

## **CHRONIC OBSTRUCTIVE PULMONARY DISEASE, A SERIOUS THREAT:**

**AWARENESS AND ADHERENCE  
FOR AN APPROPRIATE  
TREATMENT**



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## **EDITORS**

Cinzia Aru

Davide Integlia

Federico Girolamo Lioy

## **AUTHORS**

Cinzia Aru

Davide Integlia

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# INTRODUCTION

Chronic obstructive pulmonary disease (COPD) is a progressive and debilitating respiratory condition that leads to a heavy burden, both medically and financially. It affects millions of people worldwide and causes high levels of morbidity and mortality. From 1990 to 2015, the prevalence of COPD increased by 44.2% (41.7 to 46.6)<sup>1</sup> and COPD under-recognition and under-diagnosis reduces the accuracy of mortality data<sup>2</sup> figures, however, the World Health Organization (WHO) reported that COPD caused 3 million deaths in 2016.

This disease was the third leading cause of death in 2016. The lack of knowledge of the risk factors and symptoms associated with the pathology lead to underestimating this health problem and under-diagnosing it.

In the European Union, the total direct costs of COPD is €38.6 billion with a strong impact on caregivers.

COPD, characterized by irreversible airway obstruction, is usually progressive and associated with a state of chronic inflammation of the lung tissue. The long-term consequence is a remodeling of the bronchi, which causes a substantial reduction in respiratory capacity. The increased susceptibility to respiratory infections (viral, bacterial or fungal) worsens the symptoms. The

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1 GBD 2015 Chronic Respiratory Disease Collaborators, *Global, regional, and national deaths, prevalence, disability -adjusted life years, and years lived with disability for chronic obstructive pulmonary disease and asthma, 1990–2015: a systematic analysis for the Global Burden of Disease Study 2015*, The Lancet, August 2016

2 2018 GOLD Report

symptomatology interferes with normal breathing and is not fully reversible<sup>3</sup>.

Dyspnea, a sense of increased difficulty in breathing, chest heaviness, air hunger or gasping, are the major symptoms and cause of the disability and produce COPD anxiety. Chronic coughing, sputum production, wheezing and chest tightness can be present in COPD patients, while fatigue, weight loss and anorexia are common problems in patients with severe and very severe COPD. Cigarette smoking is the main risk factor for developing COPD, but other risk factors related to occupation and indoor/outdoor pollution exist and need to be recognized. Despite these facts and figures, COPD remains an unknown disease, especially amongst the population, presenting high risk factors. In the survey conducted in July 2017 by GfK Eurisko, entitled *"COPD: awareness, experience and impact on quality of life"*, in five European countries (Italy, Germany, Spain, the United Kingdom, Belgium) on a sample of 4,250 people aged 18 and above, only 35% of respondents had heard of COPD. The Italian newspaper, *Il Sole 24 Ore Sanità* highlights that to the basic question "Have you ever heard about COPD?", the answer was "no" in two out of three cases. Only 45% of Germans, 44% of the British, 41% of Spanish, 20% of Belgians and, at the end, 10% of Italians answered "yes"<sup>4</sup>.

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3 WHO, *COPD: Definition*, in [www.who.int](http://www.who.int)

4 *Il Sole 24Ore Sanità, Bpco, Indagine Eurisko: Due europei su tre non la conoscono*, 12.09.2017

A surprisingly low number, for a disease that affects 348 million people worldwide.

Prevention is fundamental to minimize the risk factors. At present, although there is no effective cure, patients can follow different treatments to control symptoms and avoid dangerous complications.

Informing citizens more about the risk factors, the symptoms and the available treatments, results in preventing the onset of new cases, diagnosing the currently underestimated cases and improving therapeutic adherence.

Promoting good therapeutic adherence is very important to increase treatment effectiveness and improve COPD patient safety and quality of life. Usually, this pathology requires the administration of complex therapies but, at the same time, in most cases the patient's self-management plays a fundamental role.

The above-mentioned Gfk Eurisko survey confirms a high rate of COPD patient non-therapeutic adherence. Out of the 75% of European respondents answering the question "Do you normally follow the prescribed treatment regularly or does it happen occasionally not to take the drugs for COPD?", 25% said they did not take medication occasionally. Out of this 25%:

- 50% answered "I feel better and I think I do not need it"
- 41% answered "I forget to take it"
- 23% answered "They did not tell me that I should always take them/with continuity"
- 13% answered "Taking too many drugs makes me feel sick"

- 11% answered "It's challenging taking several drugs every day"
- 5% answered "It is difficult to use different types of dispensers for different drugs"
- 4% answered "Therapy is not effective"
- 3% answered "It's a complicated treatment, it's easy to make a mistake".

These answers highlight the main causes that give rise to a low adherence to the prescribed therapies. It is a very big problem, because if patients under-dose or forget to take their medications, they are more likely to be inadequately treated.

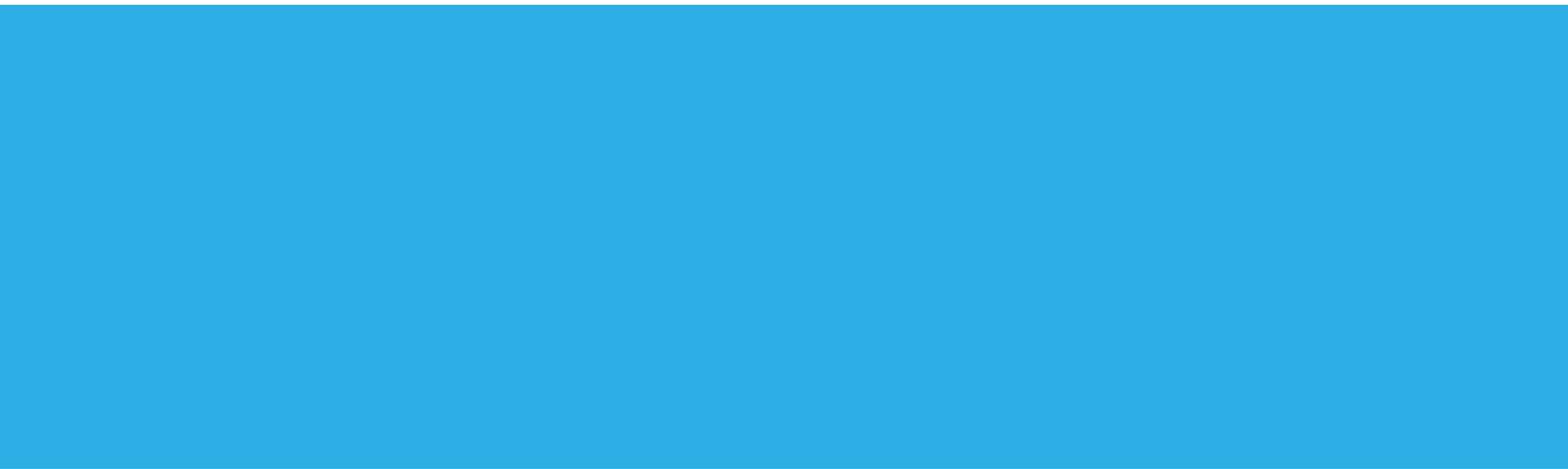
COPD treatment aims to alleviate day and night time symptoms and improve the quality of life of patients, preventing the progression and exacerbations of the disease.

35% of the COPD patients interviewed during the Gfk Eurisko survey said they were taking a drug, 42% said they were taking two different drugs, and 23% said they were taking 3 or more different drugs. Inhalation drugs are the most widely used, followed by oral drugs and sprays and the most commonly used device the dry powder inhaler (DPI).

The incorrect use of inhalers can lead to little or no medicine being inhaled or reaching the lungs, impeding drug deposition or an insufficient dose. Two thirds of COPD patients make errors using the inhaler, obtaining a low symptom control. Determinants of poor inhaler technique include an older age, use of multiple devices and lack of previous education on inhaler technique.

A greater efficacy, a faster action mechanism and the use of a single device are the first three patient needs revealed in the Gfk Eurisko survey.

Taking these data into account allows patients to increase therapeutic adherence and obtain a better quality of life.



PART

**CHRONIC OBSTRUCTIVE  
PULMONARY DISEASE:  
CAUSES AND RISKS RELATED  
TO LOW AWARENESS  
OF THE DISEASE**



# 1. CHRONIC OBSTRUCTIVE PULMONARY DISEASE: CAUSES AND RISKS RELATED TO LOW AWARENESS OF THE DISEASE

## 1.1. WHAT IS COPD?

Chronic Obstructive Pulmonary Disease (COPD) is a common, preventable and treatable disease. It is characterized by persistent respiratory symptoms and airflow limitation that is due to airway and/or alveolar abnormalities, usually caused by high exposure to noxious particles or gases<sup>5</sup> (Global Initiative for Chronic Obstructive Lung Disease (GOLD), *Global Strategy for the Diagnosis, Management, and Prevention of Chronic Obstructive Pulmonary Disease*, 2018 GOLD Report).

The WHO highlights that this is not simply a “smoker’s cough” but an under-diagnosed, life-threatening lung disease. The symptoms interfere with normal breathing and it is not fully reversible<sup>6</sup>. This disease was considered the third leading cause of death in 2016 with 3 million people dying from COPD<sup>7</sup>.

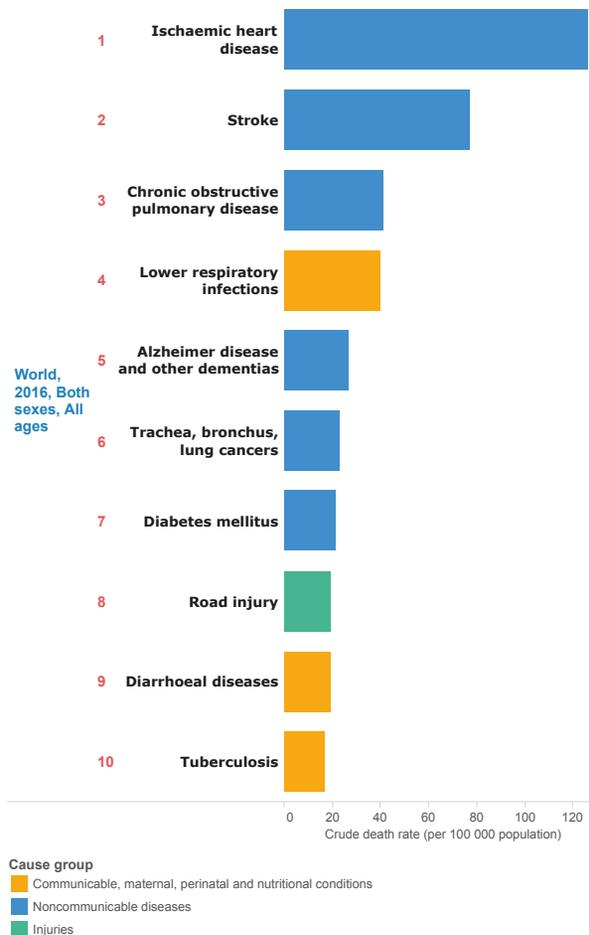
COPD is the result of a complex interplay of long-term cumulative exposure to noxious gases and particles, combined with numerous factors including genetics, airway hyper-responsiveness and poor lung growth during childhood. Often, the prevalence of COPD

is directly related to tobacco smoking and outdoor, occupational and indoor air pollution (due to biomass fuels and burning of wood).

The two main symptoms of COPD are coughing and dyspnea. Often the cough is chronic, more intense in the

**Fig. 1.1** Top ten causes of death in 2016

Source: WHO



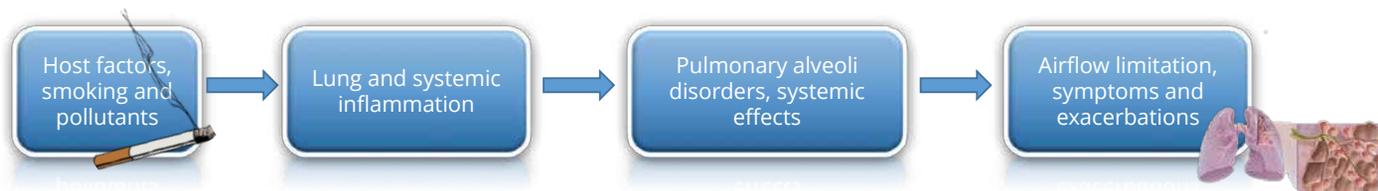
5 Global Initiative for Chronic Obstructive Lung Disease, *Global Strategy for the Diagnosis, Management, and Prevention of Chronic Obstructive Pulmonary Disease*, 2018 report

6 WHO, *COPD: Definition*, in [www.who.int](http://www.who.int)

7 WHO, *The top 10 causes of death*, in [www.who.int](http://www.who.int), 24.05.2018

**Fig. 1.2** Development of COPD: from etiology to clinical manifestations

Source: I-Com processing on GOLD 2018 data



morning and characterized by the production of mucus. Dyspnea appears gradually over a period of several years and in the most serious cases it can limit normal daily activities. Typically, these people are subject to chronic respiratory infections, which may occasionally result in relapses accompanied by aggravated symptoms. As the disease progresses, these episodes tend to become more frequent.

The inhalation of noxious particles or cigarette smoke gives rise to lung inflammation.

Inflammation is a normal response but in COPD patients it is modified and may even cause parenchymal tissue destruction (emphysema), and disruption of normal repair and defense mechanisms (small airway fibrosis). The pathological changes lead to gas trapping and progressive airflow limitation, due to small airway disease and parenchymal destruction, varying from individual to individual. The *Global Strategy for the Diagnosis, Management, and Prevention of Chronic Obstructive Pulmonary Disease* (2018 GOLD Report) reports that “these changes do not always occur together, but evolve

at different rates over time. Chronic inflammation causes structural changes, narrowing of the small airways and destruction of the lung parenchyma that leads to the loss of alveolar attachments to the small airways and decreases lung elastic recoil. In turn, these changes diminish the ability of the airways to remain open during expiration. A loss of small airways may also contribute to airflow limitation and mucociliary dysfunction is a characteristic feature of the disease”.

The repeated injury and repair due to chronic inflammation, observable from the presence of increased numbers of specific inflammatory cell types in different parts of the lung, gives rise to a structural change. This problem increases with disease severity and persists even after giving up smoking.

The factors regarding why this inflammatory response is amplified are not yet known, but they may be genetically determined. Oxidative stress, protease-antiprotease imbalance, inflammatory cells, inflammatory mediators, peribronchiolar and interstitial fibrosis represent crucial factors for the development of the disease.

COPD patients show an increase in biomarkers of oxidative stress (e.g., hydrogen peroxide, 8-isoprostane) in the exhaled breath condensate, sputum, and systemic circulation. The oxidative stress is further increased during exacerbation. Oxidants are generated by inhaled particulates and cigarette smoke, released from inflammatory cells. There may also be a reduction in endogenous antioxidants. The imbalance in the lungs between proteases that break down connective tissue components and antiproteases that counterbalance this action is present in COPD patients. The disease is also characterized by increased numbers of macrophages in peripheral airways, lung parenchyma and pulmonary vessels. There is also an increase in activated neutrophils and lymphocytes that include Tc1, Th1, Th17 and ILC3 cells. Some patients also show an increase in eosinophils, Th2 or ILC2 cells, especially where there is a clinical overlap with asthma. The inflammatory mediators of COPD attract inflammatory cells from circulation, amplify the inflammatory process and induce structural changes. Smokers and COPD patients show to have an excessive production of growth factors with inflammation possibly preceding the development of fibrosis, contributing to the development of small airway limitation and eventually emphysema (2018 GOLD Report).

Hypoxemia and hypercapnia, due to gas exchange abnormalities, are present in COPD patients, and the transfer of oxygen and carbon dioxide worsens as the disease progresses. Reduced ventilation may also be present. The 2018 GOLD Report also highlights

that “reduced ventilation may also be due to reduced ventilatory drive or increased dead space ventilation. This may lead to carbon dioxide retention when it is combined with reduced ventilation, due to increased effort to breathe because of severe limitation and hyperinflation coupled with ventilatory muscle impairment”. Not all COPD patients have symptomatic mucus hypersecretion, while pulmonary hypertension may develop late in the course of COPD. However, even in mild COPD, there are abnormalities in the pulmonary microvascular blood flow.

COPD patients show exacerbation of respiratory symptoms in the case of bacteria or viruses, environmental pollutants or unknown factors, with bacterial or viral infections giving rise to increased inflammation. The exacerbation increases hyperinflation and gas trapping. Pneumonia, thromboembolism and acute cardiac failure may also mimic or aggravate an exacerbation of COPD.

Furthermore, the 2018 GOLD Report highlights that “most patients with COPD have concomitant chronic diseases linked to the same risk factors i.e., smoking, aging, and inactivity, which may have a major impact on health status and survival. Airflow limitation and particularly hyperinflation affect cardiac function and gas exchange. Inflammatory mediators in the circulation may contribute to skeletal muscle wasting and cachexia, and may initiate or worsen comorbidities such as ischemic heart disease, heart failure, osteoporosis, normocytic anemia, diabetes, and metabolic syndrome”. COPD should be considered in all patients with dyspnea,

chronic coughing or sputum and/or a history of exposure to risk factors for the disease. The objectives of the COPD assessment are to determine the severity of the disease, including the severity of the airflow limitation, the influence of the disease on the patient's state of health and the risk of future events (such as exacerbation, hospital admissions and death) and to recommend therapy (Global Initiative for Chronic Obstructive Lung Disease, *Strategia Globale per la Diagnosi, il trattamento e la prevenzione della BPCO, 2018 GOLD Italian version Report*). The 2018 GOLD Report the indicators for considering a diagnosis of COPD:

- Dispnea that is: progressive over time; characteristically worse with exercise; persistent
- Chronic cough: may be intermittent and may be unproductive; recurrent wheeze
- Chronic sputum production: any pattern of chronic sputum production may indicate COPD
- Recurrent lower respiratory tract infections
- History of risk factors: host factors (such as genetic factors, congenital/developmental abnormalities etc.); tobacco smoke (including popular local preparations), smoke from home cooking and heating fuels; occupational dusts, vapors, fumes, gases and other chemicals
- Family history of COPD and/or childhood factors: for example low birthweight, childhood respiratory infections etc.

These indicators are not diagnostic themselves, but the presence of multiple key indicators increases the probability of COPD diagnosis.

Spirometry, which measures how deeply a person can breathe and how fast air can move into and out of the lungs, is required to make the diagnosis, confirming the presence of persistent airflow limitation.

The familiar terms 'chronic bronchitis' and 'emphysema' are now included within the COPD diagnosis<sup>8</sup> but, as reported by Enocson A. et al.<sup>9</sup>, this remains largely under-diagnosed. Case-finding is encouraged by many professionals, but there is a lack of information on the patients' views and perspectives. Patient engagement can be limited by denial or lack of recognition of symptoms, however, the decision to undertake screening can be helped by raising public awareness of the risk factors and early symptoms of COPD.

## 1.2. A LARGELY UNKNOWN PATHOLOGY

Knowing a pathology is the first step in treating it, especially in a historical period characterized by a chronic and polymorbid population.

COPD was classified by the WHO as the third cause of death globally and knowing the causes that promote its development, the symptoms, the treatments available and how to take drugs, can result in preventing the onset of this serious respiratory disease and treating it in the best way possible.

Chronic Obstructive Pulmonary Disease (COPD) is a

<sup>8</sup> WHO, COPD: Definition, in [www.who.int](http://www.who.int)

<sup>9</sup> Enocson A. et al., *Case-finding for COPD in primary care: a qualitative study of patients' perspectives*, Int J Chron Obstruct Pulmon Dis, May 2018

condition that heavily affects all aspects of daily living, often worsening an individual's quality of life. Despite being the third leading cause of death in the world, it is little known by Europeans, as revealed by research conducted by GfK Eurisko - only 35% of respondents, in fact, have heard of COPD.

To the basic question "Have you ever heard about COPD?" two times out of three, the answer was "no". Only 45% of Germans, 44% of the British, 41% of Spanish, 20% of Belgians and, lastly, 10% of Italians answered "yes". A surprisingly low number, for a disease that affects 348 million people worldwide. This data was reported by *Il Sole 24 Ore Sanità*<sup>10</sup> on the results obtained by the Eurisko survey entitled "*COPD: awareness, experience and impact on quality of life*". In this survey conducted in July 2017 by GfK Eurisko in five European countries (Italy, Germany, Spain, the United Kingdom, Belgium) on a sample of 4,250 people aged 18 and above, on average, 35% had "heard about COPD" and only 10% had associated it with Chronic Obstructive Pulmonary Disease.

The Eurisko survey, whose goal was to show the extent to which COPD is known, was carried out through 4,000 interviews with ordinary citizens (800 per country) and 250 interviews (50 per country) among patients suffering from the disease and using the prescribed drug.

Although the percentage of people who are aware of COPD is very low, these people correctly consider it a serious or very serious illness in 95% of the interviews (93% in Italy, 98% in Spain, 96% in Germany, 95% in UK,

98% in Belgium) and rank it as fifth of the most severe pathologies, after cancer, heart attacks, strokes and Alzheimer's disease.

The data also shows that among those in the general population who know about the disease, 80% consider smoking the first cause, followed by pollution (54%), family history (37%), alcohol consumption (12%), suffering from other diseases (1%), the workplace (1%), while 4% said they did not know the cause.

One of the most important problems that emerged from the survey concerns the sources by which the population is informed about this pathology. The results show that the media (TV, radio, Internet) are the main sources of information. 36% of respondents who said they had heard about COPD, gave the following answer "I heard about it on the TV/radio". 24% said "via the Internet", 23% "information from newspapers/magazines", 19% from "Friends/family", 10% "my family doctor spoke to me about it", 7% "my specialist spoke to me about it", 5% "He is a doctor/nurse", 2% "studied at work", 2% "do not know".

Even more surprising than the low disease awareness amongst the general population are the conclusions of David K.J. et al. 2015<sup>11</sup>, who analysed the knowledge and application of GOLD by doctors through a questionnaire in 12 countries: "this survey of physicians in 12 countries practicing in the primary care and respiratory specialty settings showed high awareness of COPD-management

10 *Il Sole 24Ore Sanità, Bpco, Indagine Eurisko: Due europei su tre non la conoscono*, 12.09.2017

11 Davis K.J., *Continuing to Confront COPD International Physician Survey: physician knowledge and application of COPD management guidelines in 12 countries*, Int J Chron Obstruct Pulmon Dis., 2015

guidelines. Frequent use of guideline-recommended COPD diagnostic practices was reported; however, gaps in the application of COPD-treatment recommendations were observed, warranting further evaluation to understand potential barriers to adopt guideline

recommendations.”

Promoting the knowledge of COPD, its symptoms and available treatments, not only among patients but also among doctors, is important to make correct diagnoses and to effectively treat patients.

PART

**LOW CITIZEN AWARENESS  
HAS A NEGATIVE IMPACT  
ON DISEASE PREVENTION  
AND MANAGEMENT**



## 2. LOW CITIZEN AWARENESS HAS A NEGATIVE IMPACT ON DISEASE PREVENTION AND MANAGEMENT

Improving COPD patient awareness of the severity of the disease and its consequences allows patients to enhance their decision-making role and self-care in collaboration with doctors and various health professionals. A better knowledge of COPD increases the number of diagnoses and facilitates the sending of patients to pulmonologists, obtaining suitable treatment for the pathology<sup>12</sup>.

The Italian portal of the Epidemiology for Public Health (EPICENTRO), set up by the National Center for Disease Prevention and Health Promotion of the *Istituto Superiore di Sanità (ISS)*, shows the consequences of a low patient awareness of COPD, especially in the early stages<sup>13</sup>.

An individual exposed to certain substances or dust in the workplace, smokers, not being aware of the causes that lead to the development of the disease, can develop COPD as they are unable to link these factors to its development. Underestimating the risk factors can, in turn, lead to the development of a mild form of the disease, where the patient, who may have, in general, a cough and chronic expectoration, is not aware that they

have an impaired lung functioning.

In the presence of exacerbation or dyspnea during exertion, coughing and expectoration, the patient requires medical intervention because of chronic respiratory symptoms, or a flare-up of the disease. The further worsening of symptoms leads to chronic respiratory failure, with repeated relapses and a very compromised quality of life.

As reported, greater patient awareness promotes a decrease in the risk of developing COPD, promoting a better prevention and better management of the disease.

Another important point regarding patient awareness involves how one becomes ill and the knowledge regarding the treatments available for this disease.

As highlighted by the Italian Ministry of Health, the objective of COPD treatment is to alleviate symptoms and to improve tolerance to effort, to improve patient quality of life. Another goal of therapy is to prevent the progression of the disease and its future flare-ups<sup>14</sup>.

According to the results of the above-mentioned GfK Eurisko survey, to the question “consider your personal situation. How likely do you believe you may have a chronic obstructive pulmonary disease/COPD problem in the future?”, only 16% of Europeans responded “very likely” (3%) or “fairly likely” (13%), 56% answered “not very likely”, 28% “not at all likely”. Regarding the possibility of treating the disease, the general population was also asked to complete the following sentence - “COPD is

12 EFA, EFA books on Minimum Standards of Care for COPD Patients in Europe

13 As highlighted in the document available online entitled “Percorso broncopneumopatia cronica ostruttiva (BPCO) e insufficienza respiratoria in BPCO (Path to chronic obstructive pulmonary disease (COPD) and respiratory failure in COPD)”, of the Azienda USL 3 Pistoia Epicentro, Raccolta normativa e documenti sulla gestione integrata in Italia, in [www.epicentro.iss.it](http://www.epicentro.iss.it)

14 Italian Ministry of Health, *Broncopneumopatia cronica ostruttiva*, in [www.salute.gov.it](http://www.salute.gov.it)

a disease that...". In this regard, 6% answered "can be treated with a drug treatment", 19% "can improve with a drug treatment", 33% "can be kept under control/ stopped with a drug treatment but cannot improve", 6% "cannot be treated or stopped", while 36% answered "I don't know".

Being aware of COPD results in preventing new cases, avoiding known risk factors, consulting a specialist as soon as possible, taking the prescribed therapies

correctly and, consequently, slowing down the disease's development and achieving a better quality of life.

Therefore, low awareness of the pathology results in:

- underestimating the symptoms associated with COPD
- under-diagnosing the disease
- promoting the progression of the disease
- incorrectly evaluating the treatment intake
- risk of deterioration in the quality of life of patients and caregivers.

PART

3

LIVING WITH COPD



## 3. LIVING WITH COPD

### 3.1. THE SYMPTOMATOLOGY OF COPD

Despite the important symptomatology, which tends to increasingly lower the quality of life of patients over the years, COPD remains a universally under-diagnosed pathology. Pere Almagro and Joan B. Soriano report that “findings from several epidemiological investigations have shown that 75% or more of patients with COPD remain undiagnosed, without substantial changes in recent years. This fact is mainly related to a scarcity of clinical suspicion and underuse of spirometry, but probably also to an inherited nihilism on the effectiveness of treatments in the early stages of COPD”<sup>15</sup>.

Lack of diagnosis and poor therapeutic adherence lead to a worsening of the symptoms.

The most characteristic symptom of COPD is a chronic and progressive dyspnea and in 30% of patients there is coughing with sputum production. These symptoms, that may vary from day-to-day, may precede the development of airflow limitation for many years. An important airflow limitation may also be present without chronic dyspnea and/or coughing and sputum production and vice versa (2018 GOLD Report). The assessment of the pathology is carried out by determining the level of airflow limitation, its impact on the patient’s health status and the risk of future events (such as exacerbation, hospital admissions or death).

<sup>15</sup> Almagro P. et al., *Underdiagnosis in COPD: a battle worth fighting*, The Lancet, April 2017

The 2018 GOLD Report shows that the assessment must consider the following aspects of the disease separately:

- the presence and severity of the spirometric abnormality
- current nature and magnitude of the patient’s symptoms
- history of moderate and severe exacerbations and future risk
- presence of comorbidities.

Chronic Obstructive Pulmonary Disease (COPD) is, therefore, a respiratory disease characterized by irreversible airway obstruction, being variable in severity. The disease is usually progressive and is associated with a state of chronic inflammation of the lung tissue, that in most patients involves the peripheral areas of the lung<sup>16</sup>. The long-term consequence is a remodeling of the bronchi, which causes a substantial reduction in respiratory capacity. Exacerbating this clinical picture is the increase in susceptibility to respiratory infections of viral, bacterial or fungal origin. There is currently no effective cure, but several treatments are available to control the symptoms and to avoid dangerous complications. On the other hand, prevention is fundamental, to minimize risk factors (cigarette smoking in first place). Knowing the risk factors, the symptoms of COPD and the treatments available is important to prevent the onset of the disease and slow down its course, as described above, improving patient quality of life.

<sup>16</sup> Crisafulli E et al., *Respiration* 2017; 93(1):32-41

### 3.2. DISEASE BURDEN AND THE IMPACT ON QUALITY OF LIFE

COPD is a pathology capable of drastically lowering a patient's quality of life. Despite this, the pathology is not well known, a factor that can lead to under-reporting the actual cases and thus dissuading patients from going to the doctor in the disease's early stages. The 2018 GOLD Report shows that: "COPD is a leading cause of morbidity and mortality worldwide that induces an economic and social burden that is both substantial and increasing. COPD prevalence, morbidity and mortality vary across countries and across different groups within countries". It is also known that almost 90% of COPD deaths occur in low- and middle-income countries<sup>17</sup>.

From 1990 to 2015, the prevalence of COPD increased by 44.2% (41.7 to 46.6)<sup>18</sup>, under-recognition and under-diagnosis of COPD reduces the accuracy of mortality data<sup>19</sup> but the WHO shows that COPD caused three million deaths in 2016<sup>20</sup>.

Morbidity measures include physician visits, emergency department visits, hospitalizations, and to date studies on the available data indicate that morbidity due to COPD increases with age. Other concomitant chronic conditions may be present (e.g.,

cardiovascular disease, musculoskeletal impairment, diabetes mellitus). These chronic conditions may impair a patient's health status, interfere with COPD management and cause hospitalization and increase costs (2018 GOLD Report).

The economic burden is also heavy. The 2018 GOLD Report shows that "COPD is associated with significant economic burden. In the European Union, the total direct costs of respiratory disease are estimated to be about 6% of the total healthcare budget, with COPD accounting for 56% (38.6 billion Euros) of the cost of respiratory disease" and "any estimate of direct medical expenditure for home-based care under-represents the true cost of home-based care to society, because it ignores the economic value of the care provided by family members to people with COPD."

COPD lowers patient quality of life, a fact perceived in the Eurisko survey. According to the same survey, which also involved people with COPD, it emerged that 75% have an awareness of a worsening of the quality of life correlated also to exacerbations.

The most common symptoms of the disease are:

- weariness/tiredness (48%)
- breathlessness/shortness of breath (46%)
- dry cough (40%)
- tightness of the chest, difficulty breathing (31%)
- frequent waking-up at night (28%)
- trouble falling asleep (27%)
- shortness of breath (27%)
- persistent cough with catarrh (27%)
- acute coughing fits with catarrh (25%)

17 WHO, *Burden of COPD*, in [www.who.int](http://www.who.int)

18 GBD 2015 Chronic Respiratory Disease Collaborators, *Global, regional, and national deaths, prevalence, disability -adjusted life years, and years lived with disability for chronic obstructive pulmonary disease and asthma, 1990–2015: a systematic analysis for the Global Burden of Disease Study 2015*, The Lancet, August 2016

19 2018 GOLD Report

20 WHO, The top 10 causes of death, 24 May 2018

- waking up very early in the morning (25%)
- severe coughing fits when waking up (23%)
- continuous presence of catarrh (22%)
- chest pain (21%)
- hoarseness/loss of voice (18%)

Apart from the list of individual symptoms, the data also reveals the serious impact of the disease on quality of life. According to the Eurisko survey, COPD influences:

- life in general in 75% of cases
- work and daily activities in 66%
- social life, relationships and family life in 56%
- life as a couple in 51% of cases.

More in detail, patients with COPD stated that:

- in 79% of cases they have difficulty doing any type of sporting activity
- in 62% of cases they can not dedicate themselves as they would like to their hobby
- in the same percentage (62%) they can not take care of children or play with them
- in 56% of cases they limit their travel
- in 53% of cases they limit being intimate with their partner
- in 47% of cases they limit meeting friends in 42% of cases they cannot go out, go to a restaurant, to the cinema, to the theater, to a pub.

Finally, it is important to consider the problems of those who take care of patients with COPD. An example of how much the disease weighs on caregivers is offered by Marc Miravittles et al.<sup>21</sup>, showing that the higher level

<sup>21</sup> Miravittles M. et al., *Caregivers' burden in patients with COPD*, International Journal of COPD, February 2015

of dependence is associated with more severe problems in caregivers. They analysed data from the Survey on Disabilities, Personal Autonomy, and Dependency Situations (Encuesta sobre Discapacidad, Autonomía personal y Situaciones de Dependencia [EDAD]- 2008) to obtain information on COPD patients and their caregivers in Spain and evaluated the impact on caregivers. A total of 461,884 individuals with one or more disabilities and with COPD were identified, and 220,892 informal caregivers were estimated. Results showed that:

- 35% of informal caregivers had health-related problems due to the caregiving provided
- 83% had leisure/social-related problems
- 38% out of caregivers of working age recognized having profession-related problems.

The caregivers' problems increase with increasing patient dependency. The study highlights that "caregivers of patients with great dependence showed a 39% higher probability of presenting health-related problems, 27% more professional problems, and 23% more leisure problems compared with those with nondependent patients".

Therefore, the burden of this pathology for the patient and for those taking care of them is very heavy. The quality of life for COPD patients and for caregivers decreases as the patient's disability progresses. Increasing the awareness of the pathology in the general population allows for a better intervention especially during the early stages of the disease, slowing down the course and improving the lives of both patients and caregivers.



PART

4

**THERAPEUTIC ADHERENCE,  
A KEY FACTOR TO IMPROVE  
TREATMENT EFFICACY**



## 4. THERAPEUTIC ADHERENCE, A KEY FACTOR TO IMPROVE TREATMENT EFFICACY

### 4.1. THE CONCEPT OF THERAPEUTIC ADHERENCE

In its 2003 report on medication adherence, the WHO quoted the Haynes et al. definition of adherence to long-term therapy: “the extent to which a person’s behaviour – taking medication, following a diet, and/or executing lifestyle changes, corresponds with agreed recommendations from a health care provider.”

The WHO highlights that adherence requires the patient’s agreement to the recommendations and that patients should be active partners with health professionals in their own care. Good communication between patient and health professional is also a must for an effective clinical practice<sup>22</sup>. Promoting good therapeutic adherence practices are very important to increase the effectiveness of adherence and the safety of patients.

Most of the care needed for chronic conditions is based on patient self-management. Usually these diseases require complex multi-therapies and, often, it is necessary to use medical technology for monitoring patients. Changing the patient’s lifestyle is not easy, but patients face various potentially life-threatening risks if health recommendations are not followed as prescribed.

22 WHO, *Adherence to long-term therapies, evidence for action*, 2003

The risks due to a low compliance are:

- more intense relapses
- increased risk of dependence
- increased risk of abstinence and rebound effect
- increased risk of developing resistance to therapies
- increased risk of toxicity
- increased likelihood of accidents.

A part from the above mentioned risks, there is also the most obvious one related to the undertreatment of a degenerative disease like COPD. If patients underdose or forget their medication, they are more likely to be inadequately treated. It is therefore clear that a low adherence to the prescribed treatments leads to low efficacy and a low quality of life of patients suffering from chronic diseases. The characteristics of COPD make it difficult for patients not only to recognize the presence of the disease but also to treat it appropriately once diagnosed.

### 4.2. THE LOW THERAPEUTIC ADHERENCE OF COPD PATIENTS

Despite the severity of COPD, the level of compliance is very low<sup>23</sup>. Sanduzzi A. et al. report that “poor compliance with the medical therapy is characterized by a predisposition to unhealthy behaviors and lifestyles and is associated with several factors, which can be correlated with the prescribed medications

23 Sanduzzi et al., *COPD: adherence to therapy*, Multidisciplinary Respiratory Medicine, 2014

(number of medications to be taken, difficulties in handling the device, complex regimes, side effects, cost of medications...) or with other causes (old age, physical and cognitive impairment, instructions for use not properly explained or understood, poor trust in the therapies and/or in the physician, weak will, fears or unexpressed problems, underestimation of the severity of the disease, lack of symptoms)". They also highlight that underuse and improper use is most frequent in patients older than 65 years of age with polypharmacy. Older patients can have in fact multiple comorbidities, such as diabetes, chronic ischemic heart disease, depression, systemic hypertension, thus taking other medications. As well as forgetfulness and the cost of doses, the number of medicines prescribed and the associated adverse effects are causes of low adherence. In older people there is also the possibility of depression, which affects 10% to 42% of stable COPD patients, being mainly related to therapy discontinuation and to a decrease in the number of medication days (Sanduzzi et al., 2014).

The Sanduzzi study shows that many patients cannot use inhalers correctly. A lack of perceived benefit led to 30% of patients with COPD intentionally discontinuing their therapy. Training patients and caregivers in the correct inhaler preparation and use is an essential component in achieving reliable and repeatable medication delivery.

The optimal choice of the most suitable inhaler is a complex decision taken by doctor and patient. The most commonly used device is the dry powder inhaler

(DPI). However, many patients rely on using pMDIs to manage their condition, being familiar with this kind of device as a reliever, finding its use linear and intuitive. Or they benefit from the use of pMDIs because this allows them to use spacers and thus have more time and freedom during the inhalation maneuver.

It should also be kept in mind that in the most severe stages of the disease, a DPI inhaler may fail to activate due to an inappropriate peak inspiratory flow, which would prevent an effective dose of drug from reaching the lungs.

The Gfk Eurisko survey confirms that the pathology is characterized by a high rate of non-therapeutic adherence.

Only 35% of the interviewed patients take one drug, 42% take two different drugs and 23% take three or more different drugs. This means that many patients must manage multiple inhalers, a problem that is reflected in treatment adherence.

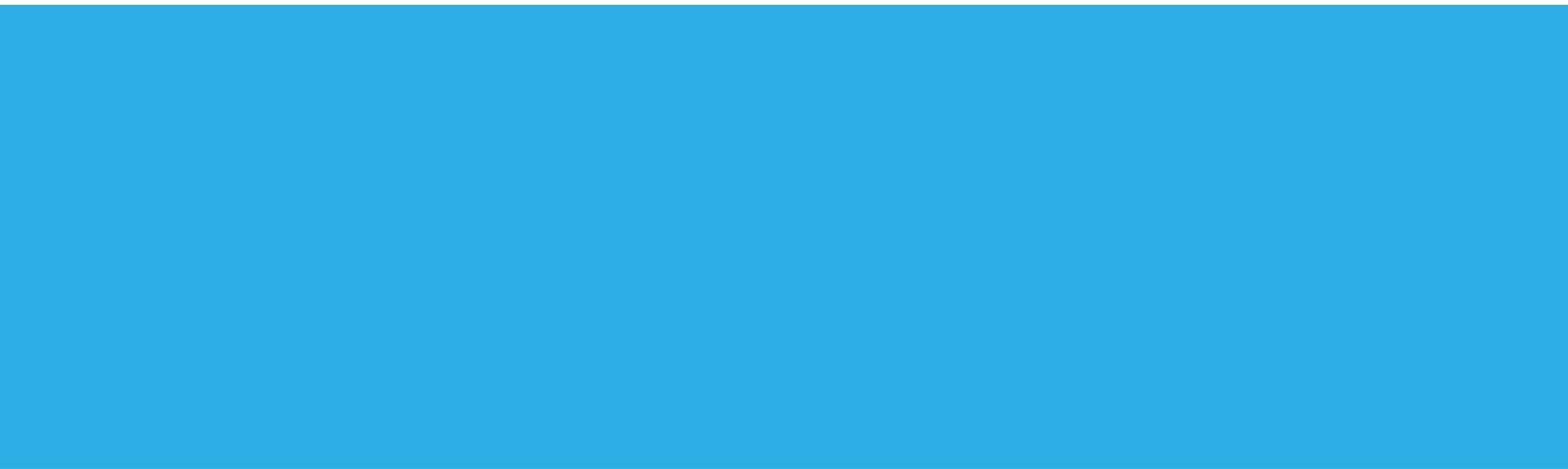
Of the 75% of European respondents to the question "Do you normally follow the prescribed treatment regularly or does it happen occasionally not to take the drugs for COPD?", 25% said they did not take medication occasionally. Of this 25%:

- 50% answered "I feel better and I think I do not need it"
- 41% answered "I forget to take it"
- 23% answered "They did not tell me that I should always take them/with continuity"
- 13% answered "Taking too many drugs makes me feel sick"

- 11% answered “It’s challenging taking several drugs every day
- 5% answered “It is difficult to use different types of dispensers for different drugs”
- 4% answered “Therapy is not effective”
- 3% answered “It’s a complicated treatment, it’s easy to make a mistake”.

We can therefore assume that the factors that lead to a low therapeutic adherence in this pathology are

numerous. Some concern the patient’s situation (such as the presence of depression or other diseases, age, etc.) others concern the prescribed drugs themselves (such as the number of drugs taken daily, the speed of action and the device used for administration, etc.). Taking these aspects into consideration, it is important to promote a better therapeutic adherence and, consequently, a greater efficacy of the administered therapies in COPD patients.



PART

5

COPD TREATMENT



## 5. COPD TREATMENT

### 5.1. COPD AVAILABLE THERAPIES AND DEVICES

The goal of COPD treatment is to alleviate both day and night symptoms and to improve tolerance to effort in order to improve quality of life, to prevent the progression of the disease and its flare-ups.

The cessation of smoking is a fundamental point, drug therapy and nicotine replacement therapy increase long-term abstinence rates.

Drugs can reduce COPD symptoms, frequency and severity of exacerbations, and improve health status and exercise tolerance.

Each treatment regimen must be personalized and guided by the severity of the symptoms, risk of exacerbation, side effects, comorbidities, drug availability and cost, patient response and their preference and ability to use the different devices for drug delivery.

The inhalation technique should be checked periodically and it has been found that influenza and anti-pneumococcal vaccinations reduce the incidence of lower respiratory tract infection.

In general, the following points illustrated by the 2018 GOLD Report must also be taken into account:

- “Pulmonary rehabilitation improves symptoms, quality of life and physical and emotional participation in everyday activities”;
- “In patients with severe resting chronic hypoxemia, long-term oxygen therapy improves survival”;

- “In patients with stable COPD and resting or exercise-induced moderate desaturation, long-term oxygen treatment should not be prescribed routinely. However, individual patient factors must be considered when evaluating the patient’s need for supplemental oxygen”;
- “In patients with severe chronic hypercapnia and a history of hospitalization for acute respiratory failure, long-term non-invasive ventilation may decrease mortality and prevent re-hospitalization”;
- “In select patients with advanced emphysema refractory to optimized medical care, surgical or bronchoscopic interventional treatments may be beneficial”;
- “Palliative approaches are effective in controlling symptoms in advanced COPD”.

Moreover, giving up smoking has been found to have the greatest effect on the natural history of COPD. If time and resources are dedicated to giving up smoking, it is possible obtain long-term abstinence rates of 25%.

At the moment, there is no conclusive evidence from clinical studies that any of the drugs available for COPD are able to change a long-term decline in lung function. The choice of each class of drug depends on the availability of the drug, on cost and favorable clinical response, balanced by the side effects. Each therapeutic regimen must be personalized, since the relationship between the severity of symptoms, the severity of the limitation to airflow and the severity of exacerbations can vary from one patient to another.

The main drugs used in the treatment of stable COPD

include bronchodilators, anticholinergics, xanthine derivatives, combination therapy with bronchodilators, anti-inflammatory drugs, inhaled corticosteroids, triple inhalation therapy, oral corticosteroids, phosphodiesterase inhibitors -4 (PDE4), antibiotics, mucolytic agents (mucocinetics, mucoregulators) and antioxidant agents (NAC, carbocysteine).

As far as non-pharmacological treatment for patients with stable COPD is concerned, oxygen therapy or ventilatory support can be used. In the first case, survival can be increased in patients with severe resting hypoxemia, while non-invasive ventilation (NIV) in the form of non-invasive positive pressure ventilation (NPPV) may improve admissions-free survival in selected patients after recent hospitalization, particularly in those with marked and persistent daytime hypercapnia ( $\text{PaCO}_2 \geq 52$  mmHg) (2018 GOLD Report, Italian version).

Surgical therapy in stable COPD includes:

- pulmonary volumetric reduction surgery
- bullectomy
- transplants
- bronchoscopic operations.

Among the main points concerning COPD palliative therapy, end of life and hospice care, the 2018 GOLD Report explains that:

- Opiates, neuromuscular electrical stimulation (NMES), chest wall vibration (CWW) and fans blowing air onto the face can relieve breathlessness;
- In malnourished patients, the nutritional supplementation improves respiratory muscle

strength and overall health-related quality of life;

- Fatigue can be improved by self-management education, pulmonary rehabilitation, nutritional support and mind-body interventions.

Knowing the treatments available and using them appropriately allows for preventing the progression and exacerbations of this disabling pathology, improving the quality of life of COPD patients.

## 5.2. KNOWN TREATMENTS AND PATIENT PREFERENCES

Being aware of COPD treatments and patient preferences leads to a better disease management by increasing therapeutic adherence. The results of the mentioned GfK Eurisko survey, present some important information regarding what patients think about available treatments.

35% of COPD patients interviewed said they were taking a drug, 42% said they were taking two different drugs, 23% said they were taking 3 or more different drugs.

Inhalation drugs are the most used, followed by oral drugs and sprays.

The data obtained from the survey shows the difficulty in taking two different inhaler drugs in one day. The answers to the question “What are the particular problems/difficulties you encounter in having to take 2 different inhalation drugs in one day?” were, in order of importance: “I risk forgetting taking one of the two”, “It’s inconvenient”, “It makes me feel more ill”, “Using

two inhalation devices working in different ways is complicated”, “It’s challenging”.

The Eurisko survey subsequently focused on the unmet needs of patients, asking them “How much do you personally agree with each of the following statements?”.

The answers were the following:

- In 85% of cases, “I would like to have a drug that makes me improve”;
- In 77% of cases, “I would like to have an available drug that acts more quickly”;
- In 65% of cases, “I would like to use only one delivery device”;
- In 60% of cases, “I would like to take just one drug for COPD”;
- In 59% of cases, “I would like to have an available drug with a delivery device simpler to use”;
- In 53% of cases, “If I had an available drug that I could take less frequently I would be able to follow the treatment better”.

The request for greater efficacy, an action mechanism allowing for the drug to act faster and the possibility of using only one device are, therefore, the first three needs expressed by COPD patients.

More than two thirds of patients make at least one mistake in using an inhalational device and there is a significant relationship between poor inhaler use and symptom control in COPD patients. Determinants of poor inhaler technique in asthma and COPD patients include:

- older age
- use of multiple devices

■ lack of previous education in inhaler technique

Chorão P. et al., report that “inhaled therapy is the cornerstone in the management of asthma and chronic obstructive pulmonary disease (COPD). There are two main groups of inhaler devices: metered dose inhalers (MDI) and dry powder inhalers (DPI). Many devices have been developed and each has specificities on how to prepare the dose and deliver the drug to the airways. Although different devices have technological improvements to airway drug delivery, important limitations remain. In fact, decades after the introduction of inhaler devices, their incorrect use remains an obstacle to achieve optimal disease outcomes<sup>24</sup>”.

The 2018 GOLD Report (Italian version) highlights 3 fundamental points concerning the correct management of the patient who needs inhalation therapy:

- the choice of the inhalation device must be assessed individually and depend on the accessibility, costs, prescriber and, above all, on patient ability and preferences;
- instructions must be provided and show the correct inhalation technique when prescribing a device to verify that the patient’s inhalation technique is correct; and at each visit it is advisable to re-evaluate and ensure that the patient continues to use their device correctly;
- the inhalation technique (and therapy adherence)

24 Chorão P. et al., *Inhaler devices in asthma and COPD – An assessment of inhaler technique and patient preferences*, Respiratory Medicine, July 2014

should be evaluated, before concluding that the therapy in place requires changes.

Not taking into account the factors listed above can in fact lead to errors during the administration of the drug that can decrease the effectiveness of the treatment.

The systematic review of impact on health outcomes by Usmani et al.<sup>25</sup> reports errors made while using inhalers. Inhaled drug delivery is seen as the cornerstone treatment for COPD but devices can be used incorrectly, generating a reduction in the drug delivery to the lungs and of the effectiveness of treatment.

The incorrect use of inhalers can result in little or no medicine being inhaled or reaching the lungs, impeding

drug deposition or the delivery of an insufficient dose.

The use of only one inhalation device can therefore improve the outcomes associated with treatment for COPD. The correct management of a single device is easier to achieve than the correct use of multiple devices, especially in patients who, as we have seen, may be of an advanced age or suffer from other disorders, including depression.

Patients must be explained how inhaled devices should be used, ensuring that they are used correctly and that by using only one device there can be an increase in the effectiveness of the treatments administered and therapeutic adherence.

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<sup>25</sup> Usmani O. S. et al., *Critical inhaler errors in asthma and COPD: a systematic review of impact on health outcomes*, review, Respiratory Research 2018

# CONCLUSIONS



# CONCLUSIONS

Chronic Obstructive Pulmonary Disease (COPD) is the third leading cause of death in the world. It is a common but also preventable and treatable disease.

The disease is characterized by persistent respiratory symptoms due to airway inflammation and obstruction, especially in the lung periphery. The airflow limitation is due to airway and/or alveolar abnormalities caused by exposure to noxious particles or gases, including cigarette smoke.

Despite being preventable and despite the fact that its symptoms lower the quality of life of those affected and of caregivers, it remains a widespread disease. The low knowledge and awareness of the pathology make it underdiagnosed and, in the case of an established disease, patients are unable to treat it correctly.

Only 35% of the respondents of the Gfk Eurisko survey have heard of COPD, a fact that highlights that the disease is not well known in Europe, although it causes three million deaths. Low awareness is a serious problem, as European citizens often underestimate the risk factors, confuse the symptoms of COPD with those of another pathology and do not follow the prescribed therapies correctly.

COPD is a treatable pathology, currently available treatments result in retarding the disease's progression, and improving the quality of life of patients and caregivers. Among the main drugs used in the treatment of this disease there are inhaled drugs, allowing for the deposition of the drug in the respiratory tract. Unfortunately, the incorrect use of

inhalers leads to a decrease in effectiveness, as the drug fails to arrive at and sufficiently deposit the effective dosage in the airway.

Improved results are now possible, however this can be achieved only if the available treatments are known and the devices used correctly.

Increasing patient awareness of the disease and the availability of devices, making drug delivery easier, is an important step to increasing therapeutic adherence and achieving improved effectiveness.

Greater efficacy, greater speed of action and the use of a single device are the main unmet needs of patients regarding treatment.

The Gfk Eurisko survey shows that the first unmet need of patients is the availability of a drug to improve their health status (85% of responders), the second the availability of a drug that acts more quickly (77% of responders), while the third is the use of only one delivery device (65% of responders).

In conclusion, to make patients more aware of the risk factors associated with the development of the disease (primarily cigarette smoking), increasing awareness of COPD symptoms (highlighting the progressive decrease in the quality of life) and informing patients about available therapies and how they must be used, results in improving effectiveness, potentially reducing the patient/caregiver disease burden and the related costs for the healthcare system.

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**I-Com – Istituto per la Competitività**

**Rome**

Piazza dei Santi Apostoli 66

00187 Rome, Italy

Phone +39 06 4740746

[info@i-com.it](mailto:info@i-com.it)

[www.i-com.it](http://www.i-com.it)

**I-Com – Institute for Competitiveness**

**Bruxelles**

Rond Point Schuman 6

1040 Bruxelles, Belgium

Phone +32 (0) 22347882

[www.i-comEU.eu](http://www.i-comEU.eu)