. Theophylline is used as a bronchodilator in the pharmacotherapy of COPD for many decades. Due to narrow therapeutic index, the plasma concentration of theophylline range was maintained at 12 to 20 mg/L. Theophylline has anti-inflammatory effects as small airways and reduction of hyperinflation leading to reduction in dyspnea. The proposed mechanisms of action of theophylline are: nonselective phosphodiesterase inhibition, stimulation of adenosine release, adenosine receptor antagonism, increased intracellular cAMP, inhibition of mediators (prostaglandins, tumor necrosis factor), inhibition of nuclear factor- $\kappa$ B, increased apoptosis, inhibition of intracellular calcium release and increased nitric oxide synthase activity.

Doxofylline is a newer xanthine bronchodilator that differs from theophylline. Doxofylline has a selective guanine nucleotide-binding protein (G-protein) coupled receptor (GPCR) mechanism of action. Similar to theophylline its mechanism of action is related to the inhibition of phosphodiesterase activities, but in contrast it has decreased affinity towards adenosine A1 and adenosine A2 receptors. The bronchodilator effect of doxofylline has been demonstrated in bronchial asthma and chronic obstructive pulmonary disease (COPD).

Source: Highlights

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70%	<a href="#">111x7101-446-4147-0166-7000a01010</a>
70%	the Global initiative for Chronic Obstructive Lung Disease (GOLD). The GOLD definition describ...
60%	<a href="#">111x7101-346-5147-0166-7000a01010</a>
	It is usually progressive and associated with an abnormal inflammatory response in the lungs af...
	Alternative sources
	Sources not used

1 INTRODUCTION COPD is an important public health problem which is preventable as well as treatable. It is one of the major cause of chronic morbidity and mortality throughout the world. It is the fourth leading cause

**70%** The Global Initiative for Chronic Obstructive Lung Disease (GOLD) as a disease state characterized by airflow limitation that is not fully reversible.

The chronic airflow limitation characteristic of COPD is caused by a mixture of small airway disease (obstructive bronchiolitis) and parenchymal destruction (emphysema), the relative contributions vary from person to person. The goals of drug therapy are not only to improve lung function, but also to improve the quality of life, exercise capacity, and to prevent exacerbations. Theophylline is used as a bronchodilator in the pharmacotherapy of COPD for many decades. Due to narrow therapeutic index, the plasma concentration of theophylline range was maintained at 12 to 20 mg/L. Theophylline has anti-inflammatory effects as small airways and reduction of hyperinflation leading to reduction in dyspnea. The proposed mechanisms of action of theophylline are: nonselective phosphodiesterase inhibition, stimulation of adenosine release, adenosine receptor antagonism, increased intracellular cAMP, inhibition of mediators (prostaglandins, tumor necrosis factor), inhibition of nuclear factor- $\kappa$ B, increased apoptosis, inhibition of intracellular calcium release and increased nitric oxide synthase activity.

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the Global initiative for Chronic Obstructive Lung Disease (GOLD). The GOLD definition describes COPD as a disease state characterized by airflow limitation that is not fully reversible.

## INTRODUCTION

COPD is an important public health problem which is preventable as well as treatable. It is one of the major cause of chronic morbidity and mortality throughout the world. It is the fourth leading cause of death<sup>1</sup>. COPD has been defined by The Global Initiative for Obstructive Lung Disease <sup>2</sup> (GOLD) as a disease state characterized by airflow limitation that is fully not reversible. The chronic airflow limitation characteristic of COPD is caused by a mixture of small airway disease (obstructive bronchiolitis) and parenchymal destruction (emphysema), the relative contributions vary from person to person<sup>3</sup>. The goals of drug therapy are not only to improve lung function, but also to improve the quality of life, exercise capacity, and to prevent exacerbations<sup>4</sup>

Theophylline is used as a bronchodilator in the pharmacotherapy of COPD for many decades. Due to narrow therapeutic index, the plasma concentration of therapeutic range was maintained at 10 to 20 mg/L. Theophylline has anti inflammatory effects on small airways and reduction of hyperinflation leading to reduction in dyspnea. The proposed mechanisms of action of Theophylline are Nonselective Phosphodiesterase inhibition, stimulation of epinephrine release, Adenosine receptor antagonism, increased interleukin-10 release, inhibition of mediators (prostaglandins, tumor necrosis factor), inhibition of nuclear factor- B, increased apoptosis, inhibition of intracellular calcium release and increased histone deacetylase activity<sup>5</sup>.

Doxofylline is a newer xanthine bronchodilator that differs from theophylline. Doxofylline has a dioxalane group in position-7. Similar to theophylline its mechanism of action is related to the inhibition of phosphodiesterase activities, but in contrast it has decreased affinity towards adenosine A1 and adenosine A2 receptors. The bronchodilating effect of doxofylline has been demonstrated in bronchial asthma and chronic obstructive pulmonary disease clinical trials. Contrary to other bronchodilators, experimental and clinical studies has shown that doxofylline is devoid of stimulatory effects. The arrhythmogenic action of bronchodilators have negative impact on the morbidity and mortality of patients with respiratory diseases which is devoid in doxofylline usage. The unique cardiovascular safety profile of doxofylline makes it unnecessary to monitor the serum levels of the drug.

Although doxofylline shares most of the characteristics of the methylxanthine drugs, experimental studies has shown that it is associated with less extra-respiratory effects than theophylline<sup>6,7,8</sup>. It is suggested that decreased affinities toward adenosine A1 and A2 receptors may account for the better safety profile of doxofylline<sup>9,10,11</sup>. Moreover, unlike theophylline, doxofylline does not interfere with the influx of calcium into the cells nor does it antagonize calcium channel blocker receptors<sup>12</sup>

There is a need to address the well known safety issues in using theophylline. We need a better drug with greater efficacy and safety profile to treat COPD.

Though few previous studies have advocated the efficacy and safety of doxofylline over theophylline, the comparison of the clinical efficacy and safety profile of doxofylline with theophylline in the Indian population has been less studied. Therefore, the present study is designed to compare the clinical efficacy and safety of oral theophylline and doxofylline in patients with Grade1-2 COPD (Based on GOLD Criteria) attending the outpatient department of Chest Medicine in Tirunelveli Medical College Hospital.

## **REVIEW OF LITERATURE**

### **DEFINITION**

Global Initiative for Chronic Obstructive Lung Disease (GOLD) defines Chronic Obstructive Pulmonary Disease (COPD) as a common preventable and treatable disease, characterized by persistent airflow limitation that is progressive and associated with an increased chronic inflammatory response in the airways and lungs to noxious particles or gases.<sup>13</sup>

### **HISTORICAL BACKGROUND**

Emphysema was the first to be recognized when looked in a historical perspective. Dating back to 17th and 18th centuries, clinicians recognized a condition which was termed as abnormally “voluminous” lungs<sup>14</sup>. In 1789, Baillie demonstrated the classical pathologic features of emphysema in a series of illustrations.

Later renowned clinician and pathologist, Laennec described and documented chronic bronchitis. In the year 1821, Laennec in his book, “A Treatise on the Diseases of Chest,” describes lungs that are hyperinflated and they do not empty well<sup>15</sup>. But, upon pathologic inspection, he noted that “the bronchus of trachea are often accumulated with mucous fluid.” In those times, smoking was uncommon and he attributed the primary cause of this disease to environmental and genetic factors. It is imperative to note that Laennec identified both the characteristic features of COPD: chronic bronchitis and emphysema.

In 1940s, majority of the clinicians were becoming familiar with this disease entity characterized by dyspnea on exertion with physical signs of emphysema and chronic bronchitis in a group of patients<sup>16</sup>. However, the reliability of diagnosis of this condition remained a question mark until the advent of spirometer. John Hutchinson invented the spirometer in the year 1846. It was capable of measuring only vital capacity. Hundred years later, Tiffeneau introduced the concept of timed vital capacity for the measurement of airflow that allowed spirometer to become a major diagnostic modality for obstruction of airflow<sup>17</sup>. In 1950s, clinicians recognized the specific flow volume patterns in spirometry indicative of emphysema<sup>18</sup>. In 1956, the book of Hinshaw and Garland depicted spirograms showing obstruction of airflow in emphysema<sup>19</sup>.

In 1962, Two important scientific conferences, the CIBA Guest Symposium<sup>20</sup> in 1959 and the American Thoracic Society (ATS) Committee on Diagnostic Standards<sup>21</sup> laid the foundation for the modern day definition of COPD. In the year 1965, Dr. William Briscoe was the first person to introduce the term “COPD” at the ninth Aspen Emphysema Conference. In 1976, Drs. Charles Fletcher and Richard Peto in their landmark book documented that smoking cessation attenuates lung function loss whereas continued smoking accelerates the disease and strongly supported the link between smoking and the development of COPD<sup>22</sup>.

## **EPIDEMIOLOGY :**

COPD is the fourth most common specific cause for death globally and predicted to become third by 2030, if there is no interventions addressing the risks - tobacco smoking, exposures to biomass fuels and environmental pollution <sup>23-24</sup>

COPD causes a significant burden in terms of impaired quality of life and disability

<sup>25</sup>The general perception is that COPD prevalence is not well measured despite its importance . Accurate prevalence information is necessary for various reasons such as documentation of COPD's impact on quality of life, costs and disability and it also helps in public health planning <sup>26</sup>. It is important to find out prevalence rates at the baseline that would help researchers to monitor trends in success or failure of control efforts.

The physiological case definition for COPD was obstruction of airflow. This was the most common case definition that is being used in prevalence studies <sup>27-28</sup>.

Spirometry is the single most important physiological criterion but cut-off points of spirometry curves for detecting airflow obstruction differ in a significant manner <sup>29</sup>.

Prevalence estimates of COPD are highly dependent on the age group but lung function declines with age.

Prevalence estimates also vary based on smoking frequencies since smoking is a primary risk factor for COPD. Now there are controversies attributed to the relative impact of smoking on the COPD development in females and males with the rise in smoking frequencies in females. The role of other inhaled exposures like biomass fuel, ambient air pollution, occupational smoke or dust to population prevalence

rates were not clearly determined for most countries . Global prevalence of COPD based on Current epidemiological situation is 11.7%(8.4%–15.0%)<sup>30</sup>

Prevalence of COPD has been constantly rising in younger population groups. In 2010,the highest prevalence was estimated in the Americas 15.2%, and the lowest in South East Asia 9.7% .The increase in percentage of COPD cases between 1990 and 2010 was the highest in the Eastern Mediterranean region (118.7%), followed by the Africa (102.1%), and Europe recorded the lowest increase (22.5%). In the year 2010, there were around 230 million COPD cases among urban population (prevalence rate - 13.6%) and 153.7 million among rural population (prevalence rate - 9.7%). The overall prevalence in men aged 30 years or more was 14.3% compared to 7.6% in women<sup>30</sup>. In continuation of the 2011 United Nations high level political declaration on non-communicable diseases<sup>31</sup>. In 2012, the World Health Assembly , adopted a new health goal -the “25 by 25 goal” focusing on reducing premature deaths due to COPD and other non-communicable diseases by 25% by the year 2025<sup>32</sup>.

COPD was responsible for about 5% of global disability–adjusted life years totaling 76.7 million people and 5% of total deaths that is 2.9 million people based on the 2010 Global Burden of Disease study<sup>33-34</sup>

## **SUBTYPES OF COPD**

### **CHRONIC BRONCHITIS**

Chronic bronchitis is defined in clinical terms as the presence of cough and sputum production for most days over 3 months for 2 consecutive years. This clinical



definition does not include the presence of airflow limitation. It is thought to result from an innate immune response to inhaled toxic particles and gases, particularly in tobacco smoke. Inflammation is present in the epithelium of the central airways and in the mucus-producing glands in chronic bronchitis.<sup>35,36</sup> This airway inflammation is associated with increased mucus production, reduced mucociliary clearance, and increased permeability of the airspace epithelial barrier. The contribution that mucus hypersecretion makes to the airflow limitation in COPD is still uncertain. In the early stages of COPD, its contribution is small because mucus production in smokers with normal lung function does not appear to predict later development of COPD.<sup>37</sup> However, in the later stages of the disease, chronic mucus hypersecretion may accelerate the loss of FEV1 due to an increased risk of exacerbations.<sup>38</sup> Chronic mucus hypersecretion may result from an inflammatory response in the submucosal glands. Inflammatory cells release serine proteases that are potent secretagogues for mucus.<sup>39</sup> Oxidants derived from cigarette smoke and released from inflammatory leukocytes may also stimulate the overproduction of mucin by induction of the MUC5AC gene

## **EMPHYSEMA**

Emphysema is defined as enlargement of the airspaces distal to the terminal bronchioles, due to destruction of the alveolar walls.<sup>40</sup> Distal airspace enlargement with alveolar destruction reduces maximal expiratory airflow by decreasing the lung elastic recoil. The centrilobular or centriacinar form of emphysema results from dilatation or destruction of the respiratory bronchioles, is the type most closely

associated with tobacco smoking, and is thought to be more associated with severe small-airway obstruction.<sup>41</sup> The panlobular or panacinar form of emphysema, which is associated with  $\alpha$ -1-antitrypsin ( $\alpha$ -1-AT) deficiency, results in a more even dilatation and destruction of the entire acinus. Although one or the other of these types may predominate, there is great heterogeneity. The distribution of these types of emphysema is different with an upper lobe predominance common in centrilobular emphysema and lower lobe predominance in panlobular emphysema. The reason for this is not clear and whether different pathogenic mechanisms are involved is also unknown. There is a relationship between the degree of emphysema and pack-years of smoking, but the relationship is not strong.<sup>35</sup> Around 40% of smokers develop substantial lung destruction from emphysema, and emphysema can be found in some individuals who have normal lung function.<sup>35</sup>

## **ETIOLOGY**

COPD results from a gene-environment interaction. In developed countries, smoking tobacco is the predominant risk factor. Among people with the same smoking history, not all will develop COPD due to differences in genetic predisposition to the disease, or in how long they live. In places where solid fuels are burned, biomass fuel exposure is probably the dominant risk factor. Other factors associated with COPD include second-hand tobacco exposure, age, level of education, tuberculosis, hospitalization for childhood respiratory illness, a family history of COPD, and the number of years worked in dusty jobs.<sup>42</sup> Clearly, multiple risk factors may be

present in a single individual.. Risk factors for COPD may also be related in more complex ways. Risk factors for the development of COPD are environmental and host based .

## **RISK FACTORS**

### **ENVIRONMENTAL FACTORS**

#### **SMOKING**

#### **BIOMASS FUEL EXPOSURE**

#### **AMBIENT AIR POLLUTION**

#### **OCCUPATIONAL EXPOSURES**

#### **LOW SOCIOECONOMIC STATUS**

### **HOST FACTORS**

#### **GENETIC**

#### **ASTHMA AND AIRWAY HYPERREACTIVITY**

#### **RECURRENT INFECTIONS**

### **TOBACCO SMOKING**

Globally, cigarette smoking is the most commonly encountered risk factor for COPD. Smoking during pregnancy poses a risk for the fetus, by affecting lung growth and development in utero.<sup>43,44</sup> Smoking in childhood and adolescence leads to stunting of lung growth and earlier decline in lung function than in nonsmokers.<sup>45</sup> Adult cigarette smokers have a higher prevalence of respiratory symptoms, lower

lung function, a greater annual rate of decline in FEV1, a greater loss of lung density, and a greater COPD mortality rate than nonsmokers.<sup>46,47</sup> Deterioration of FEV1 correlates with pack-years of smoking, but the relationship between amount of smoking and risk of COPD is unpredictable on an individual basis. Among former smokers, the age at smoking cessation affects the subsequent rate of deterioration of lung function. The rate is closest to never smokers for those who quit prior to age 30, but even for those who quit after age 40, deterioration is less than in continued smokers. The crucial factor seems to be the amount smoked and the extent of inhalation.<sup>48</sup> Filtered cigarettes do not differ significantly from cigarettes without filters, and other types of tobacco and marijuana are also risk factors for COPD.<sup>49,50</sup> Smoking cessation had, in several studies, been shown to be associated with both a lower prevalence of respiratory symptoms and a slower decline in FEV1, studies.<sup>48</sup> In India and other Southeast Asian countries, bidi smoking is more common than cigarette smoking. Bidis are made up of tobacco wrapped in tendu leaf. Although the amount of nicotine in a bidi is one-fourth that of a cigarette, the amount of tar is roughly five times greater. From COPD point of view, one bidi is as harmful as one cigarette. Due to the low combustibility of the tendu leaf wrapper, bidi smokers inhale more often and more deeply, thereby breathing greater amounts of tar.<sup>51</sup> Cigarette smoke contains two very different populations of free radicals, one in the tar and one in the gas phase. The tar phase contains several relatively stable free radicals, the principal radical being quinone/ hydroquinone (Q/QH2). The gas phase of cigarette smoke contains small oxygen and carbon-centered radicals that are more

reactive than are the tar-phase radicals. One of the important mechanism through which tobacco smoke exerts its harmful effects on the lungs is the oxidative stress caused by reactive oxygen species. New evidence suggests that up to 50% of smokers develop COPD.<sup>52</sup> The risk of COPD also occurs amongst people who are exposed to second-hand smoke.<sup>53,54</sup>

### **Environmental Tobacco Smoke Exposure or Second-Hand Smoke**

Environmental tobacco smoke exposure (ETS) is implicated in loss of many years of life of adults and children but COPD, specifically, as a cause of the life shortening due to ETS is not clear<sup>55</sup> Controlled experimental studies with normal volunteers indicate that short-term exposures to ETS at levels comparable to those in real-life situations have effects on serum cytokine levels and pulmonary function that if recurrent or chronic might translate into COPD.<sup>56,57</sup> However, when smoking and other risk factors are controlled both workplace and home ETS but not prenatal ETS increase the risk of development of COPD.<sup>58</sup> Data regarding in utero effects of maternal smoking on lung growth and subsequent risk of childhood wheezing or asthma are becoming evident. However, doubt exists regarding the quantitative impact on the development of COPD in individuals with only prenatal exposure. It seems likely that similar to cystic fibrosis, individuals with enhanced genetic risk factors could be adversely modulated by ETS,<sup>59</sup> but to date no definitive proof of gene-by-environment interactions for ETS have been demonstrated. The data does not suggest that ETS is harmless but rather it is less definitively causal of COPD as an independent risk than chronic smoking or occupational exposures.<sup>58</sup> Avoidance

in individuals with existing lung disease is clearly indicated given the association with exacerbation. The attitude that there is no risk-free dose of ETS, is likely the safest approach; this applies to all ETS-related diseases and not just COPD.<sup>55</sup>

### **Biomass fuel exposure**

Biomass fuel exposure is the term covering exposure to smoke from wood, animal dung, crop residues, and coal, typically burned in open fires or primitive stoves. Biomass fuel exposure is an important source of indoor air pollution in undeveloped countries there is increasing evidence that this exposure is an important risk factor for COPD.<sup>60-62</sup>

It is estimated that about half of the global population (3 billion people) live in homes that use biomass fuel for cooking and heating purposes. Burning of biomass solid fuel emits very high levels of indoor air pollutants, both particulate matter as well as the gaseous pollutants. Many of these homes are poorly ventilated, exposing these individuals to very high levels of indoor air pollutants. Women, young girls and small children are exposed for the longest duration because they spend more time in close vicinity to the biomass smoke. During their lifetime, women are exposed for around 30–40 years, which is equivalent to 60,000 hours of exposure to biomass smoke or inhaling a total volume of 25 million liters of highly polluted indoor air.<sup>63</sup> The levels of indoor air pollutants, encountered in homes that use biomass fuel, are several orders higher than the levels in the most polluted urban cities in the world. These pollutants have the potential to produce intense oxidative stress in the lungs and the elastolytic effects of these pollutants have been found to

be worse than those caused due to tobacco smoke. The exposure to biomass smoke induces the same amount of risk of developing COPD as tobacco smoke. As 3 billion people are exposed to biomass smoke worldwide as compared to 1.1 billion smokers, biomass smoke is likely to be the biggest risk factor of COPD.<sup>63</sup>

## **OUTDOOR AIR POLLUTION**

Ambient air pollution is a growing problem in most urban cities of the world. Over the last few decades, air pollution in most cities in the developed countries has decreased appreciably due to the advent of strict legislation and improvements in engine technology, but it continues to increase markedly in most of the cities of the developing countries. Both the gaseous and particulate matter components of urban ambient air pollutants have been shown to be associated with increasing respiratory morbidity and cardiovascular mortality. One of the earliest studies that investigated an association between ambient air pollution and COPD was by Fairbairn<sup>64</sup> in 1958, who reported that postmen from England and Wales who worked in areas with higher outdoor air pollution levels, had a greater prevalence of COPD than those who worked in areas with lower ambient air pollution levels. A subsequent study from the United Kingdom showed that postmen who worked in more polluted cities had lower lung function values than those who worked in less polluted areas.<sup>65</sup> Similar observations were later reported in the general population.<sup>66</sup> More recently, living in areas closer to roads with heavy motor vehicular traffic have been shown to be associated with significant decrements in lung function,<sup>67</sup> and increased prevalence of COPD in women.<sup>68</sup>

## **OCCUPATIONAL EXPOSURES**

The association between occupational exposures and COPD has been observed for at least four decades. Earlier studies revealed that exposure to toxic gases at workplace,<sup>69</sup> grain dust in farms,<sup>70</sup> and to dust and fumes in factories,<sup>71</sup> were strongly associated with the risk of development of COPD. In 2003, the American Thoracic Society conducted a systematic epidemiological review of occupational factors associated with the development of COPD and reported that approximately 15% of COPD may be attributable to workplace exposure.<sup>72</sup> Farming as an occupation has been shown to be strongly associated with COPD. The risk of COPD, attributable to farming was 7.7% and that around 30% of the farmers had at least mild COPD. Longitudinal studies have documented the association between COPD and occupational exposures in coal miners, hard rock miners, tunnel workers and concrete manufacturing workers. In heavily exposed workers, the effect of dust exposure may be even greater than that of cigarette smoking alone.<sup>73</sup> Construction workers exposed to fumes and mineral dust have been shown to have a significantly higher risk of death due to COPD.<sup>74</sup> Prolonged exposure to silica in occupations, such as the construction industry, brick manufacturing, gold mining and in iron and steel foundries is also strongly associated with the development of COPD.<sup>75</sup> The burden of occupational COPD is likely to be high in countries of low and middle income, where occupational exposures to dust and fumes could be greater than in high-income nations, because of less stringent laws and lack of adequate facilities for reducing the exposures.



## **Childhood Lower Respiratory Tract Infections**

Since the status of lung function in very early childhood predicts ventilatory function many years later,<sup>76</sup> it is plausible that lower respiratory tract infections (LRIs) during childhood might adversely affect lung development and increase the risk of developing COPD later in life. However, lung function in children who had pneumonia up to age 2 infrequently had reduced lung function 10 years after the infection.<sup>77</sup> If there was a ventilatory defect, it was most often restrictive. Where reduced airflow was observed, an adenovirus was the predominant class of pathogens responsible for the pneumonia. It is notable that COPD exacerbations may leave only a minor lasting effect on airflow. Continued smokers enrolled in the Lung Health Study had only an additional loss of 7 mL of FEV1 per year for those having one exacerbation per year, while among those who had quit smoking, exacerbations had no permanent effect on the FEV1.<sup>78</sup>

## **PULMONARY TUBERCULOSIS**

Pulmonary tuberculosis has been shown to be associated with chronic airflow obstruction, particularly of the COPD phenotype, at the time of diagnosis,<sup>79</sup> during treatment,<sup>80</sup> and several years after the completion of treatment.<sup>81</sup> The amount of airflow obstruction is related to the extent of the disease determined radiologically, the amount of sputum produced and the length of time after the diagnosis or completion of treatment.<sup>82</sup> Apart from the airway fibrosis that may follow tubercular infections, the immune response to mycobacteria may enhance the airway inflammation that is typical of COPD. More than 2 billion people, equal to one-third

of the world's population, are infected with tubercle bacilli and an estimated 9.2 million new cases of tuberculosis are detected every year; 80% of them are present in 22 countries of the world.<sup>83</sup> Countries from Asia, Africa and Latin America have a particularly high burden of pulmonary tuberculosis. The cumulative burden of COPD associated with pulmonary tuberculosis is, therefore, likely to be much greater than previously believed, especially in the developing countries.<sup>84</sup>

### **HUMAN IMMUNODEFICIENCY VIRUS INFECTION**

Individuals with human immunodeficiency virus (HIV) who smoke have an increased risk of COPD or more specifically emphysema development.<sup>85</sup> The risk appears to be modulated by activation of alveolar macrophages with evidence of enhanced production of matrix metalloproteinases (MMPs) in these individuals.<sup>86</sup> Although HIV can infect macrophages,<sup>87</sup> it is unclear if this is a direct alteration due to HIV infection or a response to some downstream alteration of the suppression of innate immune responses, like chronic *Pneumocystis* infection.<sup>88</sup> The occurrence of COPD and pulmonary hypertension in smokers with HIV appears to be more common in individuals with a high viral load and lower CD4 cell counts and not an adverse consequence of antiretroviral therapy.<sup>89</sup> But emphysema is not reversible and relation to viral load or recovery of CD4 cell counts is not direct.

### **ASTHMA AND BRONCHIAL HYPERREACTIVITY**

Asthma and COPD are generally viewed as two different diseases with a variable overlap.<sup>90</sup> However, asthma may also be viewed as a risk factor for the development of COPD. In the Tucson study, adults with asthma were found to have a 12 fold

higher risk of acquiring COPD over time than those without asthma, after adjusting for smoking.<sup>91</sup> A Dutch study of people with asthma found that 20% of subjects developed irreversible airflow limitation<sup>92</sup> and, in a Danish longitudinal population study, self-reported asthma was associated with an excess loss of FEV1.<sup>93</sup>

In the European Community Respiratory Health Survey, bronchial hyperresponsiveness was second only to cigarette smoking as the leading risk factor for COPD, responsible for 15% of the population attributable risk.<sup>94</sup> This is in accordance with previous studies showing a strong impact of bronchial hyperresponsiveness on FEV1 decline, also in the absence of asthma.<sup>95</sup>

## **GENETIC FACTORS**

Although COPD is predominantly an environmental lung disease, it is clear that genetic susceptibility is also important. Recent studies have indicated that COPD can run in families, and for this several potential genes have been identified<sup>96</sup> A significant familial risk of airflow limitation has been observed in smoking siblings of patients with severe COPD,<sup>97</sup> suggesting that genetic, together with environmental factors, could influence this susceptibility. Deficiency of A1AT, a major circulating inhibitor of serine proteases, is the best documented genetic risk factor for developing emphysema.<sup>98</sup> Although A1AT deficiency is relevant to only a small part of the world's population, its potentiating effect on the harmful effects of smoking illustrates the interaction between genes and environmental exposures leading to COPD. Other single genes have some effect on the risk of developing COPD, including the alpha nicotinic acetylcholine receptor, as well as the hedgehog

interacting protein gene, the FAM13 gene, and the gene encoding MMP12. A few other genes have been implicated, but there remains a discrepancy between findings from analyses of COPD and lung function, as well as between genome-wide association study (GWAS) analyses and candidate gene analyses.<sup>99</sup> In addition, none of the genes yet identified by GWAS in patients with COPD overlap with genes found to have an effect on the level of lung function.<sup>100</sup>

## **LOW SOCIOECONOMIC STATUS**

Poor socioeconomic status is a risk factor independently associated with COPD and is likely to be indicative of other factors such as intrauterine growth retardation, poor nutrition (low intake of antioxidants), housing conditions, childhood respiratory tract infections, exposure to tobacco smoke, occupational risks, and biomass smoke and other indoor air pollutants. These factors might collectively contribute to the risk of COPD.<sup>101</sup> Socioeconomic status should therefore be treated as an independent risk factor for COPD.

## **Age and Gender**

Age is often listed as a risk factor for COPD. It is unclear if healthy aging as such leads to COPD or if age reflects the sum of cumulative exposures throughout life. In the past, most studies showed that COPD prevalence and mortality were greater among men than women but data from developed countries<sup>102</sup> show that the prevalence of the disease is now almost equal in men and women, probably reflecting the changing patterns of tobacco smoking. Some studies have even

suggested that women are more susceptible to the effects of tobacco smoke than men<sup>103</sup>

## **PATHOGENETIC MECHANISMS**

COPD represents the clinical expression of complex alterations in structure and function of alveolar tissue and small airways. Many processes at the tissue and cellular levels can be implicated, including inflammation, cell proliferation, apoptosis, altered phenotype of lung cells, and remodeling of the extracellular matrix . Numerous mediators, most notably proteinases, oxidants, and cytokines, are involved in these processes. Studies in genetically altered mice have proven invaluable in helping to elucidate the pathogenesis of COPD, especially emphysema. factors that recruit inflammatory cells to the lungs. The various inflammatory cells that accumulate in the peripheral tissues of the lungs release proteinases and oxidants that damage or degrade extracellular matrix in the walls of alveoli, alveolar ducts, and respiratory bronchioles. In addition, agents in smoke and those released by inflammatory cells inactivate proteinase inhibitors such as  $\alpha$ -1-antitrypsin, and cause senescence and apoptosis of lung cells that produce extracellular matrix. Products of the damaged extracellular matrix, such as peptides of degraded elastin, are chemotactic for inflammatory cells; thus degradation of the extracellular matrix may lead to a feedback loop that perpetuates inflammation. These matrix-derived products may also elicit immune responses that lead to destruction of extracellular matrix. Not shown are the role of mechanical forces that may also promote deformation of lung tissue.

## **INFLAMMATION**

### **Innate Immune Responses**

As reflected in the definition of COPD, inflammation occupies a central role in current thinking about the pathogenesis of COPD. The inflammation paradigm is that smoking and other types of inhaled irritants lead to recruitment of innate inflammatory cells to the lungs and airways and that products of these recruited cells injure lung tissue and disrupt normal mechanisms of lung repair. Indeed, inflammation is prominent in airways and lung parenchyma in biopsies, surgical specimens, and postmortem material from individuals with COPD.<sup>104</sup> Other indicators of inflammation are increased inflammatory cells in bronchoalveolar lavage fluid (BALF)<sup>105</sup> and sputum and increased volatile products of inflammatory cells in exhaled breath.<sup>106</sup> Systemic inflammation is also present in current smokers, with elevations in white blood cell counts, neutrophil subsets, or liver-derived acute phase reactants.<sup>107</sup> Inflammatory cells associated with COPD in the lung include predominantly neutrophils, macrophages, and sometimes eosinophils, but also dendritic cells and lymphocytes. Once the inflammatory process is initiated by smoking the process may persist long after smoking has stopped.<sup>108</sup> Systemic neutrophil counts generally decrease within weeks but activated alveolar macrophages may be present even years after smoking cessation.<sup>109</sup> Unlike nonsmokers, macrophage accumulations are found specifically in respiratory bronchioles, even in young smokers, and BALF from smokers contains many fold increases in macrophages compared to the numbers in BALF from nonsmokers.<sup>110</sup>

Besides releasing proteinases that might degrade the extracellular matrix of the lung,<sup>111</sup> alveolar macrophages in COPD make chemotactic factors that recruit other inflammatory cells to the lungs. Likewise, structural cells of the lungs in COPD produce proteinases and chemotactic factors for inflammatory cells.<sup>112</sup> Expression of interleukin-8 (IL-8), macrophage inflammatory protein-1 (MIP-1), and monocyte chemoattractant protein-1 (MCP-1), for example, are upregulated in bronchiolar epithelium in COPD.<sup>113</sup> Peptides of elastin are chemotactic for inflammatory cells and may act as epitopes for T-cell responses.<sup>114</sup> In mice, genetically induced overexpression of cytokines, such as IL-13 or interferon by lung cells leads to emphysema via a robust innate immune response, with inflammatory cell proteinases being integral in emphysema pathogenesis.<sup>115</sup>

### **Acquired Immune Responses**

Cellular and humoral immunity may also be involved in emphysema pathogenesis or the continued progression after smoking cessation. CD4+ and CD8+ T cells and B cells accumulate in alveolar and airway tissue in COPD and form bronchus-associated lymphoid tissue (BALT) in the walls of small airways.<sup>104</sup> The increasing BALT presence in small airways correlates with severity of GOLD stage.<sup>104</sup> In mice, exposure to antibodies directed at endothelial cells alone elicits alveolar septal cell destruction and emphysema. Speculation about antigens for immunologically driven emphysema in patients include microbial pathogens, peptides altered by tobacco smoke, and peptides released from lung extracellular matrix.<sup>116</sup> Difficulties in distinguishing cellular and humoral responses to microbial colonization of

advanced airway disease in COPD from pathologic self-directed immune responses will require further study,<sup>117</sup> but more targeted immune suppression in treating advanced COPD has not yet shown benefit.<sup>118</sup> Intrinsic in this issue is the accelerated emphysema in smokers with HIV, but that may be complicated by direct virus infection inducing macrophage alterations, rather than suppression of acquired immune responses.

### **PROTEINASE–ANTIPROTEINASE IMBALANCE**

The discovery in the 1960s of  $\alpha_1$ -AT deficiency associated early-onset emphysema and the production of emphysema in experimental animal models with elastolytic enzymes have promoted the imbalance of proteinases relative to their inhibitors as a key factor in emphysema development.<sup>119</sup> Although additional mechanisms, like apoptosis and oxidant stress, have been uncovered in recent years, the importance of proteinase excess continues to prevail as an important mechanism in emphysema development. Proteinases of several biochemical classes, and different specific inhibitors, are implicated in the pathogenesis of emphysema. Serine proteinases, especially neutrophil elastase, and several matrix metalloproteinases, have been the proteinases for which there are the most data. It is notable that both neutrophils, which are the source of neutrophil elastase and MMP-12 from alveolar macrophages are largely related to continued smoking. Progression after smoking cessation may follow different pathways. As discussed in the genetics section many of these genes have been implicated in candidate gene studies but not genome-wide association studies.<sup>120</sup> Although neutrophil elastase and its main inhibitor  $\alpha_1$ -AT have



predominated the proteinase–antiproteinase imbalance hypothesis, MMPs appear prominent in mouse models and in samples from smokers and individuals with COPD. It is likely a combination of many local imbalances involving different proteinases and antiproteinases contribute to the progressive lung destruction. Several aspects of proteinases in COPD should be noted, as a straightforward destructive mechanism only is likely an oversimplification. In addition to destruction of lung elastin and other matrix components, proteinases process cytokines and surface receptors involved in the inflammatory and immune responses.<sup>121</sup> Inflammatory cells may not be the exclusive sources of the proteinases as structural cells also produce matrix-degrading proteinases.<sup>122</sup> Even the apparently simple emphysema model of placing elastases in the lungs of experimental animals results in complex responses that can be altered by nonproteinase-related mechanisms including stem cell and immunologic responses.<sup>123</sup> It must also be emphasized that little is known about proteinases in the pathogenesis of the small airway pathology of COPD. Virtually all of the information about proteinases in COPD pertains to emphysema pathogenesis despite clear evidence of small airway obliteration in advanced disease.

### **OXIDANT–ANTIOXIDANT IMBALANCE**

Reactive oxygen species in cigarette smoke or released by inflammatory cells and structural cells of the lungs in response to smoke may lead to lung injury. Up to 20 mg of tar may be deposited in a smoker's lung per cigarette smoked. This tar contains more than 1017 stable, long-lived radicals per gram. The gas phase of

tobacco smoke contains 1015 organic radicals per puff of smoke, although in general these small oxygen- and carbon-centered species are more short-lived and reactive than the radicals in the particulate phase. In addition, tobacco smoke appears to “prime” neutrophils and alveolar macrophages to generate elevated amounts of reactive oxygen species, such as hydrogen peroxide, hydroxyl radicals, and superoxide radicals. The lung tissue of smokers contains significantly more iron than that of nonsmokers,<sup>124</sup> providing a catalyst for the production of hydroxyl radicals from H<sub>2</sub>O<sub>2</sub>. This is of interest given the finding of an iron-binding protein polymorphism in the genome wide association studies of smokers with COPD.

Smokers also demonstrate increased production of neutrophil myeloperoxidase, which is capable of yielding oxidized halogens such as hypochlorous acid (HOCl). Oxidants modify and inactivate proteins, such as protease inhibitors (  $\alpha$ 1-AT and secretory leukoprotease inhibitor), and histone deacetylase 2 (HDAC2), which is involved in glucocorticoid mediated anti-inflammatory responses. Oxidants can affect lipids, DNA, and some specific end products, such as 4-hydroxy-2- nonenal (4-HNE) and 8-hydroxy-2 -deoxyguanosine (8-OHdG), may be markers of COPD.<sup>125</sup> Oxidants can promote inflammation and proteinase expression, facilitate proteinase-mediated extracellular matrix degradation by enhancing matrix molecule susceptibility to proteolytic cleavage, and participate in nonenzymatic degradation of matrix molecules like type I collagen. In experimental animals the combination of cigarette smoke and elastase leads to greater emphysema than either insult alone, suggesting that these insults do not elicit identical responses.<sup>126</sup> Animal models of

antioxidant deficiency result in increased susceptibility to both cigarette smoke and direct elastase-induced disease.

## **APOPTOSIS AND SENESENCE**

Emphysematous human lung specimens demonstrate increased apoptotic and senescent cells compared to healthy lung specimens.<sup>127</sup> An early theory of emphysema development was that alveolar vascular destruction preceded loss of alveolar tissue. Consistent with this early theory, the blockade of vascular endothelial growth factor (VEGF) signaling in alveolar endothelial cells or genetic downregulation of VEGF production in alveolar epithelium produces apoptosis and noninflammatory emphysema in rodents.<sup>128</sup> In vitro, cigarette smoke induces apoptosis of several lung cell types.<sup>129</sup> An important feature of experimental models of emphysema due to apoptosis is that there is minimal inflammation.<sup>130</sup> Of interest, the BICD1 gene polymorphism linked to emphysema encodes for a protein in the apoptosis pathway. In contrast to the expanding body of information linking emphysema to apoptosis, there is only scant information about apoptosis of the cells of small airways in COPD. Much remains to be learned about apoptosis in the context of COPD airway disease. Senescence of lung cells as a cause of emphysema stems from the knowledge of alveolar loss with aging and animal models<sup>131</sup> where accelerated aging results in emphysematous changes. Lung fibroblasts isolated from human lungs with COPD demonstrate increased markers of senescence and senescent fibroblasts do not maintain the extracellular matrix.<sup>132</sup> However, much of the information regarding telomeres in human COPD relates to inflammatory cell

telomere shortening, with telomere length being a biomarker of chronic lifelong inflammatory excess present in individuals with COPD.<sup>133</sup> Whether lung epithelial cells are driven to an injury-related replicative senescence is unknown, but human diseases of telomere deficiency and excess alveolar epithelial apoptosis tend to result in pulmonary fibrosis and not COPD.<sup>134</sup>

## **MUCUS HYPERSECRETION**

Airway mucus is a normal protective barrier that is constantly replenished and cleared in health. Mucin glycoproteins, the main components of mucus, have a core protein rich in serine and threonine, to which carbohydrates and cysteine residues are attached. Mucus is secreted from submucosal glands and airway goblet cells. In COPD there is hyperplasia of goblet cells and hypertrophy of glands with an increase in the ratio of glandular mucus cells to serous cells. The changes in COPD are associated with an alteration of the mucus proteins (MUCs) to favor a predominance of MUC5B over the typical MUC5AC form, and an increase in the MUC2 form, which is uncommon in normal lung mucus.<sup>135</sup> Other alterations in the mucus layer in COPD include greater acidity, less mucin glycosylation, and decreased antimicrobial peptides. Mediators responsible for mucus hypersecretion include proteinases, cytokines, oxidants, and epidermal growth factor receptor (EGFR) ligands.<sup>136</sup> The negative charge of mucus glycoproteins results in sequestration of proteases, volatile hydrocarbons and possibly preservation of the hydration of the ciliated layer, resulting in protection of the underlying lung and likely improved carcinogen clearance. However, the symptoms of mucus

hypersecretion are common complaints in individuals with COPD; quantity and location of mucus may be particularly important in symptomatic COPD. Determining the relationship between chronic cough and sputum in patients with COPD and the natural history of COPD has been elusive.<sup>137</sup> Reports vary from finding weak to strong correlations between cough and sputum production and COPD progression, COPD exacerbations, and mortality.<sup>138</sup> A relationship between chronic mucus hypersecretion in small airways and adverse outcomes is plausible as histological analysis of small airway pathology in COPD demonstrated that the extent of small airway luminal obstruction by mucus correlated with the GOLD stage and was inversely correlated with survival after lung volume reduction surgery.<sup>139</sup> Whether the mucus glycoproteins are a beneficial factor that mark the degree of inflammation (e.g., a biomarker of inflammation) or are themselves a pathologic factor in the severity of symptoms or progression of disease is an important question, as treatment of mucus hypersecretion without adequate suppression of the inciting inflammation may result in undesired consequences<sup>140</sup>

#### **CLINICAL FEATURES:**

The characteristic symptoms of COPD are chronic and progressive dyspnea, cough, and sputum production that can be variable from day-to-day<sup>141</sup>. Chronic cough and sputum production may precede the development of airflow limitation by many years. Individuals, particularly those exposed to COPD risk factors, who present with these symptoms should be examined to search for an underlying cause(s) and appropriate interventions taken. Conversely, significant airflow limitation may

develop without chronic cough and sputum production. Although COPD is defined on the basis of airflow limitation, in practice the decision to seek medical help is usually determined by the impact of a symptom on a patient's daily life. A person may seek medical attention either because of chronic symptoms or because of a first exacerbation.

### **Dyspnea**

Dyspnea, a cardinal symptom of COPD, is a major cause of disability and anxiety associated with the disease. Typical COPD patients describe their dyspnea as a sense of increased effort to breathe, heaviness, air hunger, or gasping<sup>142</sup>. However, the terms used to describe dyspnea vary both by individual and by culture<sup>143</sup>.

### **Cough**

Chronic cough, often the first symptom of COPD to develop<sup>144</sup>, is frequently discounted by the patient as an expected consequence of smoking and/or environmental exposures. Initially, the cough may be intermittent, but later is present every day, often throughout the day. The chronic cough in COPD may be unproductive. In some cases, significant airflow limitation may develop without the presence of a cough.

### **Sputum production**

COPD patients commonly raise small quantities of tenacious sputum after coughing bouts. Regular production of sputum for 3 or more months in 2 consecutive years is the epidemiological definition of chronic bronchitis<sup>145</sup>, but this is a somewhat arbitrary definition that does not reflect the range of sputum production in COPD

patients. Sputum production is often difficult to evaluate because patients may swallow sputum rather than expectorate it, a habit subject to significant cultural and gender variation. Patients producing large volumes of sputum may have underlying bronchiectasis. The presence of purulent sputum reflects an increase in inflammatory mediators, and its development may identify the onset of a bacterial exacerbation<sup>146</sup>.

### **Wheezing and Chest Tightness**

Wheezing and chest tightness are nonspecific symptoms that may vary between days, and over the course of a single day. Audible wheeze may arise at a laryngeal level and need not be accompanied by auscultatory abnormalities. Alternatively, widespread inspiratory or expiratory wheezes can be present on listening to the chest. Chest tightness often follows exertion, is poorly localized, is muscular in character, and may arise from isometric contraction of the intercostal muscles. An absence of wheezing or chest tightness does not exclude a diagnosis of COPD, nor does the presence of these symptoms confirm a diagnosis of asthma.

### **Additional Features in Severe Disease**

Fatigue, weight loss and anorexia are common problems in patients with severe and very severe COPD<sup>147</sup>. They are prognostically important<sup>148</sup> and can also be a sign of other diseases (e.g., tuberculosis, lung cancer), and therefore should always be investigated. Cough syncope occurs due to rapid increases in intrathoracic pressure during prolonged attacks of coughing. Coughing spells may also cause rib fractures, which are sometimes asymptomatic. Ankle swelling may be the only symptomatic

pointer to the development of cor pulmonale. symptoms of depression and anxiety merit specific enquiry in the clinical history because they are common in COPD<sup>149</sup> and are associated with increased risk of exacerbations and poorer health status.

## **COMPLICATIONS**

### **PNEUMOTHORAX**

Pneumothorax may develop spontaneously in patients with COPD. Depending on the degree of respiratory impairment, a pneumothorax may result in significant dyspnea and even acute respiratory failure. Pneumothorax was treated similarly in COPD as in other conditions, although patients with severe emphysema are at increased risk for persistent air leaks, which may be difficult to treat.

### **GIANT BULLAE**

Emphysema may present with large bullae that can occupy a good portion of the hemithorax. Surgical treatment can be considered if compression of adjacent lung tissue is significant and surgical intervention is expected to improve pulmonary mechanics.<sup>150</sup> Bullae may also become infected. An increased frequency of lung cancer has been reported in association with large bullae, seen either as a mass within the bulla or a thickening of the wall.

### **PNEUMONIA**

Pneumonia is not uncommon in patients with COPD and should be in the differential diagnosis for any patient with COPD presenting with increased dyspnea, cough, sputum production, and/or fever, which can make it difficult to distinguish from an acute exacerbation of COPD without a chest radiograph. While COPD is



believed to increase the risk for pneumonia, epidemiologic data are limited.<sup>151</sup> Inhaled corticosteroids (ICS), which are frequently employed in the treatment of COPD because they reduce the frequency of COPD exacerbations, have been associated with an increased risk for pneumonia, particularly in older patients with COPD. All patients with COPD should be immunized against pneumococcus.

### **COR PULMONALE**

Cor pulmonale refers to altered structure or function of the right ventricle resulting from pulmonary hypertension (PH) associated with chronic lung disease. The prevalence of cor pulmonale in COPD is not known with certainty but reported prevalence ranges from 1% to more than 70% depending on the patient population examined and the methodology employed for defining PH.<sup>152</sup> When PH develops in the setting of COPD, the severity tends to be modest; severe resting PH due to COPD is relatively uncommon. Signs and symptoms of cor pulmonale include an increase in dyspnea, chest pain, and syncope. Severe cor pulmonale often presents with an increase in lower extremity edema, which should prompt further investigation. Other physical examination findings include right ventricular heave, prominent pulmonic component to the second heart sound, tricuspid regurgitation murmur, and a right-sided S4. Electrocardiographic findings may include right axis deviation, evidence of right ventricular hypertrophy, and right bundle-branch block, but overall these findings are rather insensitive for diagnosis of PH. Echocardiography can be diagnostically helpful although not infrequently images are limited in patients with parenchymal lung disease and hyperinflation. In

addition, the correlation between echocardiogram and right heart catheterization is imperfect; sensitivity tends to be better than specificity, suggesting that normal results on echocardiogram can help exclude significant cor pulmonale. Right heart catheterization remains the “gold standard” for diagnosis. PH in COPD is associated with worse outcomes, including increased risk for hospitalization and worse survival. There are few data to support the use of vasodilators for treatment of PH in COPD. Oxygen is the only therapy for PH in COPD and also improves mortality in appropriately selected patients.<sup>152</sup>

## **SLEEP DISORDERS**

As many as 40% of COPD patients report sleep difficulties such as poor sleep quality or difficulties initiating or maintaining sleep.<sup>153</sup> The combination of COPD and obstructive sleep apnea (OSA) is commonly referred to as “overlap syndrome.” The frequency of OSA in the COPD patient population has been estimated to be approximately 16%, which is roughly similar to that of the general population, although the consequences of OSA in patients with COPD are more significant. Compared to patients with OSA alone or with COPD alone, patients with COPD with OSA tend to have more severe nocturnal hypercapnia and hypoxemia as well as increased risk for PH. OSA in COPD is also associated with poorer quality of life, frequent exacerbations, and increased mortality. Diagnosis of OSA in COPD is important because continuous positive airway pressure therapy for patients with

overlap syndrome has been associated with both decreased risk of death and decreased incidence of severe exacerbations

### **Key Indicators for Considering a Diagnosis of COPD.**

Dyspnea

Chronic cough

Chronic sputum production

History of exposure to risk factors

Family history of COPD

### **DIAGNOSIS AND EVALUATION:**

#### **Assessment of Symptoms**

In the past, COPD was viewed as a disease largely characterized by breathlessness. A simple measure of breathlessness such as the Modified British Medical Research Council (mMRC) Questionnaire was considered adequate for assessment of symptoms, as the mMRC relates well to other measures of health status<sup>154</sup> and predicts future mortality risk<sup>155</sup>. However, it is now recognized that COPD has multiple symptomatic effects. For this reason, a comprehensive symptom assessment is recommended rather than just a measure of breathlessness.

#### **COPD Assessment Test (CAT)**

The COPD Assessment Test is an 8-item unidimensional measure of health status impairment in COPD<sup>156</sup>. It was developed to be applicable worldwide and validated

translations are available in a wide range of languages. The score ranges from 0-40, and has been extensively documented in numerous publications<sup>157</sup>

### **Spirometry**

Pulmonary function testing and, in particular, spirometry is essential to establish a diagnosis of COPD. While symptoms suggest a diagnosis, unfortunately their predictive value for a diagnosis of COPD is poor. Several screening tools have been developed, including questionnaires Spirometry can be performed in the physician's office and should be done in any patient with symptoms (e.g., cough, sputum, dyspnea) and risk factors. When performing spirometry, a subject exhales forcefully and the FEV1 is compared against the total air exhaled, which is the FVC. COPD is defined by a reduction in the FEV1/FVC ratio. The degree of FEV1 reduction defines the severity of airflow obstruction. The flow volume loop in COPD typically has a concave appearance and the volume time curve demonstrates a prolonged expiratory time

The ATS and the Global Initiative for Chronic Obstructive Lung Disease (GOLD) recommend that post-bronchodilator values be used to help distinguish COPD from asthma. GOLD recommends an FEV1/FVC less than 0.70 as the threshold for presence of airflow obstruction.<sup>158</sup> Rather than using the fixed ratio, the ATS/ERS recommends using the fifth percentile for the lower limit of normal. In general, the fixed ratio approach leads to overdiagnosis in older subjects because the FEV1/FVC ratio declines with age, even in healthy individuals.<sup>159</sup>

COPD severity has typically been graded based on FEV1% predicted, which is part of the GOLD

### **GOLD Classification of Severity of Airflow**

In Patients with FEV1/FVC < 0.70

**GOLD 1:** mild FEV1 ≥ 80% predicted

**GOLD 2:** moderate 50% ≤ FEV1 < 80% predicted

**GOLD 3:** severe 30% ≤ FEV1 < 50% predicted

**GOLD 4:** very severe FEV1 < 30% predicted

### **Exercise Testing**

The 6-minute walk test (6MWT) is probably the most frequently employed exercise test in COPD. The distance that a patient can walk in 6 minutes is termed the 6-minute walk distance (6MWD). An advantage of the 6MWT is that it requires little training to administer and no specialized equipment. While a 6MWT is not required to make a diagnosis of COPD, it allows the clinician to assess oxygenation during ambulation and the potential need for supplemental oxygen. 6MWD is also frequently employed during lung transplant evaluation to gauge functional status and prognosis. 6MWD has been demonstrated to relate to mortality in COPD and is a component of the BODE mortality index.<sup>160</sup> While there is good correlation between 6MWD and peak oxygen uptake in end-stage lung disease,<sup>161</sup> the 6MWT should be considered complementary to the CPET. Most patients do not achieve maximal exercise capacity during the 6MWT and consequently the 6MWD may better reflect functional exercise capacity. The 6MWD also correlates better with

quality of life measures; therapeutic interventions resulting in changes in 6MWD also correlate with improvements in dyspnea.<sup>162</sup> Some form of exercise testing is typically employed before and after pulmonary rehabilitation to assess improvement. CPET is also a necessary part of evaluation for lung volume reduction surgery (LVRS), because LVRS may provide a survival benefit for those with a low work rate after pulmonary rehabilitation.

## **IMAGING**

Chest radiography and computed tomography (CT) are the two imaging modalities most commonly used in COPD. While not required to diagnose COPD, imaging can be helpful to rule out concomitant processes. Chest radiographs are frequently obtained to investigate dyspnea or hemoptysis or to look for pneumonia, heart failure, lung cancer, or pneumothorax. Chest radiography is not particularly sensitive or specific for the diagnosis of COPD. There are certain features, however, that are often seen in COPD. Radiolucency, diaphragmatic flattening, and increased retrosternal airspace on the lateral radiograph may be seen when hyperinflation is present.

Chest CT allows better detection and quantification of emphysema than does traditional chest radiography. Areas of low attenuation are a marker of emphysema; thickened airways indicative of bronchial thickening may also be seen. If expiratory views are obtained, areas of air trapping indicative of small airway obstruction and emphysema may also be seen. CT is not indicated in the routine diagnosis or evaluation of COPD, but can be helpful when evaluating individuals with very

severe COPD. CT imaging is required to quantify emphysema extent and distribution for the purposes of LVRS. Individuals with very severe COPD undergoing transplant evaluation typically require a chest CT to rule out the presence of lung cancer and aid with surgical planning. CT imaging is also helpful when the clinician is concerned about a concomitant process such as interstitial lung disease which may be suggested on pulmonary function testing or when hemoptysis or other unexplained changes in symptoms develop.

## **LABORATORY TESTING**

### **Arterial Blood Gases**

Arterial blood gases (ABGs) are not indicated as part of the routine evaluation for patients with mild to moderate COPD. However, ABGs can be helpful to assess hypoxemia and to provide information regarding hypercapnia, particularly in individuals with more severe disease or during an acute exacerbation.

### **Erythrocytosis**

Elevated hemoglobin may be seen in COPD, particularly in the presence of chronic hypoxemia. A hemoglobin value is also helpful in the evaluation of dyspnea because anemia is a common cause of dyspnea that should be ruled out. In addition, DLCO is most accurate when adjusted for hemoglobin.

### **Serum Bicarbonate**

An elevated serum bicarbonate can suggest chronic hypercapnia; in the setting of hypercapnia, serum bicarbonate is increased due to compensatory metabolic alkalosis.

## **Alpha1-Antitrypsin Deficiency**

The ATS guidelines recommend testing for A1AT deficiency for all individuals with persistent airflow obstruction.<sup>163</sup> A1AT is a protease that inactivates neutrophil elastase. Clinical features suggestive of A1AT deficiency include emphysema at a young age, emphysema in an individual with minimal or no smoking history, lower lobe predominant emphysema, and a family history of emphysema. However, A1AT deficiency can also be present in patients with more typical COPD presentations. In individuals with established COPD, diagnostic testing is recommended. The chest radiograph and CT show the predominantly lower lobe distribution of emphysema, consistent with a panacinar pattern and different from the more common centriacinar pattern

## **Sputum.**

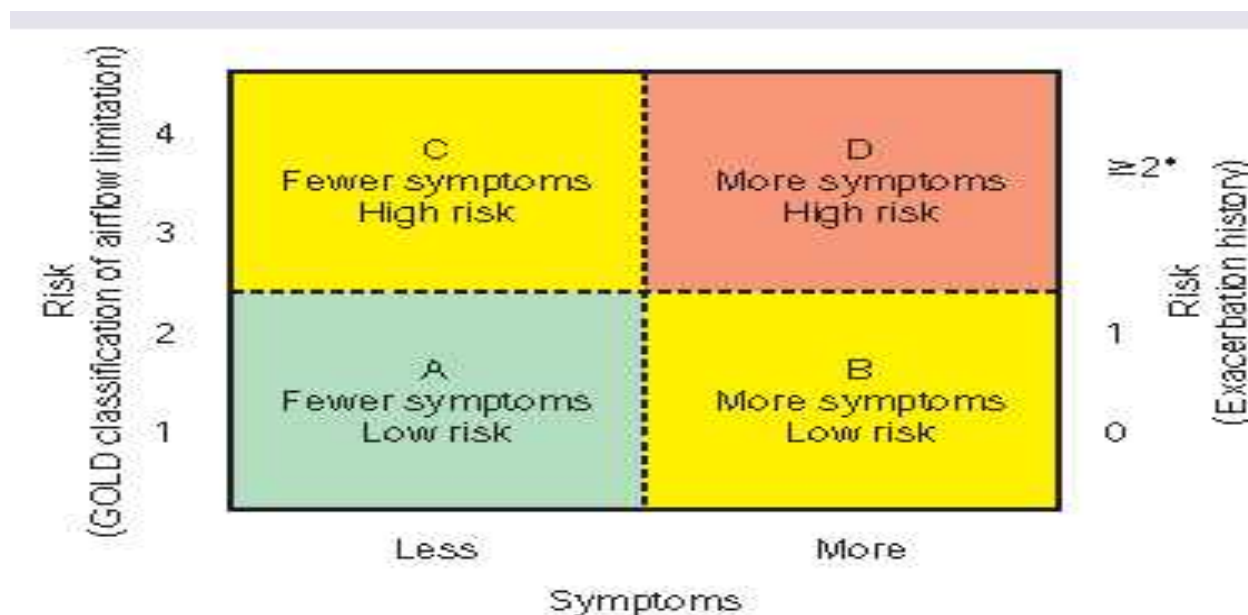
Sputum evaluation is not indicated in the routine diagnosis and care of the COPD patient. In patients with stable disease, sputum examination typically reveals a predominance of macrophages and few bacteria. During exacerbations, the number of organisms on Gram stain typically increases. The most common pathogens identified on sputum culture include *Haemophilus influenzae*, *Moraxella catarrhalis* and *Streptococcus pneumoniae*. However, the relationship between identification of organisms in sputum and pathogenic contribution to acute exacerbations has been questioned because longitudinal studies have suggested that the incidence of bacterial isolation from sputum during an acute exacerbation of COPD was no different from that of the stable state,<sup>164</sup> although bacteria identified in sputum



during stable COPD have been associated with a greater exacerbation frequency and lung function decline. In general, exacerbations typically respond to empirical treatment.

### **GOLD COMBINED ASSESSMENT PROPOSAL**

GOLD has recently proposed a new multidimensional system for the assessment and management of COPD



The groups can be summarized as follows:

#### **Patient Group A** – Low Risk, Less Symptoms

Typically GOLD 1 or GOLD 2 (Mild or Moderate airflow limitation); and/or 0-1 exacerbation per year and no hospitalization for exacerbation; and CAT score < 10 or mMRC grade 0-1

#### **Patient Group B** – Low Risk, More Symptoms

Typically GOLD 1 or GOLD 2 (Mild or Moderate airflow limitation); and/or 0-1 exacerbation per year and no hospitalization for exacerbation; and CAT score  $\geq$  10 or mMRC grade  $\geq$  2

**Patient Group C** – High Risk, Less Symptoms

Typically GOLD 3 or GOLD 4 (Severe or Very Severe airflow limitation); and/or  $\geq$  2 exacerbations per year or  $\geq$  1 with hospitalization for exacerbation; and CAT score  $<$  10 or mMRC grade 0-1

**Patient Group D** – High Risk, More Symptoms

Typically GOLD 3 or GOLD 4 (Severe or Very Severe airflow limitation); and/or  $\geq$  2 exacerbations per year or  $\geq$  1 with hospitalization for exacerbation; and CAT score  $\geq$  10 or mMRC grade  $\geq$  2

**DIFFERENTIAL DIAGNOSIS**

- Asthma
- Congestive Heart Failure.
- Bronchiectasis
- Tuberculosis
- Obliterative Bronchiolitis
- Diffuse Panbronchiolitis

## **MANAGEMENT**

### **GENERAL PRINCIPLES OF TREATMENT**

Goals of treatment of COPD are:

- To reduce symptoms- relief of dyspnea, improved exercise tolerance, and improved health status
- To reduce risk by preventing and treating exacerbations
- Preventing disease progression

Reducing mortality

- To minimize the adverse effects of medications.

Reduction of Risk Factors

In the case of COPD, risk reduction refers to interventions that may decrease the likelihood of developing the disease, slow disease progression, decrease exacerbations, and reduce mortality. Although our knowledge of the factors that contribute to each of these is limited, there are substantial data on some factors that contribute to each of these.

#### **Smoking Cessation**

Throughout the developed world, cigarette smoking is the most important risk factor for the development of COPD. Public health and educational programs aimed at discouraging people from smoking and efforts to help active smokers stop are probably the most important intervention for COPD. National Institutes of Health–sponsored Lung Health Study demonstrated that in smokers with COPD, smoking cessation reduced the rate of decline in lung function, whereas inhaled

bronchodilator did not.<sup>165</sup> In a 14.5-year follow-up to the Lung Health Study, Anthonisen and colleagues reported that the lung-function benefit continued for persistent quitters; there was also a mortality (all cause) benefit for those who maintained abstinence. Perhaps more important, even those whose smoking cessation was intermittent experienced a benefit compared with continued smokers.<sup>166</sup> Smoking cessation education and support should be offered to every patient with COPD, at every visit.

### **Biomass Fuel**

In the developing world, cigarette smoke is less of an issue than is exposure to biomass fuel, used for cooking and heating. The exposure is particularly great for women and their young children, who may spend the greater part of each day indoors with an unvented fire, fueled by wood, dung, or kerosene. Such exposure has been associated with chronic bronchitis and COPD.<sup>167</sup> Guarnieri and colleagues showed that something as simple as a vented stove can decrease gene expression for markers of inflammation in sputum.

### **Environmental Controls**

Allergens and air pollutants may have an impact on COPD. In addition, a growing body of evidence suggests that long term exposure to even low levels of air pollution increase the risk for COPD.<sup>168</sup> Also, people with COPD who also have allergic disease have higher levels of respiratory symptoms and are at higher risk for COPD exacerbations. As a consequence, people with COPD should avoid noxious

exposures, heed air quality warnings, and be cautious of ongoing occupational exposures.

### **Prevention of Respiratory Infections**

A significant proportion of COPD exacerbations are triggered by respiratory infections. Although there are some data to suggest that patients with COPD are more susceptible to respiratory infections because of impaired mucociliary clearance, a more important issue is that those with COPD are more susceptible to the consequences of respiratory tract infections. As a general rule, every patient with COPD should be immunized annually against influenza, which is effective at reducing the incidence of influenza regardless of the severity of COPD, and has been demonstrated to reduce mortality in older adults.<sup>169</sup> In addition all should be vaccinated against *S. pneumoniae*. More recently, Chronic antibiotics for prophylaxis trials with erythromycin and moxifloxacin have demonstrated a reduction in exacerbations. There has been a particular interest in macrolide antibiotics, because of their demonstrated value in diffuse panbronchiolitis and in cystic fibrosis, and because they may have anti-inflammatory as well as antimicrobial properties.

### **Prevention of Exacerbations**

Exacerbations of COPD are sentinel events and are closely associated with disease progression. Increasing severity of COPD is associated with increased exacerbations and need for hospitalization, but for every stage of severity, severe exacerbations are associated with increases in short-term and long-term all-cause mortality.<sup>170</sup>

Exacerbations have an independent negative effect on prognosis, and mortality increases with the frequency of hospitalizations. Although supporting data are lacking, the hope is that, by preventing exacerbations, lung function may be preserved and deterioration prevented. ICS, long-acting  $\beta$ -agonists, long-acting muscarinic antagonists, and macrolide antibiotics have all been shown to reduce exacerbations. Unfortunately, even patients taking these medications may still experience as many as 1.4 exacerbations per year.

#### TREATMENT RECOMMENDATIONS :

<b>Patient Group</b>	<b>Recommended First choice</b>	<b>Alternative Choice</b>	<b>Other Possible Treatments<sup>†</sup></b>
A	SAMA prn or SABA prn	LAMA or LABA or SABA and SAMA	Theophylline
B	LAMA or LABA	LAMA and LABA	SABA and/or SAMA Theophylline
C	ICS + LABA or LAMA	LAMA and LABA or LAMA and PDE4-inh. or LABA and PDE4-inh.	SABA and/or SAMA Theophylline
D	ICS + LABA and/or LAMA	ICS and LABA and LAMA or ICS and LABA and PDE4-inh. or LAMA and LABA or LAMA and PDE4-inh.	Carbocysteine SABA and/or SAMA Theophylline

## **Bronchodilators**

Medications that increase the FEV1 or change other spirometric variables, usually by altering airway smooth muscle tone, are termed bronchodilators. Bronchodilators are recommended for all patients with COPD. Pharmaceutical classes of bronchodilators include  $\beta_2$ -agonists, antimuscarinics (anticholinergics), and methylxanthines. Bronchodilator medications are central to symptom management in COPD.

- Inhaled therapy is preferred.
- The choice between  $\beta_2$ -agonist, anticholinergic, theophylline, or combination therapy depends on availability and individual patient response in terms of symptom relief and side effects.
- Bronchodilators are prescribed on an as-needed or on a regular basis to prevent or reduce symptoms.
- Long-acting inhaled bronchodilators are convenient and more effective at producing maintained symptom relief than short-acting bronchodilators.
- Combining bronchodilators of different pharmacological classes may improve efficacy and decrease the risk of side effects compared to increasing the dose of a single bronchodilator.

Even patients who do not respond to bronchodilator testing in the pulmonary function laboratory should be given a clinical trial of bronchodilators. Although the increase in FEV1 may be modest, it may be sufficient to improve lung emptying and, by this mechanism, reduce dynamic hyperinflation.<sup>171</sup> In multiple studies,

bronchodilators have been shown to reduce dyspnea and increase exercise tolerance in patients with chronic stable COPD.<sup>172</sup>

### **-Adrenergic Agonists**

These medications bind directly to  $\beta$ -receptors located on airway smooth muscle and dilate the airway. Less prominent effects include increased ciliary beat frequency that promotes mucus transport along the mucociliary escalator and improved respiratory muscle endurance.<sup>173</sup>  $\beta$ -agonists are available in both short-acting and longacting preparations, and can be administered by inhalation, orally, subcutaneously, or intravenously. For treatment of COPD,  $\beta$ -agonists should only be given as inhaled aerosols, because the other routes are associated with an unacceptably high risk of systemic adverse effects.

**Short-acting beta agonists (SABAs)** include albuterol (salbutamol), levalbuterol, terbutaline, and fenoterol. Albuterol is a racemic mixture of both (R)- and (S)-enantiomers of albuterol; levalbuterol is the (R)-enantiomer alone. The (R)-enantiomer is thought to be responsible for bronchodilation while the (S)-enantiomer is believed to cause tremor, tachycardia, and perhaps airway inflammation. Thus, levalbuterol would be expected to be better tolerated than albuterol. In fact, for most patients with stable COPD who use their short-acting  $\beta$ -agonist for symptom management, the added advantage of levalbuterol over albuterol is probably not significant.<sup>174</sup> Albuterol is also available in combination with ipratropium (a muscarinic antagonist) Short-acting  $\beta$ -agonists for inhalation are available in solution for administration by nebulizer, as well as by metered-dose



inhaler and dry powder inhaler (DPI). The combination of albuterol and ipratropium is available in a soft mist inhaler. Many studies have shown that metered dose inhalers, DPIs, and soft mist inhalers are as effective as nebulizers in patients who are able to use the devices properly. Unfortunately, the proper technique for using different devices is not the same, and patients need detailed instruction and periodic assessment of their technique. In addition, DPIs require a much higher inspiratory flow than do metered-dose inhalers and some patients with moderate-to-severe COPD may not be able to generate adequate flows. For these individuals and for those whose medical or mental status makes coordinated breathing efforts difficult, nebulized  $\beta_2$ -agonists may be preferable.<sup>175</sup>

The major advantage of short-acting  $\beta_2$ -agonists is their rapid onset of action, within 5 to 15 minutes after inhalation. Their effects last for 2 to 6 hours. Most patients with COPD demonstrate a modest improvement in FEV<sub>1</sub>, and many studies and meta-analyses support their use for COPD.<sup>176</sup> The combination of albuterol and ipratropium results in greater and more sustained improvement in lung function than either drug alone.<sup>177</sup> When used at the recommended doses, inhaled short-acting  $\beta_2$ -agonists are thought to be safe.

The major adverse effects include tremor, anxiety, tachycardia, and hypokalemia. Adverse effects are dose-dependent and are less common with inhaled compared with systemic dosing, and when inhaler technique is optimized. Fortunately, tachyphylaxis to the systemic side effects of  $\beta_2$ -agonists is greater than tachyphylaxis to the bronchodilator effect.

**Long-acting  $\beta$ -agonists (LABAs)** typically produce bronchodilation that lasts for 12 hours or more. Salmeterol was the first LABA to be studied extensively. Its onset of action is much slower than that of albuterol, on the order of 20 to 30 minutes. Formoterol has a similar duration of action, but an onset of action that is nearly identical to albuterol.

Both salmeterol and formoterol must be taken twice daily. Arformoterol is the (R)-enantiomer of formoterol. Indacaterol has a rapid onset and a duration of action of nearly 24 hours, and thus requires only once daily dosing. The bronchodilator effect of indacaterol is greater than that of salmeterol or formoterol. Vilanterol is another LABA with a rapid onset of action and a duration of action of approximately 24 hours. It is not used as monotherapy, but used in combination with the ICS fluticasone. Many studies have demonstrated a benefit of LABAs in patients with stable COPD.<sup>178</sup> Salmeterol and formoterol significantly improve lung function, dyspnea, quality of life, and the rate of exacerbations.<sup>179</sup> Salmeterol has been shown to reduce hospitalizations. Indacaterol improves dyspnea and health status, and reduces exacerbations. The adverse effects reported with LABAs are similar to those described for short-acting  $\beta$ -agonists. Monotherapy with an LABA appears to be both safe and efficacious. LABAs are frequently combined with an ICS in the same inhaler, and currently available preparations include salmeterol/fluticasone, formoterol/budesonide, formoterol/mometasone, and vilanterol/fluticasone. Many studies have shown that combination therapy is often more effective than either

agent alone, and various guidelines provide recommendations for how and when to escalate treatment beyond short-acting bronchodilators.

### **Antimuscarinics**

Antimuscarinics, also known as anticholinergics or muscarinic antagonists, block the effects of acetylcholine on M3 muscarinic receptors on airway smooth muscle. The newer quaternary amines such as ipratropium and glycopyrrolate, as well as tiotropium and aclidinium, are better tolerated because they do not cross the blood-brain barrier. In addition, both tiotropium and aclidinium have pharmacokinetic selectivity for the M3 receptor and dissociate more rapidly from M2 receptors, which are found on cholinergic nerve terminals and inhibit acetylcholine release. Thus, the relative lack of M2 binding by these muscarinic antagonists may allow acetylcholine to bind to M2 receptors, thereby inhibiting further acetylcholine release and reducing bronchoconstriction.

**Short-acting muscarinic antagonists (SAMAs)** include ipratropium and oxitropium. They increase FEV1 with an onset of action of 10 to 15 minutes and a duration of action of 4 to 6 hours. Ipratropium improves lung function, increases exercise capacity, decreases dyspnea, and decreases cough.<sup>180</sup> The magnitude of bronchodilation with ipratropium is comparable to that seen with albuterol but, when used in combination, their effects are additive and the duration is longer.

**Long-acting muscarinic antagonists (LAMAs)** include tiotropium and aclidinium, which are slower in onset than ipratropium, but last longer, with bronchodilation lasting at least 12 hours after aclidinium<sup>216</sup> and more than 24 hours after

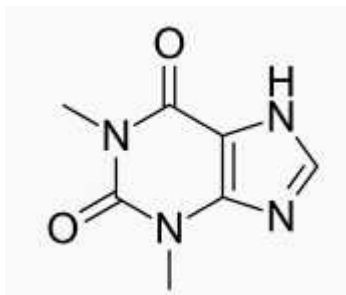
tiotropium. Tiotropium decreases symptoms, improves health status, and reduces exacerbations by 20% to 25%<sup>181</sup> and hospitalizations. It appears to improve the effectiveness of pulmonary rehabilitation, perhaps by decreasing dynamic hyperinflation. In general, both short- and long-acting muscarinic antagonists have good safety profiles.

The most common side effects are dry mouth and urinary retention. Medication that contacts the eye, either by hand contact or by aerosolization, can cause blurred vision and can precipitate glaucoma. A metaanalysis of ipratropium and tiotropium in COPD<sup>182</sup> suggested that anticholinergic therapy was associated with an increased risk of cardiovascular death, myocardial infarction, and stroke

### **METHYLYXANTHINES**

Methylxanthines are a group of structurally related compounds that are widely used in the treatment of patients with asthma, chronic obstructive pulmonary disease (COPD) and chronic cor pulmonale. Their effect is a generalised reduction of airway obstruction that decreases the overall resistance of the airways, improves blood gas exchange and reduces the dyspnoea. It has been recognised that these drugs may provide benefits above and beyond the usual bronchodilation. Unfortunately, therapy with xanthines is generally associated with a number of adverse events, affecting the cardiovascular system, the central nervous system and the gastrointestinal system.

**Theophylline**, also known as 1,3-dimethylxanthine, one of the three naturally occurring methylated xanthine alkaloids



**Mechanism of action** Three distinct cellular actions of methylxanthines have been defined—(a) Release of  $\text{Ca}^{2+}$  from sarcoplasmic reticulum, especially in skeletal and cardiac muscle.

(b) Inhibition of phosphodiesterase (PDE) which degrades cyclic nucleotides intracellularly. The concentration of cyclic nucleotides is increased. Bronchodilatation, cardiac stimulation and vasodilatation occur when cAMP level rises in the concerned cell. Several isoenzymes of the PDE superfamily exist in different tissues. Theophylline is a subtype nonselective and weak PDE inhibitor, but PDE4 inhibition is mainly responsible for bronchodilatation. However, some selective PDE4 inhibitors like Cilomilast and Roflumilast have been disappointing clinically in efficacy as well as side effects.

(c) Blockade of adenosine receptors: adenosine acts as a local mediator in CNS, CVS and other organs—contracts smooth muscles, especially bronchial; dilates cerebral blood vessels, depresses cardiac pacemaker and inhibits gastric secretion.

Methylxanthines produce opposite effects.

Action (a) is exerted only at concentrations much higher than therapeutic plasma concentrations of caffeine and theophylline (ranging from 5–20 µg/ml). Action (b) and action (c) are exerted at concentrations in the therapeutic range and appear to contribute to bronchodilatation. Raised cAMP levels in inflammatory cells may attenuate mediator release and promote eosinophil apoptosis adding to the therapeutic effect of theophylline in asthma.

Adenosine A1 receptor antagonism is considered responsible for cardiac arrhythmias and seizures occurring in theophylline toxicity. Recent evidence suggests that low concentrations of theophylline enhance histone deacetylation in airway inflammatory cells, suppressing proinflammatory gene transcription. Thus, even sub-bronchodilator doses of theophylline may exert some beneficial effect in asthma.

### **Pharmacokinetics**

Theophylline is well absorbed orally; rectal absorption from suppositories is erratic. It is distributed in all tissues—crosses placenta and is secreted in milk, (V 0.5 l/kg), 50% plasma protein bound and extensively metabolized in liver by demethylation and oxidation primarily by CYP1A2. Only 10% is excreted unchanged in urine. Its elimination rate varies considerably with age. At therapeutic concentrations, the  $t_{1/2}$  in adults is 7–12 hours. Children eliminate it much faster ( $t_{1/2}$  3–5 hours) and elderly more slowly. In premature infants also the  $t_{1/2}$  is prolonged (24–36 hours). There are marked interindividual variations in plasma concentrations attained with the same dose. Theophylline metabolizing enzymes are saturable,  $t_{1/2}$  is prolonged with higher

doses (to as much as 60 hours) as kinetics changes from first to zero order. Plasma concentrations, therefore, increase disproportionately with dose. Factors which need dose reduction are— age > 60 yr ( $\times 0.6$ ), CHF ( $\times 0.6$ ), pneumonia ( $\times 0.4$ ), liver failure ( $\times 0.2-0.4$ ).

Serum Level	Therapeutic Effect
<5 $\mu\text{g/ml}$	No effect
10-20 $\mu\text{g/ml}$	Therapeutic range
> 20 $\mu\text{g/ml}$	Nausea
> 30 $\mu\text{g/ml}$	Cardiac arrhythmias
40-45 $\mu\text{g/ml}$	Seizures

### **Adverse effects**

Theophylline has a narrow margin of safety. Dose-dependent toxicity starts from the upper part of therapeutic concentration range. Adverse effects are primarily referable to the g.i.t., CNS and CVS. Headache, nervousness and nausea are early symptoms. Children are more liable to develop CNS toxicity. The irritant property of theophylline is reflected in gastric pain (with oral), rectal inflammation (with suppositories) and pain at site of i.m. injection. Rapid i.v. injection causes precordial pain, syncope and even sudden death—due to marked fall in BP, ventricular arrhythmias or asystole.

### **Interactions**

1. Agents which enhance theophylline metabolism primarily by inducing CYP1A2 lower its plasma level: dose has to be increased by the factor given in parenthesis.

Smoking (1.6), phenytoin (1.5), rifampicin (1.5), phenobarbitone (1.2), charcoal broiled meat meal(1.3).

2. Drugs which inhibit theophylline metabolism and increase its plasma level are—erythromycin, ciprofloxacin, cimetidine, oral contraceptives, allopurinol; dose should be reduced to 2/3.

3. Theophylline enhances the effects of—furosemide, sympathomimetics, digitalis, oral anticoagulants, hypoglycaemics.

4. Theophylline decreases the effects of—phenytoin, lithium.

5. Aminophylline injection should not be mixed in the same infusion bottle/syringe with—ascorbic acid, chlorpromazine, promethazine, morphine, pethidine, phenytoin, phenobarbitone, insulin, penicillin G, tetracyclines, erythromycin.

### **Preparations and dose**

(i) Theophylline (Anhydrous) Poorly water soluble, cannot be injected. 100–300 mg TDS (15 mg/kg/day)

Only sustained release (SR) tab./caps. are used, because fast release tabs. produce high peak and low trough plasma concentrations. Because solubility of theophylline is low, a number of soluble complexes and salts have been prepared, particularly for parenteral use.

(ii) Aminophylline (Theophylline-ethylenediamine; 85% theophylline) water soluble, can be injected i.v. but not i.m. or s.c.—highly irritating. 250–500 mg oral or slow i.v. injection; children 7.5 mg/kg i.v.; AMINOPHYLLINE 100 mg tab, 250 mg/10 ml inj.



(iii) Hydroxyethyl theophylline (Etophylline, 80% theophylline) water soluble; can be injected i.v. and i.m.(but not s.c.), less irritating; 250 mg oral/i.m./i.v.;

DERIPHYLLIN 100 mg tab., 300 mg SR tab., 220 mg/2 ml inj.

(iv) Choline theophyllinate (Oxtriphylline; 64%theophylline) 250–500 mg oral,

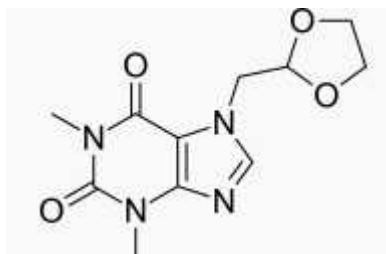
CHOLIPHYLLINE 125 mgcap., 125 mg/5 ml elixir.

(v) Theophylline ethanolate of piperazine 250–500 mg

oral or i.v.; CADIPHYLLATE 80 mg/5 ml elixir,

ETOPHYLLATE 125 mg/5 ml syrup.

### **Doxophylline**



Doxofylline 7- (1, 3 dioxolane-2-yl methyl) is a newer xanthine derivative which differs from theophylline in containing the dioxolane group at position 7.

Mechanism of action :

Inhibits the phosphodiesterase enzymes, but decreased affinities towards the adenosine A<sub>1</sub> and A<sub>2</sub> receptors, which has been claimed as a reason for its better safety profile

Doxofylline does not antagonize calcium channels, nor does it interfere with the influx of calcium into the cells, which probably reduces the cardiac side effects.

Moreover, it does not affect sleep rhythm, gastric secretions, heart rate and rhythm and CNS functioning.

### **Pharmacokinetics :**

Oral administration

Peak plasma levels were reached after 1 hour. Oral Bioavailability is 62.6%. Plasma protein binding is 48%. completely metabolized in the liver. Hydroxyl ethyl theophylline is the detectable metabolite. Around 4% is excreted unchanged in urine.

Doxofylline reaches steady state in about 4 days after repeated administrations. The elimination half life is 8-10 hrs allowing twice daily administration.

### **ADVERSE EFFECTS:**

Nausea, vomiting, epigastric pain, cephalalgia, irritability, insomnia, tachycardia, extrasystole, tachypnea, and occasionally hyperglycemia and albuminuria, may occur. If a potential oral overdose is established, the patient may present with severe arrhythmias and seizure; these symptoms could be the first sign of intoxication.

### **SPECIAL PRECAUTIONS**

The half-life of xanthine derivatives is influenced by a number of known variables. It may be prolonged in patients with liver disease, in patients with congestive heart failure, in those affected with chronic obstructive lung disease or concomitant infections, and in those patients taking certain other drugs (erythromycin, troleandomycin, lincomycin, and other antibiotics of the same group, allopurinol,

cimetidine, propranolol, and anti-flu vaccine). In these cases, a lower dose of Doxofylline may be needed. Phenytoins, other anti-convulsants and smoking may cause an increase in clearance with a shorter mean half-life: in these cases higher doses of Doxofylline may be needed. Use with caution in patients with hypoxemia, hyperthyroidism, liver disease, renal disease, in those with history of peptic ulcer and in elderly. Frequently, patients with congestive heart failure have markedly prolonged drug serum levels following discontinuation of the drug.

### **Use in Pregnancy and Lactation**

Animal reproduction studies indicate that Doxofylline does not cause fetal harm when administered to pregnant animals nor can affect reproduction capacity. However, since there is limited experience in humans during pregnancy, xanthines should be given to a pregnant woman only if clearly needed. Doxofylline is contraindicated in nursing mothers.

### **DRUG INTERACTIONS**

Doxofylline should not be administered together with other xanthine derivatives, including beverages and foods containing caffeine. Toxic synergism with ephedrine has been documented for xanthines.

Concomitant therapy with erythromycin, troleandomycin, lincomycin, clindamycin, allopurinol, cimetidine, propranolol and anti-flu vaccine may decrease the hepatic clearance of xanthines causing an increase in blood levels.

### **Dosage:**

Adult Dose: 400 mg OD or BD

children 12 mg/kg/day

### **Phosphodiesterase-4 Inhibitors**

Phosphodiesterase-4 (PDE-4) inhibitors act by blocking the breakdown of cyclic adenosine monophosphate. By this mechanism, they decrease airway inflammation; they have no direct bronchodilator activity. Roflumilast is an oral PDE-4 inhibitor that has been approved for patients with chronic bronchitis and a history of exacerbations. In a meta-analysis of 23 randomized trials, the PDE-4 inhibitors reduced exacerbations and produced a modest increase in FEV1.<sup>183</sup> When roflumilast was added to salmeterol or tiotropium, the prebronchodilator FEV1 increased. Because its effect on exacerbations is much greater than its effect on airway function, guidelines recommend that roflumilast be used in combination with a long-acting bronchodilator.<sup>187</sup> Use of PDE-4 inhibitors has been limited by the side effects. The most common are nausea, anorexia, abdominal pain, diarrhea, weight loss, sleep disturbances, and headache.<sup>184</sup> Monitoring weight during treatment is warranted.<sup>187</sup>

### **Corticosteroids**

#### **Inhaled Corticosteroids**

Airway as well as systemic inflammation are critical components of the pathogenesis of COPD.<sup>185</sup> Therefore, corticosteroids, with their anti-inflammatory effects, are an important intervention. ICS offer the additional advantage of minimizing systemic exposure. ICS have been shown to improve symptoms, lung function, and quality of life, and to reduce the frequency of COPD exacerbations,

especially in patients with an FEV1 less than or equal to 60% of predicted. The improvement in FEV1 achieved with ICS is typically less than that observed with bronchodilators.<sup>186</sup> The reduction of exacerbations by ICS is more significant and is comparable to that observed with LABAs or LAMAs. Guidelines recommend that ICS be used in combination with a long acting bronchodilator in subjects who are prone to exacerbations, but that they not be used as monotherapy.<sup>187</sup> In TORCH trial where 6112 subjects with moderate-to severe COPD were randomly treated for 3 years with placebo, fluticasone, salmeterol, or the fluticasone/salmeterol combination, Celli and colleagues reported that each active treatment arm reduced the rate of decline in FEV1. Whether this benefit reflects the reduction in exacerbations or a more direct effect on the airway, perhaps by decreasing inflammation, is not known. ICS are relatively safe, especially in comparison to systemic corticosteroids.

The most common adverse effects are oral candidiasis (thrush) and dysphonia, both of which can be minimized by careful inhalation technique followed by rinsing the mouth and gargling. Increased skin bruising is probably a manifestation of capillary fragility. Reduced bone density has been reported after long-term treatment with triamcinolone, but studies with budesonide and fluticasone have not found similar results, perhaps because these patients with COPD had a high prevalence of osteoporosis at baseline.<sup>188</sup> Finally, although ICS clearly reduce the frequency of exacerbations in COPD, they have been associated with an increased incidence of pneumonia.

## **Systemic Corticosteroids**

With rare exceptions, the use of systemic corticosteroids should be reserved for the treatment of exacerbations. In patients with stable disease, even when severe, the risk of adverse effects is probably greater than the likelihood of benefit. Chronic use of systemic corticosteroids is associated with increased mortality,<sup>189</sup> which may reflect corticosteroid effects or the underlying severity of the COPD. Occasionally, in exacerbation-prone patients who require frequent courses of high dose systemic corticosteroids, a very low daily dose of corticosteroids may protect against exacerbations and thereby reduce the total annual steroid exposure. If this unusual approach is followed, the lowest possible dose of corticosteroids should be used. Spirometric stability may be useful in encouraging patients who are experiencing nonpulmonary benefit that dose reduction is safe.

## **Combination Therapy**

Patients who remain symptomatic after a period of treatment with a single long-acting bronchodilator (either LABA or LAMA) may benefit from addition of a second drug. Choices include either an ICS or a second long-acting bronchodilator from the other pharmacologic class. ICS should probably be considered as the first addition in patients with evidence of airway inflammation and those with frequent exacerbations. There was no difference in exacerbations, but mortality was less in the salmeterol/fluticasone group and health status was better. Pneumonia was more frequent in the salmeterol/fluticasone group. Combinations of formoterol/budesonide, formoterol/mometasone, and vilanterol/fluticasone have

also been shown to improve some clinical outcomes. Finally, guidelines suggest “triple inhaler therapy” for subjects whose symptoms are not controlled by any of the combinations already described.<sup>187</sup> This recommendation is in part empirical, because each of the drugs or combinations have been shown to be effective. However, several retrospective cohort studies have described decreased mortality, and fewer exacerbations and hospitalizations with triple therapy.<sup>190,191</sup> The only prospective data comes from the UPLIFT trial, in which patients were randomized to receive “usual care” with or without tiotropium. In those patients who were already taking an ICS and a LABA , the addition of tiotropium significantly improved lung function, reduced exacerbations, and improved health related quality of life.<sup>192</sup> Further studies are needed to define the role of triple-therapy

## **NONPHARMACOLOGIC TREATMENT**

### **Mucus Clearance**

In patients with mucus hypersecretion and airflow obstruction, it may be very difficult to mobilize secretions. Maneuvers such as controlled cough and the huff cough can be helpful. In the former, patients take a deep breath, hold their breath for a few seconds, then cough two or three times with their mouth open and without taking another breath. The sequence is then repeated several times. Huff coughing involves one or two forced expirations starting at mid-lung volume and performed with the glottis open. Mucus clearance can also be facilitated by having patients breathe or cough through a device that generates high amplitude oscillations, or with

an external percussive device. These maneuvers are considered safe, but data supporting their use is limited.

### **Oxygen Therapy**

The long-term administration of oxygen (> 15 hours per day) to patients with chronic respiratory failure has been shown to increase survival in patients with severe resting hypoxemia . Long-term oxygen therapy is indicated for patients who have:

- ) SaO<sub>2</sub> at or below 88%, with or without hypercapnia confirmed twice over a three week period
- ) SaO<sub>2</sub> of 88%, if there is evidence of pulmonary hypertension, peripheral edema suggesting congestive cardiac failure, or polycythemia

A decision about the use of long-term oxygen should be based on the resting PaO<sub>2</sub> or saturation values repeated twice over three weeks in the stable patient. Current data do not support the use of ambulatory oxygen in patient populations that do not meet the above criteria. Although air travel is safe for most patients with chronic respiratory failure who are on long-term oxygen therapy, patients should ideally be able to maintain an in-flight PaO<sub>2</sub> of at least 6.7 kPa .This can be achieved in those with moderate to severe hypoxemia at sea level by supplementary oxygen at 3 L/min by nasal cannulae or 31% by Venturi facemask<sup>361</sup>. Those with a resting PaO<sub>2</sub> at sea level > 9.3 kPa (70 mmHg) are likely to be safe to fly without supplementary oxygen<sup>362,363</sup>, although it is important to emphasize that a resting



PaO<sub>2</sub> > 9.3 kPa (70 mmHg) at sea level does not exclude the development of severe hypoxemia when travelling by air.

### **Exercise**

Exercise training to improve cardiorespiratory function may be helpful; the type of exercise does not appear to be important and aerobic exercise or upper limb exercises are equally effective. Respiratory muscle training using resistive inspiratory loading may reduce breathlessness, but a meta-analysis of controlled studies of respiratory muscle training alone has provided no evidence of overall benefit.<sup>193</sup> Controlled breathing techniques, such as pursed-lip breathing and diaphragmatic breathing, result in reduced dyspnea, particularly in patients with hyperventilation.

### **Nutrition**

Nutrition is important in patients with COPD as many of them are malnourished and underweight, although marked cachexia is now uncommon. Several patients with COPD are obese because of reduced physical activity. They should lose weight, particularly if they have sleep disturbances, metabolic syndrome or frank type II diabetes. Antioxidant vitamin supplements should also be indicated. The place of androgens and anabolic steroids to build muscle bulk in COPD has not been established.

### **Pulmonary Rehabilitation**

Rehabilitation concerns prevention of deconditioning and allowing the patient to cope with his/her disease. Rehabilitation programs are successful in prospective

randomized trials in the terms of increased performance and quality of life, even though they may not improve lung function.<sup>194</sup> Patients with moderate-to-severe COPD should be considered for pulmonary rehabilitation programs, which include educational advice and physiotherapy. There is evidence that pulmonary rehabilitation also increases the efficacy of bronchodilator therapy.

### **Artificial Ventilation**

Artificial ventilation devices have improved enormously. Non-invasive ventilation using nasal intermittent positive pressure ventilation has been an important advancement in the management of acute exacerbations of COPD in hospital and more recently for the control of hypercapnic respiratory failure at home, thus reducing the need for hospitalization. Nasal intermittent positive pressure ventilation corrects the hypercapnia and respiratory acidosis, while resting the respiratory muscles. Good results in the management of acute exacerbations have been reported, with significant reduction in mortality and time spent in hospital.

### **Surgery**

Several surgical techniques have been successfully applied to more severe emphysema. These include heart-lung transplantation, now largely replaced by single-lung transplantation in carefully selected patients.<sup>195</sup> Lung volume reduction surgery (LVRS) by excision of badly affected emphysematous lung is effective in highly selected patients with bilateral predominantly upper lobe emphysema and evidence of air trapping. There is sustained improvement in lung function and reduction in symptoms with a reduction in exacerbations. Patients with a very poor

diffusing capacity had an increased mortality. Therefore, patient selection is very important. More recently bronchoscopic lung volume reduction surgery has been developed to avoid the surgical morbidity and mortality of LVRS. Several devices, including valves, coils and irreversible non-blocking techniques (bronchoscopic thermal vapor ablation, polymeric lung volume reduction) designed to collapse and remodel hyperinflated lung are currently in development.

### **RELATED STUDIES:**

#### **STUDIES ON DOXOFYLLINE:**

1. A Randomised control trial in COPD pts conducted by Dolcetti et al showed doxofylline increased FEV1 when compared with placebo.no signs of adverse effects were found.
2. A retrospective study conducted by Bagnato et al showed that doxofylline use caused adverse event of 6% and patient dropout on relation to adverse events were 5%
3. Goldstein MF et al conducted a landmark randomized controlled trial where doxofylline showed a significant increase in FEV1 compared to placebo group.
4. Bagnato et al conducted a study in the age group of 6-12 years showed significant improvement of the spirometric parameters in the doxofylline group.

5. Villani F et al conducted a trial showing that doxofylline significantly increased the FEV1 Value compared to the placebo arm but adverse effects like dyspepsia and anxiety were reported.

#### **COMPARATIVE STUDIES ON THEOPHYLLINE AND DOXOFYLLINE:**

1. Rupali Bajrang et al conducted a study ,Comparating the Efficacy And Safety Of Doxofylline Versus Theophylline in Bronchial Asthma And Copd Patients at government medical college and hospital, Aurangabad for one month and it was found that FEV1, FEF and PEFr was significantly improved in doxofylline group than theophylline group.
2. MD Faiz Ak ram et al conducted arandomized, prospective and open label study in patients of COPD in TB chest department of a medical college hospital . 154 patients were divided in theophylline group and doxofylline group Results of the study showed that there was no statistically significant difference with respect to spirometric variables and symptom score in the two groups and there was no significant difference in two groups with respect to side effects ( $p>0.05$ ).
3. Goldstein MF et al conducted a landmark randomized controlled trial where doxofylline was as effective as theophylline in broncho dilating effect but with lesser adverse effects.
4. Comparative study of the efficacy and safety of theophylline and doxofylline in patients with bronchial asthma and chronic obstructive pulmonary disease

done by Dushyant Lal et al in Vishwanathan Chest Hospital, Delhi with 60 patients showed that doxofylline was more effective as evidenced by improvement in PFT as well as clinical symptoms, and reduced incidence of adverse effects and emergency bronchodilator use.

5. Panduranga Rao Nagawaram et al conducted an open label, randomized, prospective parallel group study of 12 weeks duration in patients of COPD comparing theophylline and doxofylline in TB chest department of Osmania medical college hospital. There was no statistically significant difference with respect to spirometric variables and symptom score in the two groups and no significant difference in two groups with respect to side effects
6. Margay SM et al conducted a clinical trial to study the efficacy and safety of doxofylline and theophylline in bronchial asthma and COPD and concluded that both theophylline and doxofylline improved the lung function tests and symptoms in patients of mild Bronchial Asthma, but doxofylline has a better profile in terms of safety.
7. Comparative Study of Efficacy and Adverse Effect Profile of Theophylline and Doxofylline in Patients with COPD by Kurli Sankar et al showed that doxofylline can be used as an effective alternative to patients who cannot tolerate the adverse effects of theophylline.

With the above extensive literature review, this study was designed to compare the efficacy and safety of doxofylline and theophylline and to prove the advantages of doxofylline.

## **AIM OF THE STUDY**

To compare the safety and efficacy of oral doxofyline with theophylline in  
Grade 1-2 COPD patients.

## **MATERIALS AND METHODS**

### **STUDY DESIGN:**

Randomised, Comparative, Open label, Single centre, Prospective Parallel group Study.

### **STUDY CENTRE:**

Department of Chest Medicine in Tirunelveli Medical College Hospital.

### **STUDY POPULATION:**

Grade 1-2 COPD patients (Based on GOLD Criteria) attending the outpatient department of Chest Medicine in Tirunelveli Medical College Hospital

### **STUDY PERIOD:**

One Year from April 2016 to March 2017

### **SAMPLE SIZE:**

60(each group – 30)

### **INCLUSION CRITERIA:**

1. All the stable patients who were diagnosed clinically with COPD by the outpatient department of the hospital were enlisted and those having the FEV1 within 50% to 80% of the predicted FEV1 for their age and height and showed non

reversibility of FEV/FVC<70% Value, 20 minutes after inhalation of two puffs (400 microgram) of salbutamol are taken up for the study.

2. Adults, 18 years of age and above. Irrespective of gender.

3. Patients who have given written informed consent to participate in the study.

**EXCLUSION CRITERIA:**

1. Clinically significant cardiovascular diseases, including a history of congestive cardiac failure, angina pectoris within previous 1 year.

2. Convulsive disorders.

3. Clinical significant gastro-intestinal diseases including active peptic ulcers within preceding 1 year.

4. Renal diseases, hepatic diseases, and hematologic diseases

5. Known infection with human immunodeficiency virus.

6. Presence of any acute illness.

7. Sensitivity to theophylline or theophylline like agents.

8. Pregnant and Lactating women.

9. Patients on warfarin and digoxin.



## **SCREENING:**

### **GENERAL EXAMINATION**

Nutritional status

Body weight

Height

Ankle edema

Blood pressure measurement

Respiratory examination

Cardiovascular examination

Abdominal examination

### **LABORATORY INVESTIGATIONS**

Blood Urea

Serum creatinine

Serum sodium and potassium

Serum calcium

X-Ray chest

ECG

### **TREATMENT PROTOCOL AND FOLLOW UP :**

Patients who fulfilled the inclusion criteria were enrolled in the study. For all patients, their current medical history and Diagnosis, COPD Grade was noted.

Detailed medical history with general and systemic examination was done. All the baseline investigations, Hemoglobin, total leucocyte count, differential leucocyte count, liver function test, kidney function test were done. Pulmonary function test

(spirometry) assessments, COPD Assessment Test (CAT) Questionnaire assessment were performed for every patient. Demographic data was collected from all the patients. After enrollment, each group was randomized using computerized randomized tables and divided into two subgroups. Group I patients were administered Theophylline, 100 mg twice daily and group II patients were administered doxofylline 400 mg twice daily, orally for a duration of 12 weeks. Both Group I and Group II patients were on oral short acting beta 2 agonist salbutamol 4 mg BD. Follow up visits will be at 6 weeks and at 12 weeks. Patients were instructed to attend the chest medicine clinic fortnightly to receive drugs for 14 days and they were instructed to report immediately in case of any adverse event. Adherence was monitored by pill count.

Clinical response was assessed in both Group I and Group II patients at every visit.

**PARAMETERS ASSESSED:**

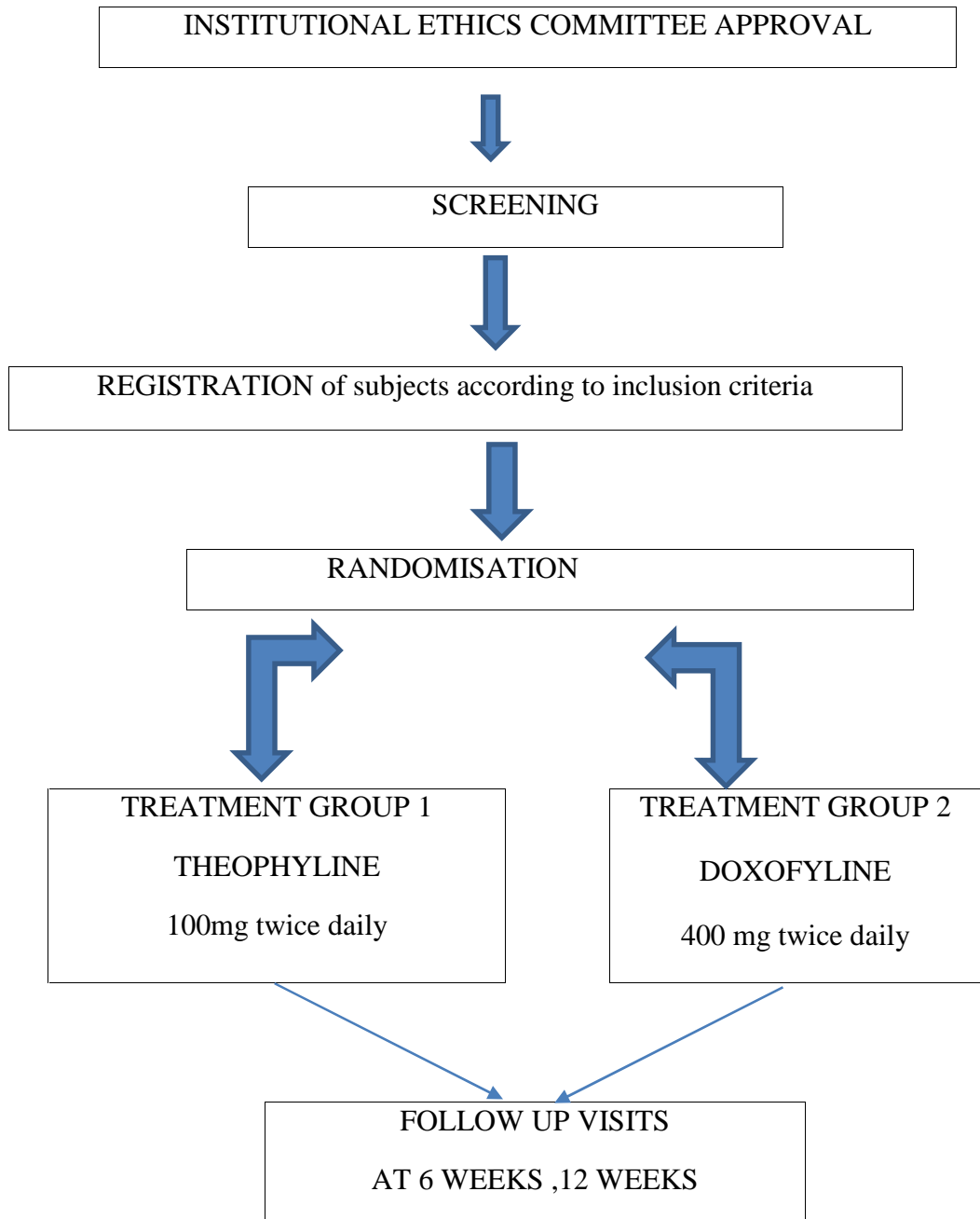
- ❖ Pulmonary function tests at baseline, 6 weeks and 12 weeks
- ❖ COPD Assessment Test (CAT) Questionnaire assessment at baseline, 6 weeks and 12 weeks
- ❖ Urea, creatinine
- ❖ serum sodium and potassium
- ❖ serum calcium
- ❖ ECG

## **STATISTICAL ANALYSIS**

For the quantitative data, forced vital capacity (FVC), forced expiratory volume in one second (FEV1) and FEV1/FVC, mean±SD values of all the variables were analysed. The significant differences among various points of time (0, 6 weeks and 12 weeks) were calculated by using analysis of variance (ANOVA) with repeated measures. The differences between values of a variable at two different time intervals were tested by the post-hoc test (Bonferroni). The differences in variables (FVC, FEV1, FEV1/FVC and symptom score) between the two groups of drugs were analyzed by Student's t-test. The above statistical analysis was done using SPSS version 23.0

Adverse effects were analysed using descriptive statistics

p-Values of < 0.05 were considered significant in all the cases.



## RESULTS

Table - 1

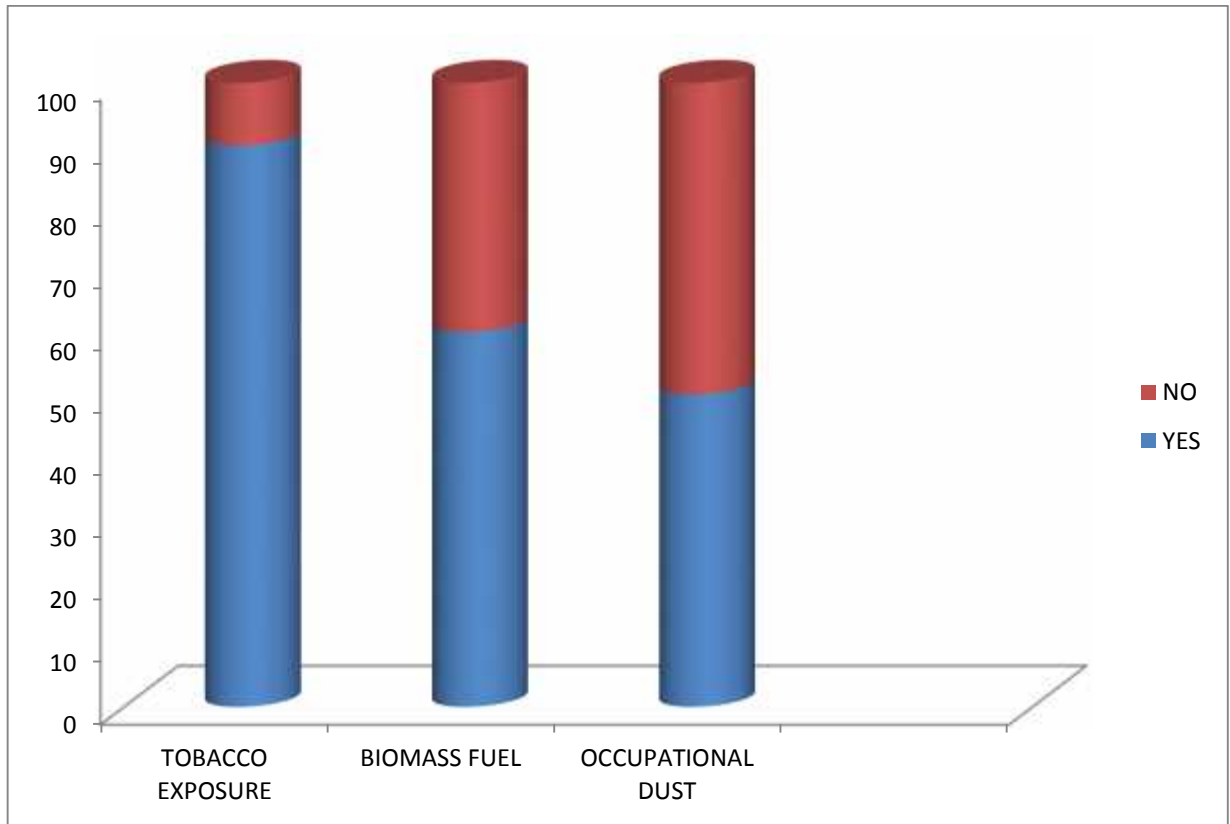
### BASELINE CHARACTERISTICS

VARIABLES		DOXOFYLLINE	THEOPHYLLINE	P VALUE
AGE		63.2±12.1	61.3±10.2	0.709
GENDER	MALE	19	18	0.667
	FEMALE	11	12	
SOCIO ECONOMIC STATUS		3.7±0.48	3.6±0.52	0.660
COUGH DURATION		6.70±5.75	4.60±4.41	0.379
GRADES OF DYSPNEA		2.4±1.07	2.7±0.95	0.517
FEV1		58.9±20.09	53.3±29.39	0.625
FVC		76.3±22.63	76.5±23.17	0.985
FEV1/FVC		75.0±13.59	65.8±14.69	0.163
CAT Score		15.3±8.30	16.9±9.27	0.689

**Table 1:** shows the baseline characteristics of the two groups were given and their p value is not significant and hence comparable.

**Figure - 1**

**PERCENTAGE OF CASES SHOWING EXPOSURE TO  
VARIOUS RISK FACTORS OF COPD**



**Figure 1:** depicts the percentage population among the study groups who were exposed to various risk factors of COPD like tobacco exposure, exposure to biomass fuel and occupational dust exposure.

**Table 2**

**COMPARISON OF FEV1 AND FVC FROM BASELINE TO 12 WEEKS IN DOXOFYLLINE GROUP (WITHIN GROUP)**

Variables	VISITS	Mean	Std. Deviation	Mean difference	P value
FEV1	BASELINE	58.9000	20.09118	-	-
	6 WEEKS	67.1000	15.97533	-8.200	0.086
	12 WEEKS	74.0000	15.54921	-15.100	0.018
FVC	BASELINE	76.3000	22.63748	-	-
	6 WEEKS	88.0000	27.27636	-11.700	0.231
	12 WEEKS	93.5000	24.70380	-17.200	0.044

**Table 2** : shows the mean and standard variation of FEV1and FVC for doxofylline group and it shows statistically significant improvement from baseline to 12 weeks

**Table 3**

**COMPARISON OF FEV1/FVC FROM BASELINE TO 12 WEEKS IN DOXOFYLLINE GROUP (WITHIN GROUP)**

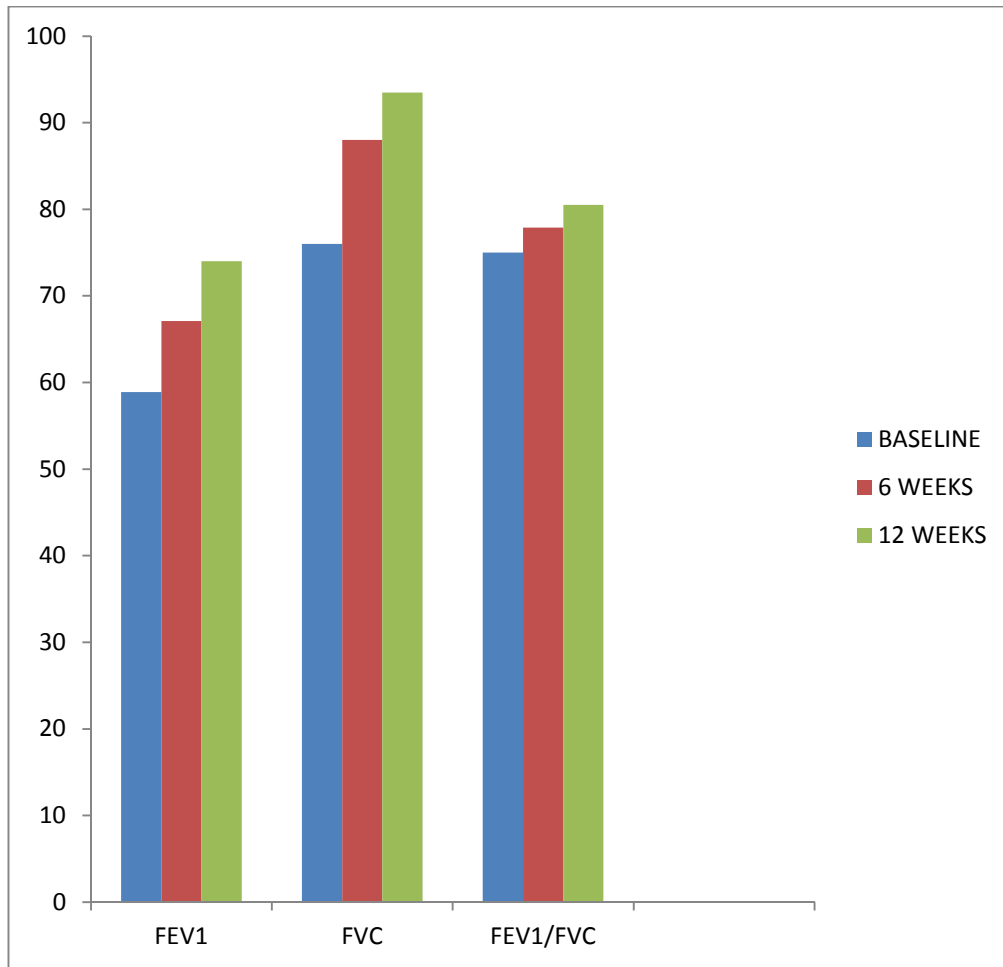
FEV1/FVC	Mean	Std. Deviation	Mean difference	p value
BASELINE	75.0000	13.58921	-	-
6 WEEKS	77.9000	14.13781	-2.900	1.000
12 WEEKS	80.5000	13.07457	-5.500	0.508

**Table 3:** shows the mean and standard variation of FEV1/FVC for doxofylline group and it shows improvement at each visit from baseline but statistically not significant.



**Figure 2**

**COMPARISON OF SPIROMETRIC CHANGES OF MEAN VALUES AT  
BASELINE, 6 WEEKS AND 12 WEEKS IN DOXOFYLLINE GROUP**



**SPIROMETRIC VARIABLE**

**Figure 2:** compares the mean spirometric variables – FEV1, FVC and FEV1/FVC in Doxofylline group. It shows significant improvement from the baseline to 12 weeks in FEV1 and FVC but not in FEV1/FVC

**Table 4**

**COMPARISON OF CAT SCORE FROM BASELINE TO 12 WEEKS IN DOXOFYLLINE GROUP (WITHIN GROUP)**

CATSCORE	Mean	Std. Deviation	Mean Difference (I-J)	P value
BASELINE	15.3000	8.30060	–	–
6 WEEKS	13.0000	7.91623	2.300	0.070
12 WEEKS	11.8000	8.10761	3.500*	0.003

**Table 4:** shows the mean and standard variation of CAT Score for doxofylline group and it shows statistically significant improvement from baseline to 12 weeks.

**Table 5**

**COMPARISON OF FEV1 AND FVC FROM BASELINE TO 12 WEEKS IN THEOPHYLLINE GROUP (WITHIN GROUP)**

Variables	VISITS	Mean	Std. Deviation	Mean Difference (I-J)	P value
FEV1	BASELINE	53.3000	29.39029		
	6 WEEKS	67.4000	36.96605	-14.100*	.031
	12 WEEKS	68.6000	36.65818	-15.300*	.015
FVC	BASELINE	76.5000	23.16727		
	6 WEEKS	84.8000	22.92888	-8.300	.704
	12 WEEKS	86.1000	22.79108	-9.600	.486

**Table 5:** shows the mean and standard variation of FEV1 and FVC for theophylline group. The Table shows statistically significant improvement of FEV1 from baseline to 12 weeks but for FVC, though there is improvement in mean values from baseline to 12 weeks, it was not statistically significant.

**Table 6**

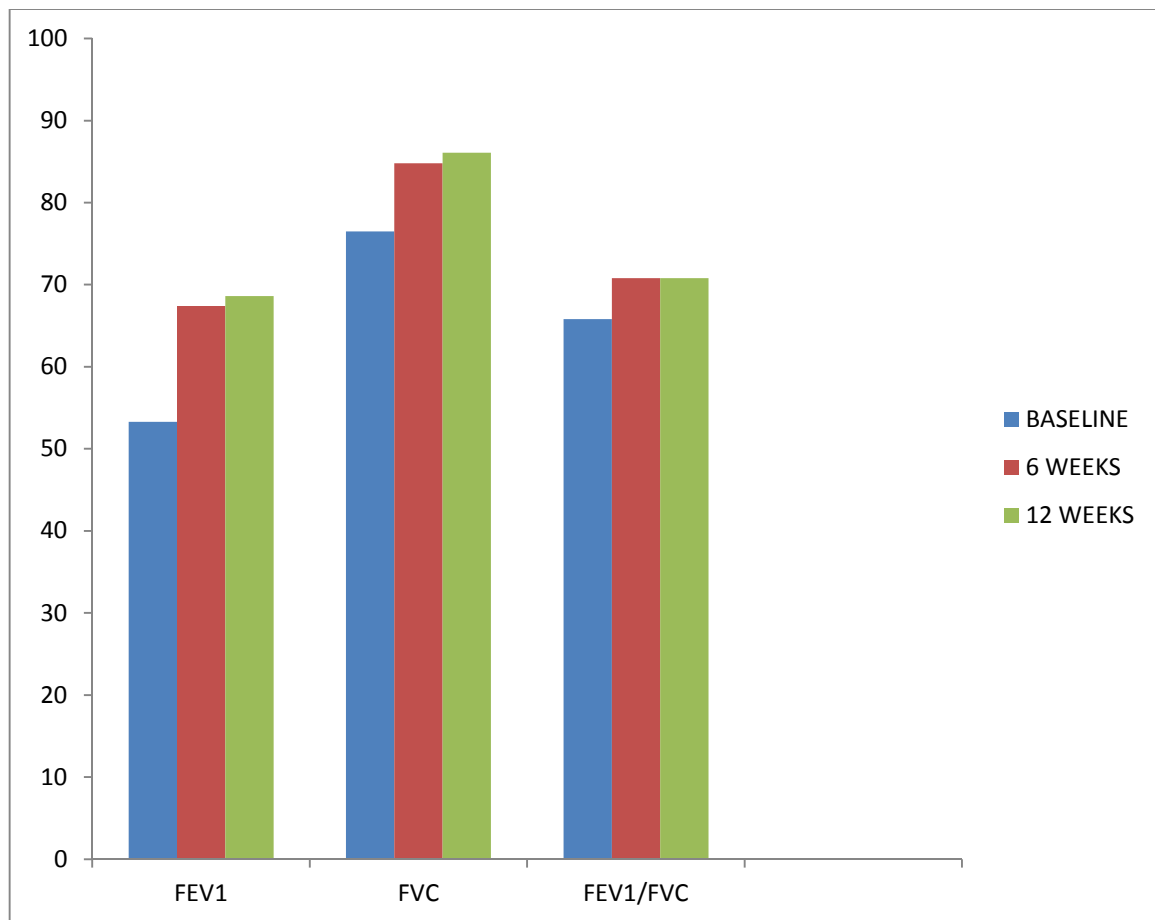
**COMPARISON OF FEV1/FVC FROM BASELINE TO 12 WEEKS IN THEOPHYLLINE GROUP (WITHIN GROUP)**

FEV1/FVC			Mean Difference	
	Mean	Std. Deviation	(I-J)	P value
BASELINE	65.8000	14.68786	–	–
6 WEEKS	70.8000	16.52473	-5.000	1.000
12 WEEKS	70.8000	16.52473	-5.000	1.000

**Table 6:** shows the mean and standard variation of FEV1/FVC for theophylline group and it shows improvement from baseline to 12 weeks but statistically not significant.

**Figure 3**

**COMPARISON OF SPIROMETRIC CHANGES OF MEAN VALUES AT  
BASELINE, 6 WEEKS AND 12 WEEKS IN THEOPHYLLINE GROUP**



**SPIROMETRIC VARIABLES**

**Figure 3:** compares the mean spirometric variables – FEV1, FVC and FEV1/FVC in Theophylline group. It shows significant improvement from the baseline to 1 weeks in FEV but not in FVC,FEV1/FVC.

**Table 7**

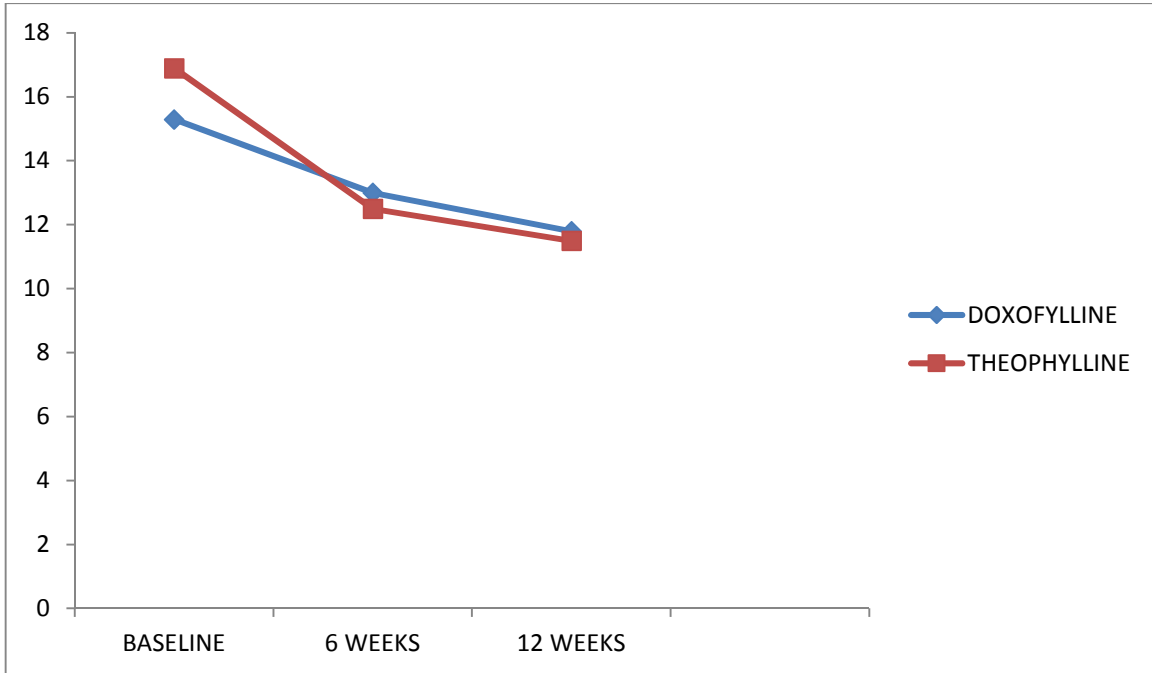
**COMPARISON OF CAT SCORE FROM BASELINE TO 12 WEEKS IN THEOPHYLLINE GROUP (WITHIN GROUP)**

CATSCORE	Mean	Std. Deviation	Mean Difference (I-J)	P value
BASELINE	16.9000	9.27901	—	—
6 WEEKS	12.5000	7.41245	4.400*	0.003
12 WEEKS	11.5000	7.39745	5.400*	0.002

**Table 7:** shows the mean and standard variation of CAT Score for theophylline group and it shows statistically significant improvement at each visit from baseline to 12 weeks.

**Figure 4**

**COMPARISON OF MEAN VALUES OF CAT SCORE AT AT BASELINE,6 WEEKS AND 12 WEEKS IN DOXOFYLLINE AND THEOPHYLLINE GROUP**



**Figure 4:** compares the mean values of CAT Score at baseline,6 weeks and 12 weeks in theophylline group and was found to be significant. Similarly for Doxofylline group, mean values of CAT Score at baseline,6 weeks and 12 weeks was found to be significant.

**Table 8**

**COMPARISON OF CHANGE IN CAT SCORE BETWEEN DOXOFYLLINE  
AND THEOPHYLLINE AT 12 WEEKS**

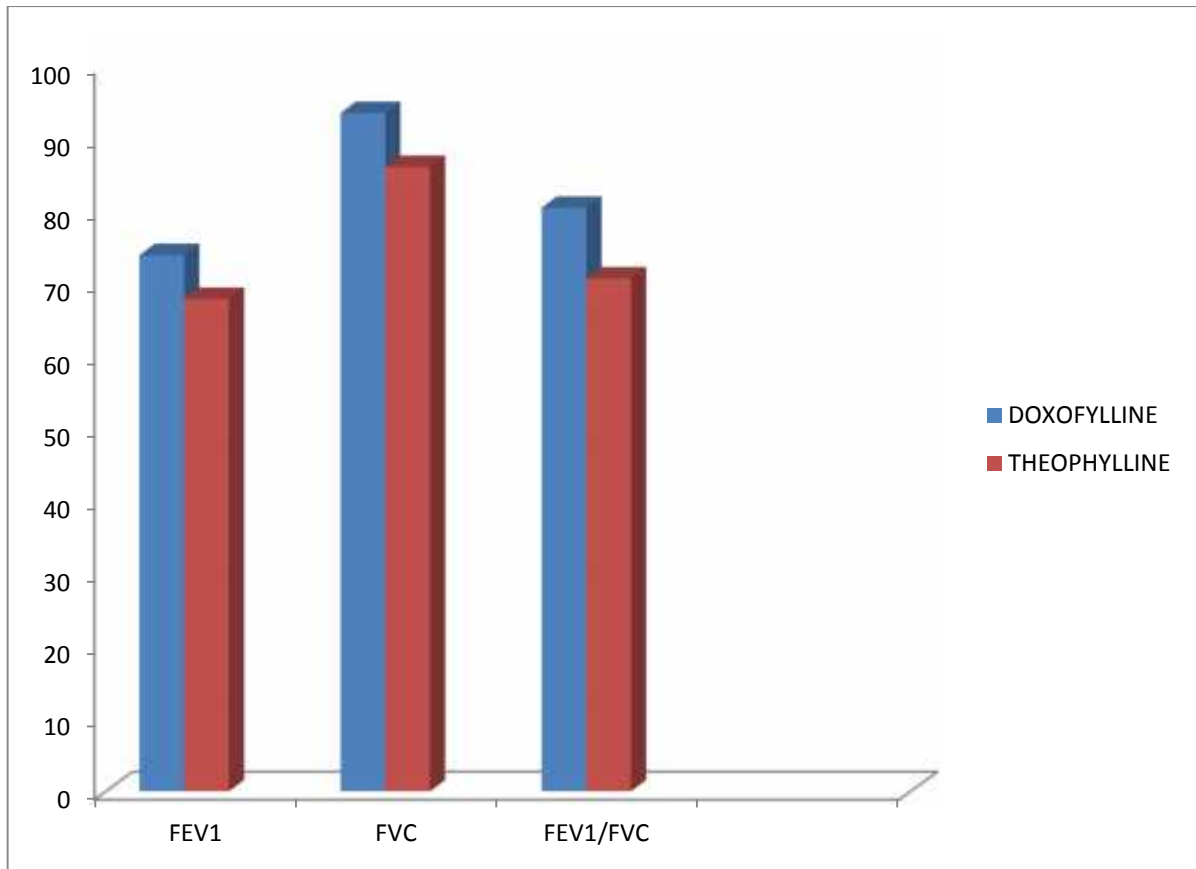
GROUP	N	Mean	Std. Deviation	t	df	P value
CAT DOXOFYLLINE SCORE	30	11.800	8.10761			
THEOPHYLLINE	30	11.500	7.39745	.086	58	0.932

**Table 8:** shows there was a increase in the mean value of CAT Score in doxofylline group in absolute numbers than the theophylline group but it was not statistically significant.



**Figure 5**

**COMPARISON OF SPIROMETRIC CHANGES OF MEAN VALUES AT 12 WEEKS BETWEEN DOXOFYLLINE AND THEOPHYLLINE GROUP**



**Figure 5:** compares the mean spirometric variables – FEV1, FVC and FEV1/FVC between the two groups. Doxofylline group shows better mean values in absolute numbers than theophylline group but not significant.

**Table 9**

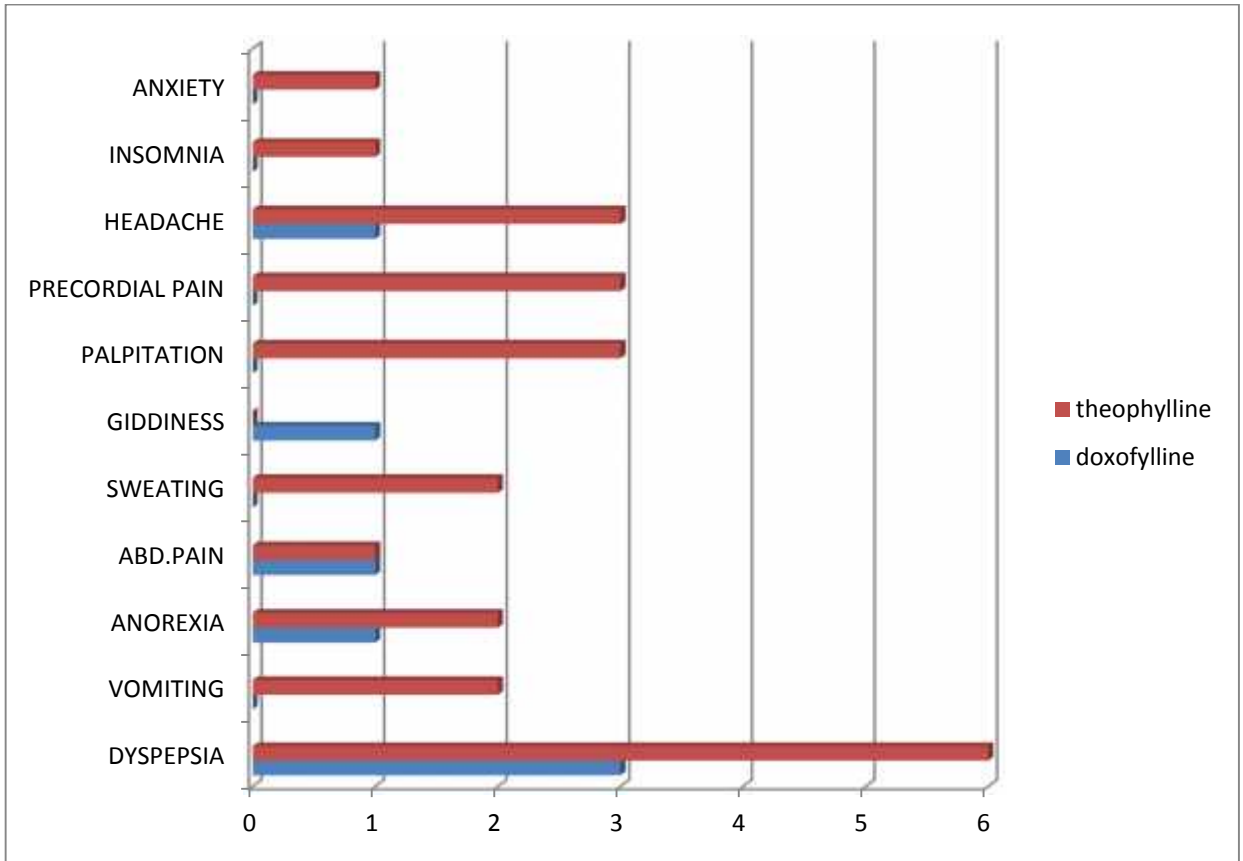
**COMPARISON OF CHANGE IN SPIROMETRIC VARIABLES BETWEEN DOXOFYLLINE AND THEOPHYLLINE AT 12 WEEKS.**

Variables	Doxofylline		Theophylline		t	df	P value
	Mean	Std. Deviation	Mean	Std. Deviation			
FEV1	74.0000	15.54921	68.6000	36.65818	0.429	58	0.673
FVC	93.5000	24.70380	86.1000	22.79108	0.696	58	0.495
FEV1/FVC	80.500	13.074	70.800	16.524	1.456	58	0.163

**Table 9:** shows there was a increase in the mean value of spirometric variables – FEV1,FVC and FEV1/FVC in doxofylline group in absolute numbers than the theophylline group but it was not statistically significant.

**Figure 6**

**COMPARISON OF ADVERSE EFFECTS OBSERVED BETWEEN DOXOFYLLINE AND THEOPHYLLINE GROUP PATIENTS**



NO. OF PATIENTS

**Figure 6:** shows the total number of patients who reported adverse drug events in both doxofylline and theophylline group were depicted here. The number of ADR in theophylline group is higher compared with doxofylline group patients. The most common adverse effect observed in both groups was dyspepsia.

## DISCUSSION

Obstructive diseases of the airways are characterized by an increase in resistance to airflow to partial or complete obstruction at any level, from the trachea and larger bronchi to the terminal and respiratory bronchioles. The major obstructive disorders are COPD (emphysema and chronic bronchitis) and bronchial asthma. COPD is a major health problem worldwide.<sup>196</sup> Its prevalence is being recognized increasingly in countries at all levels of development. In large areas of the world where indoor air pollution is generated by burning biomass for heating and cooking, COPD is prevalent among nonsmokers, especially women.<sup>197</sup> Global prevalence of COPD based on Current epidemiological situation is 11.7% (8.4%–15.0%)<sup>30</sup> Prevalence of COPD has been constantly rising worldwide. Now COPD has become the fourth leading cause of death. In patients with these diseases, PFTs show limitation of maximal airflow rates during expiration, usually measured by FEV<sub>1</sub>. Expiratory airflow obstruction may result either from anatomic airway narrowing, such as that classically observed in asthma, or from loss of elastic recoil of the lung, which characteristically occurs in emphysema.<sup>198</sup> COPD is a complex disease characterized by progressive and partly irreversible airway obstruction and ubiquitous chronic inflammation in the lung. Initial clinical symptoms are shortness of breath and occasional cough. As the disease progresses, difficulty in breathing becomes more pronounced, with limitation on even modest physical exertion, thereby disrupting daily life .

The comparison of the clinical efficacy and safety profile of doxofylline with theophylline in the Indian population was less studied. The present study was designed to compare the clinical efficacy and safety of oral theophylline and doxofylline in patients with Grade 1-2 COPD (Based on GOLD Criteria).

Diagnosis of COPD is made on clinical judgment based on a combination of history, physical examination and confirmation of the presence of airflow obstruction using lung function testing (spirometry). Spirometry provides objective information about pulmonary functions and assesses the result of therapy<sup>199</sup>

Bronchodilators are the main stay in the treatment option for symptom relief in COPD. Methylxanthines are emerging as effective option in the treatment of obstructive airway diseases and drugs such as theophylline and doxofylline have been used orally in these disorders. Their effect is a generalised reduction of airway obstruction that decreases the overall resistance of the airways, improves blood gas exchange and reduces the dyspnea. It has been recognised that these drugs may provide benefits above and beyond the usual bronchodilation. Unfortunately, therapy with theophylline is generally associated with a number of adverse events, affecting the cardiovascular system, the central nervous system and the gastrointestinal system. Doxofylline is a newer xanthine bronchodilator that differs from theophylline. Although doxofylline shares most of the characteristics of the methylxanthine drugs, experimental studies have shown that it is associated with less extra-respiratory effects than theophylline<sup>6,7,8</sup>. It is suggested that decreased

affinities toward adenosine A1 and A2 receptors may account for the better safety profile of doxofylline<sup>9</sup>

In our study, the mean age of patients in doxofylline group was  $63.2 \pm 12.1$  and the mean age of patients in theophylline group was  $61.3 \pm 10.2$ . MD Faiz et al in their comparative clinical study with doxofylline and theophylline also did their study in the age group ranged from 54 to 77 years.<sup>200</sup> The percent of males in doxofylline group was 63% and in theophylline it was 60%. Low socio economic status is a known risk factor for COPD. Prescott et al in their study, Socioeconomic status, lung function and admission to hospital for COPD reported that the risk of developing COPD was inversely proportional to socioeconomic status.<sup>201</sup> Similarly, in our study based on modified kuppusamy scale, the patients were from low socioeconomic class ranging from scale 3 to 4. The mean duration of cough was  $6.7 \pm 5.75$  years in doxofylline group and  $4.60 \pm 4.41$  in theophylline group. we have used medical research council scale for grading dyspnea and the mean grade was  $2.4 \pm 1.07$  for doxofylline group and  $2.7 \pm 0.95$  for theophylline group. Spirometric parameters were assessed at the start of the study. The mean FEV1 value for doxofylline group was  $58.9 \pm 20.09$  and for theophylline group, it was  $53.3 \pm 29.39$ . The mean FVC value for doxofylline group was  $76.3 \pm 22.63$  and for theophylline group it was  $76.5 \pm 23.17$ . the mean FEV1/FVC value for doxofylline group was  $75 \pm 13.59$  and for theophylline group it was  $65.8 \pm 14.69$ . The COPD

Assessment Test score was also assessed at the baseline and the mean score for doxofylline was found to be  $15.3 \pm 8.3$  and for theophylline it was  $16.9 \pm 9.27$ .

There was no significant difference between the two treatment groups in baseline characteristics indicating a homogenous population.

Our study showed that the mean values of FEV1 in doxofylline group increased to 74% at the end of the study (12weeks) as compared to 6weeks value (67.1%) and baseline value (58.9%). The improvement from baseline to 12 weeks was statistically significant ( $p=0.018$ ). The mean value of FVC was increased to 93.5% at 12 weeks compared to 6 weeks value of 88% and baseline value of 76.3%. Likewise the improvement from baseline to 12 weeks was statistically significant ( $p=0.044$ ). In our study though there was a significant improvement of FEV1 and FVC from baseline to 12 weeks, the improvement observed when the comparison was between baseline and 6 weeks it was not significant. It takes 12 weeks to get significant improvement of FEV1 and FVC in the doxofylline group. The mean values of FEV1/FVC in doxofylline group increased to 80.5% at 12 weeks as compared to 6 weeks value (77.9%) and baseline value (75%). Though there was an actual increase in numbers for the mean value, it was not statistically significant.

In our study, the mean values of FEV1 in theophylline group increased to 68.6% at the end of the study (12weeks) as compared to 6weeks value (67.4%) and baseline value (53.3%). The improvement from baseline to 12 weeks was statistically significant ( $p=0.015$ ). The mean value of FVC was increased to 86.1% at 12 weeks

compared to 6 weeks value of 84.8% and baseline value of 76.5%. The mean values of FEV1/FVC in theophylline group increased to 70.8% at 12 weeks as compared to baseline value (65.8%). Though there was an actual increase in numbers for the mean value for both FVC and FEV1/FVC, it was not statistically significant. These results are consistent with the study of Santra CK at Burdwan Medical College and Midnapore Medical College in West Bengal done as an open randomized multicentric trial.<sup>202</sup> In a study conducted by MD Faiz et al in 154 COPD patients comparing doxofylline with theophylline wherein individually both doxofylline and theophylline show statistically significant improvement of spirometric parameters from baseline.<sup>200</sup>

At the end of our study, when the spirometric assessment was compared between the two treatment groups, the mean value of FEV1 in doxofylline group was  $74 \pm 15.54$  compared with mean value of FEV1 of theophylline group  $68.6 \pm 36.65$  and it was statistically not significant. ( $p = 0.673$ ). The mean FVC in doxofylline group was  $93.5 \pm 24.7$  and for theophylline group it was  $86.1 \pm 22.79$ . The p value for FVC between the groups was 0.495 and it was not significant. The mean value of FEV1/FVC in doxofylline group was  $80.5 \pm 13.07$  compared with mean FEV1/FVC of theophylline group  $70.8 \pm 16.52$ . In our study, although Doxofylline group showed better mean spirometric values – FEV1, FVC and FEV1/FVC in absolute numbers than theophylline group but were not statistically significant.



Our results are consistent with those of previous studies that assessed the effects of orally administered doxofylline in the management of patients with COPD. In 2016, Panduranga rao et al in a study of 40 patients with COPD comparing doxofylline with theophylline reported similar results wherein both groups significantly improved spirometric parameters within their group but not significant when compared between the two groups ( $p > 0.05$ ).<sup>203</sup> Marino O et al. compared doxofylline with theophylline in 25 COPD patients and concluded that the spirometric variables had improved in both treatment. Melillo et al examined the clinical effects of doxofylline in 139 patients with COPD treated in a double-blind randomized fashion with either oral doxofylline or theophylline.<sup>204</sup> Both doxofylline and theophylline treatments significantly improved all pulmonary function parameters as compared to baseline ( $p < 0.05$ ), but were not statistically different from each other.

The COPD Assessment test is a standard unidimensional measure of health impairment in COPD. The mean CAT Score for doxofylline group decreased from  $15.3 \pm 8.3$  at the baseline to  $13 \pm 7.91$  in 6 weeks and further decreased to  $11.8 \pm 8.1$  at 12 weeks showing statistically significant improvement ( $p$  value = 0.003). The mean CAT Score for theophylline group decreased from  $16.9 \pm 9.27$  at the baseline to  $12.5 \pm 7.41$  in 6 weeks and further decreased to  $11.5 \pm 7.3$  at 12 weeks showing statistically significant improvement ( $p$  value = 0.002).

At the end of the study, there was an increase in the mean value of CAT Score in the doxofylline group ( $11.8 \pm 8.10$ ) than the theophylline group ( $11.50 \pm 7.39$ ) but it was not statistically significant ( $p$  value = 0.932)

The number of ADR in the theophylline group is higher compared with the doxofylline group patients. Goldstein MF et al in his multicenter clinical trial comparing doxofylline and theophylline reported that even maximum dosage of doxofylline is better tolerated than theophylline.<sup>205</sup> The most common adverse effect observed in both groups was dyspepsia. Among the two groups, theophylline induced dyspepsia was higher than the doxofylline group. In the study done by Panduranga et al in 2016, showed that gastro intestinal symptoms were the most common in both theophylline and doxofylline groups<sup>203</sup>

One of the major limitations of theophylline is its nonselectivity for the phosphodiesterase enzyme. Theophylline has an antagonistic action on the adenosine A<sub>1</sub>, A<sub>2a</sub> and A<sub>2b</sub> receptors, which is responsible for its cardiac and central nervous system stimulatory side effects. Doxofylline has been reported to have less affinity for the adenosine receptor and it has been claimed to have a better safety profile. It has been claimed to have a decreased affinity towards the adenosine A<sub>1</sub> and A<sub>2</sub> receptors. Doxofylline improves spirometric parameters and improves the obstructive symptoms of COPD patients similar to theophylline but not significantly better than theophylline. So doxofylline is as effective as theophylline but with a better safety profile. In 2015, Margay SM et al in his study of

100 patients of obstructive lung disease also reported that theophylline group patients reported higher rates of adverse effects compared to doxofylline.<sup>206</sup> From these results in our study, doxofylline seemed to be a good alternative to theophylline in the treatment of chronic obstructive pulmonary disease.

### **LIMITATIONS OF STUDY**

Sample size was not adequate compared with the rising prevalence of COPD. This being a short term study further long term follow up was not done. Long term follow up studies may bring more enduring results.

## CONCLUSION

Based on the results of this we conclude that,

- Doxofylline is found to be equally efficacious when compared to theophylline in the treatment of Grade 1-2 COPD(GOLD Criteria).
- Doxofylline has a better safety and tolerability profile when compared to theophylline.
- Doxofylline would offer an equivalent and safer alternative to theophylline in the management of COPD.

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## APPENDIX –I

### INFORMED CONSENT FORM

Study Title :

**AN OPEN LABELLED, RANDOMISED, PROSPECTIVE STUDY COMPARING THE EFFICACY AND SAFETY OF DOXOFYLLINE WITH THEOPHYLLINE IN COPD PATIENTS.**

Study Number \_\_\_\_\_

Subject's Full Name \_\_\_\_\_

Date of Birth/Age \_\_\_\_\_

Address \_\_\_\_\_

1. I confirm that I have read and understood the information sheet dated for the above study and have had the opportunity to ask questions. **OR** I have been explained the nature of the study by the Investigator and had the opportunity to ask questions

2. I understand that my participation in the study is voluntary and that I am free to withdraw at any time, without giving any reason and without my medical care or legal rights being affected.

3. I understand that the sponsor of the clinical trial/project, others working on the Sponsor's behalf, the Ethics Committee and the regulatory authorities will not need my permission to look at my health records both in respect of the current study and any further research that may be conducted in relation to it, even if I withdraw from the trial. However, I understand that my Identity will not be revealed in any information released to third parties or published.

4. I agree not to restrict the use of any data or results that arise from this study provided such a use is only for scientific purpose(s)

5. I agree to take part in the above study

Signature (or Thumb impression) of the Subject/Legal Representative: \_\_\_\_\_

Signatory's Name \_\_\_\_\_ Date \_\_\_\_\_

Signature of the Investigator \_\_\_\_\_ Date \_\_\_\_\_

Study Investigator's Name \_\_\_\_\_ Date \_\_\_\_\_

Signature of the Witness \_\_\_\_\_ Date \_\_\_\_\_

Name of the Witness

**நோயாளிகளுக்கு அறிவிப்பு மற்றும் ஒப்புதல் படிவம்**  
**மருத்துவ ஆய்வில் பங்கேற்பதற்கு**

ஆய்வு செய்யப்படும் தலைப்பு:

பங்கு பெறுபவரின் பெயர் :

பங்கு பெறுபவரின் வயது :

		பங்கு பெறுபவர் இதனை குறிக்கவும்
1	நான் மேலே குறிப்பிட்டுள்ள மருத்துவ ஆய்வின் விவரங்களை நான் படித்து புரிந்து கொண்டேன். என்னுடைய சந்தேகங்களை கேட்கவும் அதற்கான தகுந்த விளக்கங்களை பெறவும் வாய்ப்பளிக்கப்பட்டுள்ளது என அறிந்து கொண்டேன்.	<input type="checkbox"/>
2	நான் இவ்வாய்வில் தன்னிச்சையாக தான் பங்கேற்கிறேன். எந்த காரணத்தினாலோ எந்த கட்டத்திலும், எந்த சட்ட சிக்கலும் உட்படாமல் நான் இவ்வாய்வில் இருந்து விலகி கொள்ளலாம் என்றும் அறிந்து கொண்டேன்.	<input type="checkbox"/>
3	இந்த ஆய்வு சம்பந்தமாகவோ. இதைச் சார்ந்து மேலும் ஆய்வு மேற்கொள்ளும் போதும் இந்த ஆய்வில் பங்கு பெறும் மருத்துவர் என்னுடைய மருத்துவ அறிக்கையை பார்ப்பதற்கு என்னுடைய அனுமதி தேவையில்லை என அறிந்து கொள்கிறேன். நான் ஆய்வில் இருந்து விலகிக் கொண்டாலும் இது பொருந்தும் என அறிகிறேன்.	<input type="checkbox"/>
4	இந்த ஆய்வின் மூலம் கிடைக்கும் தகவலையோ. முடிவையோ பயன்படுத்திக் கொள்ள மறுக்க மாட்டேன்.	<input type="checkbox"/>
5	இந்த ஆய்வில் பங்கு கொள்ள ஒப்புக் கொள்கிறேன். எனக்கு கொடுக்கப்பட்ட அறிவுரைகளின்படி நடந்து கொள்வதுடன் ஆய்வை மேற்கொள்ளும் மருத்து அணிக்கு உண்மையுடன் இருப்பேன் என உறுதியளிக்கிறேன். என் உடல் நலம் பாதிக்கப்பட்டாலோ. அல்லது எதிர்பாராத வழக்கத்திற்கு மாறான நோய்குறி தென்பட்டாலோ உடனே இதை மருத்துவ அணியிடம் தெரிவிப்பேன் என உறுதி அளிக்கிறேன்.	<input type="checkbox"/>

பங்கேற்பவரின் கையொப்பம் /..... இடம் ..... தேதி

.....கட்டை விரல் ரேகை

பங்கேற்பவரின் பெயர் மற்றும் விலாசம் .....

ஆய்வாளரின் கையொப்பம் /..... இடம் ..... தேதி

.....

ஆய்வாளரின் பெயர் .....

மையம்.....கல்வியறிவு இல்லாதவற்கு (கைரேகை வைத்தவர்களுக்கு) இது அவசியம் தேவை

சாட்சியின் கையொப்பம் /..... இடம் ..... தேதி .....

பெயர் மற்றும் விலாசம் .....



**நோயாளிகளுக்கு அறிவிப்பு மற்றும் ஒப்புதல் படிவம்  
(மருத்துவ ஆய்வில் பங்கேற்பதற்கு)**

ஆய்வு செய்யப்படும் தலைப்பு:

பங்கு பெறுவரின் பெயர்:

பங்கு பெறுவரின் வயது:

		பங்கு பெறுவர் இதனை ✓ குறிக்கவும்
	நான் மேலே குறிப்பிட்டுள்ள மருத்துவ ஆய்வின் விவரங்களை படித்து புரிந்து கொண்டேன். என்னுடைய சந்தேகங்களை கேட்கவும், அதற்கான தகுந்த விளக்கங்களை பெறவும் வாய்ப்பளிக்கப்பட்டுள்ளது என அறிந்து கொண்டேன்.	<input type="checkbox"/>
	நான் இவ்வாய்வில் தன்னிச்சையாக தான் பங்கேற்கிறேன். எந்த காரணத்தினாலோ எந்த கட்டத்திலும், எந்த சட்ட சிக்கலுக்கும் உட்படாமல் நான் இவ்வாய்வில் இருந்து விலகி கொள்ளலாம் என்றும் அறிந்து கொண்டேன்.	<input type="checkbox"/>
	இந்த ஆய்வு சம்பந்தமாகவோ, இதை சார்ந்து மேலும் ஆய்வு மேற்கொள்ளும் போதும் இந்த ஆய்வில் பங்குபெறும் மருத்துவர் என்னுடைய மருத்துவ அறிக்கைகளை பார்ப்பதற்கு என் அனுமதி தேவையில்லை என அறிந்து கொள்கிறேன். நான் ஆய்வில் இருந்து விலகிக் கொண்டாலும் இது பொருந்தும் என அறிகிறேன்.	<input type="checkbox"/>
	இந்த ஆய்வின் மூலம் கிடைக்கும் தகவலையோ, முடிவையோ பயன்படுத்திக் கொள்ள மறுக்க மாட்டேன்.	<input type="checkbox"/>
	இந்த ஆய்வில் பங்கு கொள்ள ஒப்புக் கொள்கிறேன் எனக்கு கொடுக்கப்பட்ட அறிவுரைகளின் படி நடந்து கொள்வதுடன், ஆய்வை மேற்கொள்ளும் மருத்துவ அணிக்கு உண்மையுடன் இருப்பேன் என்று உறுதியளிக்கிறேன். என் உடல் நலம் பாதிக்கப்பட்டாலோ, அல்லது எதிர்பாராத, வழக்கத்திற்கு மாறான நோய்குறி தென்பட்டாலோ உடனே இதை மருத்துவ அணியிடம் தெரிவிப்பேன் என உறுதி அளிக்கிறேன்.	<input type="checkbox"/>

பங்கேற்பவரின் கையொப்பம் / ..... இடம் .....

கட்டைவிரல் ரேகை

பங்கேற்பவரின் பெயர் மற்றும் விலாசம் .....

ஆய்வாளரின் கையொப்பம் / ..... இடம் .....

ஆய்வாளரின் பெயர் .....

மையம் .....

கல்வியறிவு இல்லாதவற்கு (கைரேகை வைத்தவர்களுக்கு) இது அவசியம் தேவை

சாட்சியின் கையொப்பம் / ..... இடம் .....

பெயர் மற்றும் விலாசம் .....

**CASE RECORD FORM**

NAME :

AGE/SEX :

ADDRESS:

CONTACT NO :

OCCUPATION :

SOCIO ECONOMIC STATUS :

NO. OF FAMILY MEMBERS :

**PRESENTING ILLNESS:**

	<b>VISIT-I</b>	<b>VISIT-II</b>	<b>VISIT-III</b>
1. CHRONIC COUGH – DRY/PRODUCTIVE DURATION :		DRY/PROD.	DRY/PROD.
2. SPUTUM PRODUCTION : YES/NO DURATION :	YES/NO	YES/NO	YES/NO
3. DYSPNEA : PROGRESSIVE - YES/NO WITH EXERCISE : WORSE- YES/NO PERSISTENT- YES/NO	YES/NO YES/NO YES/NO	YES/NO YES/NO YES/NO	YES/NO YES/NO YES/NO
EXERCISE TOLERANCE: ACTIVITY LIMITATION :	YES/NO	YES/NO	YES/NO
H/O SLEEP DISTURBANCE : YES/NO.		YES/NO	YES/NO

**EXPOSURE TO RISK FACTORS:**

TOBACCO SMOKER – YES/NO. DURATION :      PACK YEARS:

PASSIVE SMOKER : YES/NO

IF STOPPED, HOW LONG?

SMOKE FROM HOME COOKING(BIOMASS) AND HEATING FUEL : YES/NO

OCCUPATIONAL DUST/CHEMICAL EXPOSURE: YES/NO

**PAST HISTORY:**

BIRTH WEIGHT:

H/O TUBERCULOSIS: YES/NO

H/O CHILDHOOD RESPIRATORY ILLNESS: YES/NO

H/O ASTHMA – YES/NO

H/O ALLERGY –YES/NO

H/O SINUSITIS/NASAL POLYP

H/O GERD : YES/NO

H/O CARDIOVASCULAR DISEASE/OSTEOPOROSIS/MUSCULOSKELETAL  
DISORDERS/ LUNG MALIGNANCY

H/O DM/HTN

**FAMILY HISTORY:**

FAMILY H/O COPD: YES/NO

FAMILY H/O TB: YES/NO

OTHER RESPIRATORY ILLNESS FOR FAMILY MEMBERS :YES/NO

ANY FAMILY MEMBER WHO SMOKES : YES/NO

**TREATMENT HISTORY:**

	<b>VISIT-I</b>	<b>VISIT-II</b>	<b>VISIT-III</b>
H/O EXACERBATIONS:	YES/NO	YES/NO	YES/NO
FREQUENCY :			
H/O HOSPITALISATION FOR RESP.ILLNESS: YES/NO		YES/NO	YES/NO
USE OF STEROIDS / RESCUE MEDICATIONS: YES/NO		YES/NO	YES/NO

CURRENT MEDICATIONS:

EXAMINATION :

HEIGHT:

WEIGHT:

PULSE:

BP:

ANKLE EDEMA : YES/NO

**INVESTIGATIONS:**

SPIROMETRY:

VISIT-I

VISIT-II

VISIT-III

FEV1:

FVC:

FEV1/FVC:

PEFR:

CHEST X-RAY:

ECG:

BLOOD INVESTIGATIONS:

	VISIT-I	VISIT-II	VISIT-III
Hb			
TC			
DC			
ESR			
UREA			
CREATININE			
SERUM ELECTROLYTES			

SERUM Calcium

LIPID PROFILE

CAT SCORE :

	VISIT-I	VISIT-II	VISIT-III
--	---------	----------	-----------

ADR RECORDING FORM

THEOPHYLLINE GROUP

DOXOPHYLLINE GROUP

V1

V2

V3

V1

V2

V3

Nausea

Vomiting

Dyspepsia

Anorexia

Abdominal pain

Sweating

Irreg.Pulse Rhythm

Palpitation

Precordial Pain

Headache

Insomnia

Anxiety/Irritability

Seizure

others

Your name:

Today's date:

## How is your COPD? Take the COPD Assessment Test™ (CAT)

This questionnaire will help you and your healthcare professional measure the impact COPD (Chronic Obstructive Pulmonary Disease) is having on your wellbeing and daily life. Your answers, and test score, can be used by you and your healthcare professional to help improve the management of your COPD and get the greatest benefit from treatment.

For each item below, place a mark (X) in the box that best describes you currently. Be sure to only select one response for each question.

**Example:** I am very happy    0 1 **X** 2 3 4 5    I am very sad

				SCORE
<b>I never cough</b>	0 1 2 3 4 5	<b>I cough all the time</b>		
<b>I have no phlegm (mucus) in my chest at all</b>	0 1 2 3 4 5	<b>My chest is completely full of phlegm (mucus)</b>		
<b>My chest does not feel tight at all</b>	0 1 2 3 4 5	<b>My chest feels very tight</b>		
<b>When I walk up a hill or one flight of stairs I am not breathless</b>	0 1 2 3 4 5	<b>When I walk up a hill or one flight of stairs I am very breathless</b>		
<b>I am not limited doing any activities at home</b>	0 1 2 3 4 5	<b>I am very limited doing activities at home</b>		
<b>I am confident leaving my home despite my lung condition</b>	0 1 2 3 4 5	<b>I am not at all confident leaving my home because of my lung condition</b>		
<b>I sleep soundly</b>	0 1 2 3 4 5	<b>I don't sleep soundly because of my lung condition</b>		
<b>I have lots of energy</b>	0 1 2 3 4 5	<b>I have no energy at all</b>		
				<b>TOTAL SCORE</b>

## ABBREVIATIONS

COPD	-	Chronic obstructive Lung Disease
PFT	-	Pulmonary Function Test
CAT	-	COPD Assessment Test
GWAS	-	Genome Wide Association Study
A1AT	-	Alpha1Anti trypsin
GOLD	-	Global Initiative For Chronic Obstructive Lung Disease
BALF	-	Broncho Alveolar Lavage Fluid
DPI	-	Dry Powder Inhaler
MMRC	-	Modified Medical Research Council



GROUP 1-DOXO 2-THEO	AGE	SEX	ES	COUGH YRS	SPUTUM	DYSPNEA GRADE			SMOKER Y/N	DURATION YRS	PACKYRS YRS	PASSIVE SMOKER Y/N	BIOMASS SMOKE Y/N	OCCU DUST Y/N	H/O EXACERB Y/N			ANKEDEMA Y/N	FEV1			FVC			FEV1/FVC			CATSCORE			UREA	CREA	NA	K	CA
						V1	V2	V3							V1	V2	V3		V1	V2	V3	V1	V2	V3	V1	V2	V3								
1	60	M	4	1	0	3	3	2	Y	30	18	N	N	Y	Y	Y	N	N	69	70	78	79	74	86	84	94	90	9	7	6	24	0.9	137	3.7	8.6
1	72	M	4	8	0	2	1	1	Y	40	80	N	Y	Y	Y	Y	N	N	39	46	51	76	78	78	50	58	65	15	9	8	22	1.1	139	3.6	8.8
1	69	M	4	5	5	4	3	3	Y	40	24	N	Y	Y	Y	Y	N	N	28	64	78	49	95	98	57	66	79	28	23	22	23	0.8	137	3.9	8.7
1	80	F	4	20	0	3	3	1	Y	5	5	N	Y	Y	Y	Y	N	N	64	70	85	65	72	84	96	97	101	15	10	8	25	1.1	137	3.8	8.6
1	43	M	3	5	0	1	1	1	N	0	0	Y	N	Y	Y	Y	N	N	82	88	92	117	111	111	69	79	82	9	6	7	24	1	139	3.5	8.9
1	60	M	4	4	0	2	2	2	Y	40	8	N	N	N	Y	Y	Y	N	49	56	65	58	60	66	84	93	98	10	13	9	27	1.1	136	3.6	8.8
1	66	F	4	10	0	2	2	2	N	0	0	N	Y	N	Y	Y	Y	N	78	83	85	94	137	137	75	59	62	14	14	13	24	1	135	3.7	8.9
1	43	M	3	10	10	2	1	1	Y	20	20	N	N	Y	Y	N	N	N	52	56	68	66	72	94	78	77	72	14	13	11	23	0.9	137	3.6	8.6
1	70	F	4	4	4	4	4	4	Y	50	50	N	Y	Y	Y	Y	N	N	41	48	48	54	58	58	74	83	83	32	30	30	29	1	138	3.7	8.6
1	69	F	3	1	0	1	1	1	Y	40	60	N	Y	Y	N	N	N	N	87	90	90	105	123	123	83	73	73	7	5	4	32	0.9	139	3.5	8.9
1	60	M	4	1	0	3	3	2	Y	30	18	N	N	Y	Y	Y	N	N	69	70	78	79	74	86	84	94	90	9	7	6	27	1.1	136	3.6	8.8
1	72	M	4	8	0	2	1	1	Y	40	80	N	Y	Y	Y	Y	N	N	39	46	51	76	78	78	50	58	65	15	9	8	23	0.9	137	3.6	8.6
1	69	F	4	5	5	4	3	3	Y	40	24	N	Y	Y	Y	Y	N	N	28	64	78	49	95	98	57	66	79	28	23	22	24	0.9	137	3.7	8.6
1	80	M	4	20	0	3	3	1	Y	5	5	N	Y	Y	Y	Y	N	N	64	70	85	65	72	84	96	97	101	15	10	8	22	1.1	139	3.6	8.8
1	43	M	3	5	0	1	1	1	N	0	0	Y	N	Y	Y	Y	N	N	82	88	92	117	111	111	69	79	82	9	6	7	24	1	139	3.5	8.9
1	60	F	4	4	0	2	2	2	Y	40	8	N	N	N	Y	Y	Y	N	49	56	65	58	60	66	84	93	98	10	13	9	27	1.1	136	3.6	8.8
1	66	F	4	10	0	2	2	2	N	0	0	N	Y	N	Y	Y	Y	N	78	83	85	94	137	137	75	59	62	14	14	13	22	1.1	139	3.6	8.8
1	43	M	3	10	10	2	1	1	Y	20	20	N	N	Y	Y	N	N	N	52	56	68	66	72	94	78	77	72	14	13	11	23	0.8	137	3.9	8.7
1	70	M	4	4	4	4	4	4	Y	50	50	N	Y	Y	Y	Y	N	N	41	48	48	54	58	58	74	83	83	32	30	30	23	0.9	137	3.6	8.6
1	69	F	3	1	0	1	1	1	Y	40	60	N	Y	Y	N	N	N	N	87	90	90	105	123	123	83	73	73	7	5	4	29	1	138	3.7	8.6
1	60	M	4	1	0	3	3	2	Y	30	18	N	N	Y	Y	Y	N	N	69	70	78	79	74	86	84	94	90	9	7	6	32	0.9	139	3.5	8.9
1	72	M	4	8	0	2	1	1	Y	40	80	N	Y	Y	Y	Y	N	N	39	46	51	76	78	78	50	58	65	15	9	8	24	1	139	3.5	8.9
1	69	F	4	5	5	4	3	3	Y	40	24	N	Y	Y	Y	Y	N	N	28	64	78	49	95	98	57	66	79	28	23	22	27	1.1	136	3.6	8.8
1	80	F	4	20	0	3	3	1	Y	5	5	N	Y	Y	Y	Y	N	N	64	70	85	65	72	84	96	97	101	15	10	8	24	0.9	137	3.7	8.6
1	43	M	3	5	0	1	1	1	N	0	0	Y	N	Y	Y	Y	N	N	82	88	92	117	111	111	69	79	82	9	6	7	22	1.1	139	3.6	8.8
1	60	M	4	4	0	2	2	2	Y	40	8	N	N	N	Y	Y	Y	N	49	56	65	58	60	66	84	93	98	10	13	9	22	1.1	139	3.6	8.8
1	66	M	4	10	0	2	2	2	N	0	0	N	Y	N	Y	Y	Y	N	78	83	85	94	137	137	75	59	62	14	14	13	23	0.8	137	3.9	8.7
1	43	F	3	10	10	2	1	1	Y	20	20	N	N	Y	Y	N	N	N	52	56	68	66	72	94	78	77	72	14	13	11	23	0.9	137	3.6	8.6
1	70	M	4	4	4	4	4	4	Y	50	50	N	Y	Y	Y	Y	N	N	41	48	48	54	58	58	74	83	83	32	30	30	29	1	138	3.7	8.6
1	69	M	3	1	0	1	1	1	Y	40	60	N	Y	Y	N	N	N	N	87	90	90	105	123	123	83	73	73	7	5	4	32	0.9	139	3.5	8.9
2	60	M	4	3	3	3	2	2	Y	40	80	N	N	Y	Y	Y	N	N	29	40	42	49	115	115	60	34	34	11	8	7	24	1	139	3.5	8.9
2	66	M	3	2	2	2	1	1	Y	50	60	N	N	N	Y	N	N	N	76	78	82	93	86	95	81	90	90	5	3	2	27	1.1	136	3.6	8.8
2	53	F	4	3	3	2	1	1	Y	28	34	N	Y	N	Y	Y	N	N	33	73	73	81	85	85	40	86	86	13	8	7	24	1	139	3.5	8.9
2	61	F	3	3	0	2	1	1	Y	30	9	N	N	N	Y	Y	Y	N	48	58	60	79	82	84	60	70	70	7	6	5	23	0.9	137	3.6	8.6
2	79	M	4	15	15	3	2	2	Y	50	50	N	N	N	Y	Y	Y	N	128	166	166	129	130	130	96	87	87	19	13	12	24	0.9	137	3.7	8.6
2	70	M	4	0	0.3	3	2	2	Y	45	225	N	Y	N	Y	Y	Y	N	50	59	61	73	74	74	68	79	79	26	15	13	22	1.1	139	3.6	8.8
2	62	F	4	4	4	4	4	3	Y	30	15	N	Y	N	Y	Y	Y	N	50	54	54	79	86	86	63	62	62	31	26	26	29	1	138	3.7	8.6
2	65	M	4	3	3	4	4	3	Y	20	20	N	Y	N	Y	Y	Y	N	33	36	38	48	50	52	68	72	72	23	18	17	32	0.9	139	3.5	8.9
2	56	M	3	10	10	3	3	2	Y	40	80	N	Y	N	Y	Y	Y	N	42	50	50	69	70	70	60	63	63	26	21	19	22	1.1	139	3.6	8.8
2	41	F	3	3	3	1	1	1	Y	5	1	N	Y	Y	N	N	N	N	44	60	60	65	70	70	62	65	65	8	7	7	23	0.8	137	3.9	8.7
2	60	F	4	3	3	3	2	2	Y	40	80	N	N	Y	Y	Y	Y	N	29	40	42	49	115	115	60	34	34	11	8	7	24	0.9	137	3.7	8.6
2	66	M	3	2	2	2	1	1	Y	50	60	N	N	N	Y	N	N	N	76	78	82	93	86	95	81	90	90	5	3	2	22	1.1	139	3.6	8.8
2	53	M	4	3	3	2	1	1	Y	28	34	N	Y	N	Y	Y	N	N	33	73	73	81	85	85	40	86	86	13	8	7	23	0.9	137	3.6	8.6

GROUP 1-DOXO 2-THEO	AGE	SEX	ES	COUGH YRS	SPUTUM	DYSPNEA GRADE			SMOKER Y/N	DURATION YRS	PACKYRS YRS	PASSIVE SMOKER Y/N	BIOMASS SMOKE Y/N	OCCU DUST Y/N	H/O EXACERB Y/N			ANKEDEMA Y/N	FEV1			FVC			FEV1/FVC			CATSCORE			UREA	CREA	NA	K	CA
						V1	V2	V3							V1	V2	V3		V1	V2	V3	V1	V2	V3	V1	V2	V3								
2	61	F	3	3	0	2	1	1	Y	30	9	N	N	N	Y	Y	Y	N	48	58	60	79	82	84	60	70	70	7	6	5	24	1	139	3.5	8.9
2	79	M	4	15	15	3	2	2	Y	50	50	N	N	N	Y	Y	Y	N	128	166	166	129	130	130	96	87	87	19	13	12	27	1.1	136	3.6	8.8
2	70	M	4	0	0.3	3	2	2	Y	45	225	N	Y	N	Y	Y	Y	N	50	59	61	73	74	74	68	79	79	26	15	13	29	1	138	3.7	8.6
2	62	F	4	4	4	4	4	3	Y	30	15	N	Y	N	Y	Y	Y	N	50	54	54	79	86	86	63	62	62	31	26	26	32	0.9	139	3.5	8.9
2	65	M	4	3	3	4	4	3	Y	20	20	N	Y	N	Y	Y	Y	N	33	36	38	48	50	52	68	72	72	23	18	17	23	0.9	137	3.6	8.6
2	56	M	3	10	10	3	3	2	Y	40	80	N	Y	N	Y	Y	Y	N	42	50	50	69	70	70	60	63	63	26	21	19	27	1.1	136	3.6	8.8
2	41	F	3	3	3	1	1	1	Y	5	1	N	Y	Y	N	N	N	N	44	60	60	65	70	70	62	65	65	8	7	7	24	0.9	137	3.7	8.6
2	60	M	4	3	3	3	2	2	Y	40	80	N	N	N	Y	Y	Y	N	29	40	42	49	115	115	60	34	34	11	8	7	22	1.1	139	3.6	8.8
2	66	M	3	2	2	2	1	1	Y	50	60	N	N	N	Y	N	N	N	76	78	82	93	86	95	81	90	90	5	3	2	23	0.9	137	3.6	8.6
2	53	M	4	3	3	2	1	1	Y	28	34	N	Y	N	Y	Y	N	N	33	73	73	81	85	85	40	86	86	13	8	7	22	1.1	139	3.6	8.8
2	61	F	3	3	0	2	1	1	Y	30	9	N	N	N	Y	Y	Y	N	48	58	60	79	82	84	60	70	70	7	6	5	23	0.8	137	3.9	8.7
2	79	F	4	15	15	3	2	2	Y	50	50	N	N	N	Y	Y	Y	N	128	166	166	129	130	130	96	87	87	19	13	12	29	1	138	3.7	8.6
2	70	M	4	0	0.3	3	2	2	Y	45	225	N	Y	N	Y	Y	Y	N	50	59	61	73	74	74	68	79	79	26	15	13	32	0.9	139	3.5	8.9
2	62	F	4	4	4	4	4	3	Y	30	15	N	Y	N	Y	Y	Y	N	50	54	54	79	86	86	63	62	62	31	26	26	24	0.9	137	3.7	8.6
2	65	M	4	3	3	4	4	3	Y	20	20	N	Y	N	Y	Y	Y	N	33	36	38	48	50	52	68	72	72	23	18	17	22	1.1	139	3.6	8.8
2	56	M	3	10	10	3	3	2	Y	40	80	N	Y	N	Y	Y	Y	N	42	50	50	69	70	70	60	63	63	26	21	19	24	1	139	3.5	8.9
2	41	F	3	3	3	1	1	1	Y	5	1	N	Y	Y	N	N	N	N	44	60	60	65	70	70	62	65	65	8	7	7	27	1.1	136	3.6	8.8