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guest edited by R. Antonelli Incalzi

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COPD in elderly patients

G. Paolisso

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Key words: COPD, Elderly, Therapy

INTRODUCTION

Chronic Obstructive Pulmonary Disease (COPD) is a preventable and treatable respiratory disease which is a major cause of chronic morbidity and mortality throughout the world, representing the fourth leading cause of death in the world ¹.

COPD is characterized by persistent airflow limitation that is usually progressive and associated with an enhanced chronic inflammatory response in the airways and the lung to noxious particles or gases. Exacerbations and comorbidities contribute to the overall severity in individual patients.

COPD prevalence, morbidity, and mortality varies across countries. COPD is the result of cumulative exposures over decades. Often, the prevalence of COPD is directly related to the prevalence of tobacco smoking, although in many countries, outdoor, occupational and indoor air pollution are major COPD risk factors. Globally, the prevalence and burden of COPD are projected to increase in the coming decades due to continued exposure to COPD risk factors and the aging of the population (with more people living longer and therefore expressing the long-term effects of exposure to COPD risk factors) ^{2,3}.

Age is often listed as a risk factor for COPD. Chronic obstructive pulmonary disease (COPD) is common in older people, with an estimated prevalence of 10% in the US population aged > 75 years ⁴. It is unclear if healthy aging as such leads to COPD or if age reflects the sum of cumulative exposures throughout life.

DIAGNOSIS

A clinical diagnosis of COPD should be considered in any patient with dyspnoea, chronic cough or sputum production, and a history of exposure to risk factors for the disease.

Spirometry testing is required to confirm the diagnosis and to determine the severity of the disease. Although most older people can perform spirometry adequately ⁵, some patients may be unable to perform this test (eg, patients with cognitive impairment, with limitations to vigorous respiratory efforts, sedation) ⁶. Therefore, in the large majority of patients with dementia, the diagnosis of COPD will need to be made by clinical assessment. COPD is often accompanied by chronic and age-related diseases, including cardiovascular, metabolic, osteoskeletal and neurological diseases.

Whether these are the consequence of COPD itself and/or they result from shared risk factors and molecular pathways (i.e. multimorbidity) is currently unclear ⁷⁻¹⁰. Many age-related diseases, including COPD, are associated with low-grade chronic systemic inflammation "inflammageing" ^{11,12} and this can be an important pathogenic mechanism of multimorbidity ¹³.

Many non-communicable diseases, including COPD, are associated with ageing and are often accompanied by other non-communicable diseases (multi-morbidity). The pathogenesis of each of them (including that of the ageing process), as well as their inter-relationships at the molecular, clinical and environmental levels, are extremely complex and dynamic.

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THERAPY

Inhaled medications are the cornerstone for COPD treatment and are typically administered by different types of devices, ie, pressurized metered dose inhalers, dry powder inhalers, and nebulizers. Age-related pulmonary changes may negatively influence the delivery of inhaled medications to the small airways¹⁴.

Physical and cognitive impairment, which are common in elderly patients with COPD, cause difficulties in the use of handheld inhalers in the elderly. Treatment of COPD with inhaled therapy should be customized to each older patient. The selection of inhaler device for these patients should be influenced by their abilities.

There is need to customize both diagnostic and therapeutic procedures for elderly COPD patients to achieve an appropriate disease severity stratification and deliver appropriate treatment.

In this context to achieve an optimal adherence to treatment it is as important to train patients in the use of handheld inhalers and to check that patients are using them correctly on a regular basis as to choose appropriate drugs.

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An epidemiological overview and clinical picture of COPD in the elderly

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Chronic Obstructive Pulmonary Disease (COPD) is a primary cause of disability and death in the elderly. Its prevalence is dramatically rising, mainly among females, but reliable figures are not available because many elderly, mostly the ones plagued with disability and multimorbidity, cannot perform a good quality spirometry, a sine qua non diagnostic tool. Furthermore, atypical presentations contribute to conceal COPD. Even in patients who received a standardized diagnosis of COPD the GOLD recommended staging criteria are questionable because of some imbalance between classificatory and prognostic properties. The great variety of symptoms applies to both stable and exacerbated COPD. Thus, to diagnose an exacerbation timely may be difficult if the individual pattern of symptoms has not been previously recognized. Accordingly, a truly comprehensive assessment is mandatory to clarify the unique clinical pattern of a given patient and, then, to tailor the multidimensional therapeutic strategy. Such an approach largely depends upon the specialty of the physician in care. Thus, efforts are needed to make all the specialists caring for the elderly respiratory patients share the cultural and procedural patrimony allowing recognize and optimally care these “difficult” patients.

Key words: COPD, Elderly, Disability

AN EPIDEMIOLOGICAL PERSPECTIVE

COPD, a chronic non communicable age-related condition, is primarily related to smoke. This explains its higher prevalence among males, but also the ongoing epidemiologic changes driven by the spreading of smoke addiction among females¹. However, at least one out of four or five people with COPD denies a history of smoking². Indeed, environmental factors contribute to the pathogenesis of COPD. Among these, pollution, mainly at working place for males and at home for women living in less developed countries, plays a primary role. Other highly prevalent risk factors for COPD are recurrent pulmonary infections and malnutrition². Age qualifies as a “summary” risk factor because it directly reflects the cumulative exposure to the recognized risk factors. This underlies the link between older age and COPD and makes COPD a primarily geriatric condition. This also explains the clustering of COPD with other chronic diseases sharing the same or a very similar profile

of risk, i. e. the place of COPD in the multimorbidity framework³.

Despite this solid epidemiological evidence, the true prevalence of COPD among the elderly remains uncertain. A 9% prevalence has been estimated in the general population in the 2000-2007 period, but much higher figures are known to characterize the elderly⁴. For example, in the Norwegian Hordaland County Cohort Study, the prevalence of COPD in people aged 65 and over was 28% vs 14% in the 50-64 years cohort in the 2003-05 period and 20% in the same cohort over 64 in the 1996-7 survey⁵. In Lazio, the prevalence in males dramatically rises with age from 7% in the 60-65 year cohort to 24% in the 80-85 year cohort; the corresponding figures for females are 8% and 17% (Fig. 1). The high rate of underdiagnosis is especially due to the very stringent diagnostic criteria requiring a high quality spirometry for a diagnosis of COPD to be made⁶. Indeed, in the SaRA study it has been proved that 836/1971% of people over 64 years of age attending the outpatient clinics of Geriatrics or Respiratory Medicine of 20 Italian hospitals were unable to perform spirometry or could

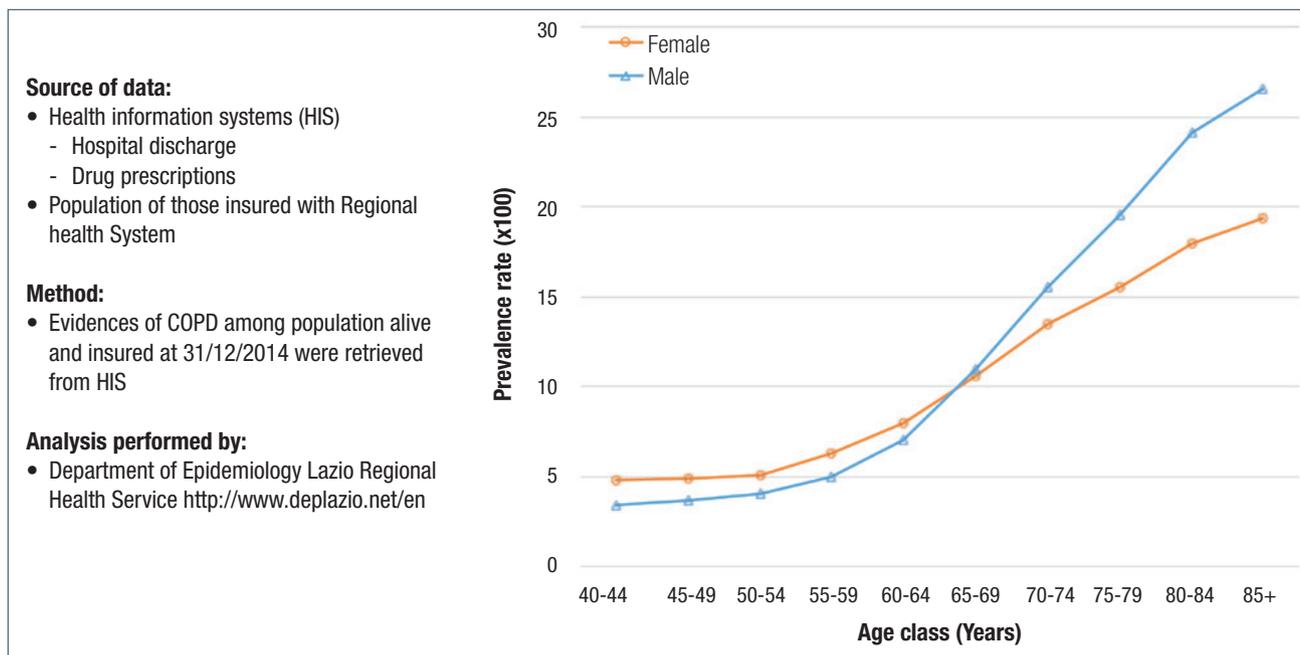


Figure 1. COPD age-specific prevalence rate at 31/12/2014 Lazio Region, Italy.

not meet the acceptability or repeatability standards of spirometry and, then, could not receive a diagnosis of COPD⁷. This fraction fell to 702/1971% if the FEV₆ was used as a surrogate of FVC⁸. However, FEV₆ is not routinely used for people unable to produce a canonical FVC and, in any case, even for FEV₆ the proportion of non achievers is unacceptably high. Risk factors for a poor quality spirometry are cognitive impairment, disability, polypharmacy, poor education and older age⁷. As a consequence, the most compromised patients are also those most likely to remain unrecognized and untreated. Furthermore, the randomized pharmacological clinical trials exclude these patients: only one out of five enrollees in a RCT is representative of the elderly people attending an ambulatory of Respiratory Medicine⁹. Thus, a double bias affects elderly people with COPD: a diagnostic bias and a therapeutic one given that the available evidence on the therapy of COPD stems from RCT excluding these patients. Broadly speaking, COPD is typically underdiagnosed at any age with the fraction of concealed cases ranging between 63% and 82% depending upon the setting and the method¹⁰. The high rate of missing also in adult and even young-adult people testifies to a lack of attention to and, more in depth, poor awareness of this disease. The problematic and frequently elusive clinical presentation partly justifies this finding. Misrecognition becomes more and more important as people age because of age-related and comorbidity-related changes in symptoms and non respiratory confounders.

THE MISLEADING SYMPTOMS

The difficulty to recognize COPD to some extent reflects the variability of the symptoms with the phenotype of COPD as well as longitudinally in the same patient. Furthermore, the chronobiology of symptoms changes from patient to patient as also highly variable is the presentation of COPD exacerbations. Finally, comorbidity and disability contribute to make symptoms a true puzzle.

A) Relationship between symptoms and phenotype: two extreme phenotypes, the bronchitic one and the emphysematous, traditionally mark the extremes of the phenotype range. A variety of other phenotypes, e. g. the asthma-like and the Combined Pulmonary lower lobe Fibrosis and upper lobe Emphysema¹¹, coexists. The bronchitic phenotype is easier to recognize, whereas the emphysematous phenotype may be missed in the elderly for many reason. First, the patient adjusts to the reduced respiratory reserve by decreasing her/his physical activity, thus preventing the onset of dyspnea and having a sort of downsized life. Interestingly, the misconception that age itself necessarily curtails our range of physical independence frequently founds this coping strategy. Also the bronchitic phenotype may be the object of misinterpretation. For instance, bronchiectases are frequently missed as comorbid or else main disease, and the missing is clinically important because physical therapy and selected

pharmacological measures have the potential for improving the health status of these patients. The epidemiology supports the link between bronchiectasis and COPD: COPD was the most common secondary diagnosis (39,8%) when bronchiectases were the main discharge diagnosis¹².

B) Chronobiology of symptoms: a notable contributor to the clinical phenotype, the circadian rhythm of symptoms would deserve much more attention than currently paid to. Indeed, distinctive clusters of symptoms have been reported and contribute to shape a clinical phenotype. For instance, nocturnal symptoms have been reported in about 60% of COPD patients¹³, and wheezing is the most common among these¹⁴. However, it is unknown whether this reflects a true asthma-like feature or to some extent an unrecognized left ventricular dysfunction underlying cardiac asthma. Furthermore, coughing and not wheezing has been rated as the most common nocturnal symptom in the recently released Assess study¹³. Insomnia is also highly prevalent in elderly COPD patients and its prevalence increases for increasing age from 65 to over 90 years, whereas such an increase is not evident in patients with chronic non respiratory diseases¹⁵. Finally chest tightness, a symptom suggesting coronary artery disease, has been reported by about one out of four COPD patients¹⁶.

C) Frequency and clinical presentation of the exacerbations: in the last five years a trend is emerging towards recognizing a new phenotype, the “frequent exacerbator”, based exclusively on the yearly number of exacerbations. Having two or more exacerbations would define such a new phenotype irrespective of which are dominant symptoms. Supporting this view is the finding of a stable number of exacerbations during the natural history of the disease in the individual patient starting from the earliest stages of COPD, also if some increase in frequency marks the passage to higher stages of the disease¹⁷. The current evidence is insufficient to confirm the existence of such an hypothetical phenotype. Indeed, in people over 75 years frequency of exacerbations is inversely related to the income, and the same is true of other chronic non respiratory conditions¹⁸. Thus, it is likely that the social dimension and not a biological one underlies the frequency of the exacerbations.

The clinical pattern of the exacerbation dramatically changes from patient to patient. In a series of 80 consecutive people attending an emergency room for exacerbated COPD, leg oedema secondary to severe hypoxia and hypercapnia, chest tightness simulating a cardiac attack, dizziness and postural

instability due to hypoxemia and fatigue were the prevailing symptoms in about 20% of patients, while dyspnea was the hallmark of typical presentation. Interestingly, patients with “atypical” presentations of the exacerbation frequently had a correct diagnosis not in the emergency room, but in the hospital ward 24-48 hours later¹⁹. Further complicating this issue is the fact that the percutaneous measurement of Oxygen saturation is frequently unreliable in the elderly and multimorbid patient due to one or more of the following factors: atrial fibrillation and other arrhythmias, venous congestion, low blood pressure, cold skin, anemia, shivering patient, movements, bright light²⁰. The remote multiparametric monitoring of elderly COPD patients allowed know different onsets of the exacerbation with selected and clinically problematic patterns such as progressive decrease in physical activity, a sort of downtailoring of the range of activity in response to worsening COPD, or increased respiratory rate without any other symptom or sign for a while²¹.

D) Impact of comorbidity and disability on symptoms: disability frequently limits the physical activity and, then, prevents the patient from reaching the threshold of dyspnea. Accordingly, alternative symptoms such as fatigue, dizziness, non specific malaise, defective attention and concentration may dominate the clinical scenario. This results in a seemingly and, thus, potentially misleading “non respiratory” pattern of symptoms. Analogously, selected comorbid diseases may act as clinical confounder. This is the case of coronary heart disease, congestive heart failure, obstructive sleep apnea syndrome and some others. Indeed, the differential diagnosis between cardiac and respiratory dyspnea, between cardiac and respiratory chest tightness and between COPD- and OSAS-related symptoms may be difficult. Furthermore, the comorbid disease itself may change in clinical presentation as a function of age. This is the case, for instance, of OSAS: in the elderly the classical pickwickian phenotype is the exception and not the rule, and both snoring and day time somnolence are not more prevalent than in non OSAS elderly people, whereas subtle cognitive dysfunction and nicturia, which is commonly ascribed to urologic problems, are distinctive clinical features²². All these problems make the diagnosis of COPD in the old and multimorbid patient, i. e. in the real life patient, the end result of a hard attempt at disentangling and interpreting several and frequently atypical, at least with regard to adult based knowledge, symptoms (Fig. 2).

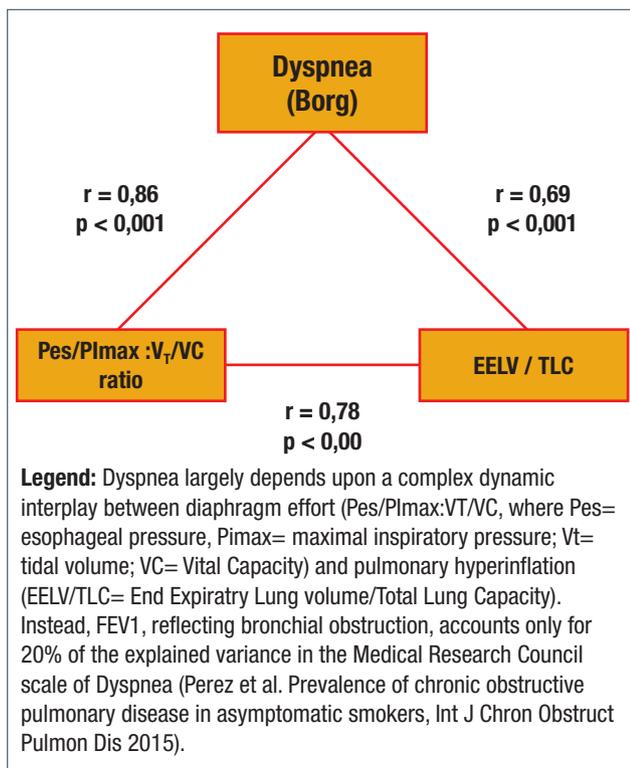


Figure 2. Inter-relationships at a standardized level of exercise (from O'Donnell et al., 1997²³ and Perez et al., 2015²⁴, mod.).

SOME NOTES ABOUT COPD STAGING

The staging of COPD was based only upon the degree of bronchial obstruction, as expressed by the FE1/FVC ratio, until 2009. With the 2009 update of GOLD guidelines a new classificatory system has been adopted and is currently recommended. This system has merit in that it takes into account the clinical disease severity as expressed by dyspnea, health status and frequency of exacerbations. However, respiratory function remains a necessary diagnostic criterium. The whole classificatory system is to some extent cumbersome as it requires a careful diagnostic procedure. Furthermore, it is intended for the pure COPD patient or, at least, for patients having COPD as the main determinant of health status. This does not occur in the majority of the elderly patients, else the main disease frequently changes with the time.

A practical application of the GOLD classificatory criteria will clarify this issue: a patient with GOLD class 2 obstruction (FEV1/FVC < 70%, FEV1 = 50-80% predicted), MRC = 1 and CAT = 8 will be classified as in stage A or B GOLD depending upon whether she/he had 1 or more than one exacerbation in the previous year. It is evident that this last criterium is problematic

in the elderly and multimorbid patient who experiences many episodes of worsening health status during one year and frequently has trouble to recognize their respiratory origin. Furthermore, the epidemiological evidence is consistent with GOLD stages having poor prognostic capacity: in the Norwegian Nord-Trøndelag Health Study 1995-1997 survival did not distinguish A from B and C from D patients²⁵. It should also be recognized that MRC score may be misleading due to the variable coping strategy used by the old patient (see previous section).

The methodological and procedural problems reported in this and in the previous section point at the need of an alternative approach to the elderly patient with a clinically founded suspect of COPD if a spirometry is lacking. In these patients the ex juvantibus criterium may be the only way of testing the suspect of COPD: an improvement in measurable outcomes such as symptoms and physical performance after the start of topical bronchodilators may be the key to a putative diagnosis of COPD as well as the only means of improving health status.

In the near future the analysis of the breath pattern through highly innovative technique like the electronic nose might allow recognize distinctive metabolic patterns marking COPD and distinguishing it from other chronic diseases. Preliminary results are highly favorable²⁶. If confirmed in larger population, these findings will pave the way to an easy diagnosis of COPD and, thus, will remove the exclusion of the frail and multimorbid patient from the standardized diagnostic and therapeutic pathways.

RELATIONSHIP BETWEEN DISEASE SEVERITY AND HEALTH STATUS

On average, health status worsens for decreasing FEV1, but the decline becomes dramatic for FEV1 < 50%²⁷. However, in the broad population of elderly COPD patients, the bronchial obstruction is weakly correlated with health status, at least in patients with mild to moderate obstruction. This finding reflects the multifactorial origin of health status impairment in these patients. Indeed, dyspnea, the main threat to personal independence and well being, largely depends upon factors which may be only barely reflected by bronchial obstruction (Fig. 3). Among these are dynamic hyperinflation, respiratory muscle fatigue and neurologic and psychologic factors such as the coping strategy. Furthermore, limitation of personal capabilities is variably determined by sarcopenia and fatigue of peripheral muscles, and in an unprecised percentage of patients peripheral factors prevail on dyspnea as determinants of health status impairment.

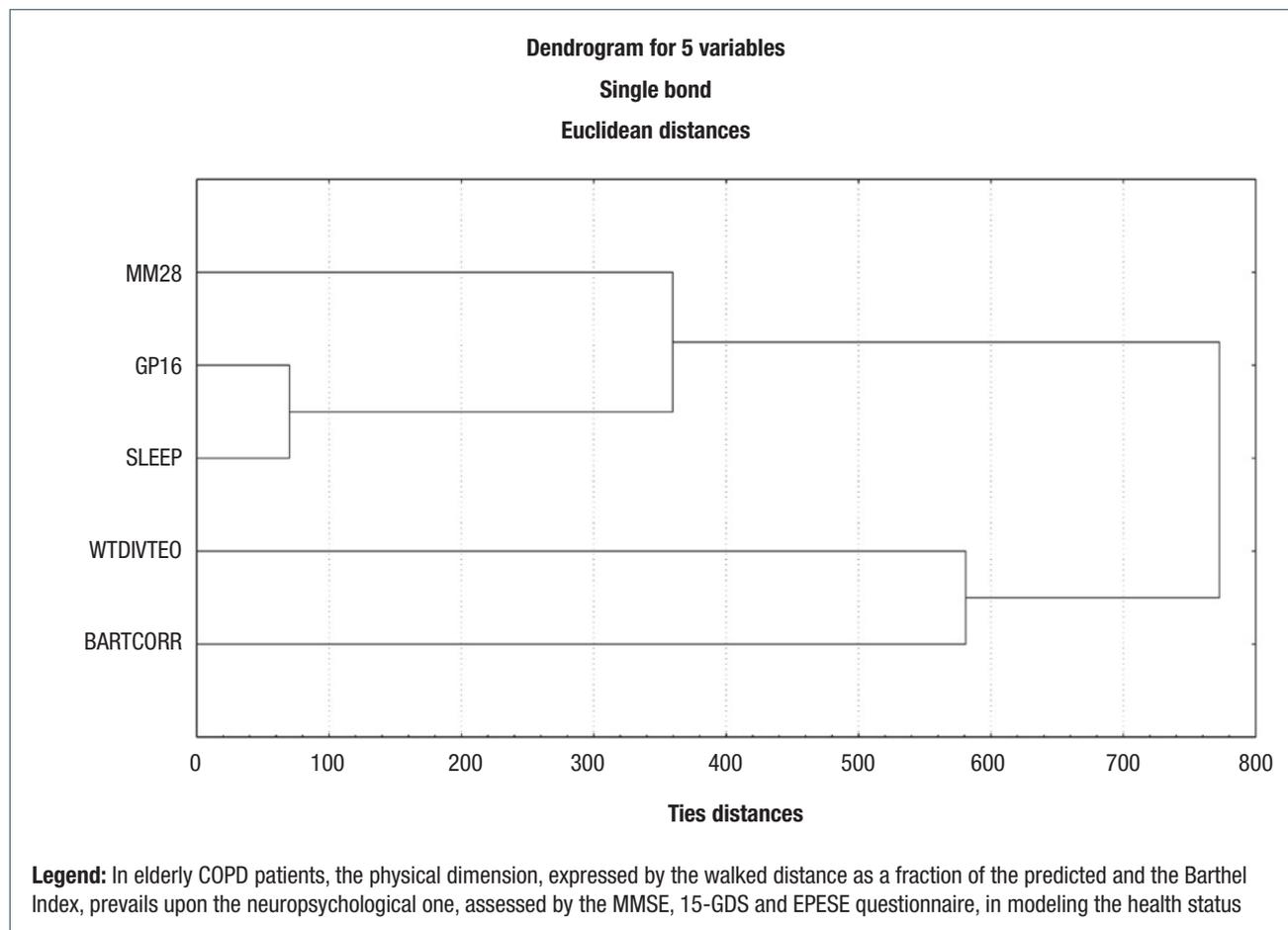


Figure 3. Performance based dendrograms (source: SaRA) (from Antonelli Incalzi et al., 2009²⁸, mod.).

In the SaRA study, it has been proved that 34% of people with mild to moderate bronchial obstruction ($FEV_1 = 50\text{-}79\%$ predicted) were in the lower cluster of health status, whereas 15% of people with severe obstruction ($FEV_1 < 35\%$) were in the upper cluster²⁸. Interestingly, clustering was primarily based on “physical” factors, and secondarily on affective/cognitive factors and sleep troubles (Tab. I). These findings explain the leading role of rehabilitation as a therapy for health status impairment in COPD: by improving physical capabilities, rehabilitation produces a notable improvement in health status, and age does not weaken, else it might strengthen this effect²⁹. Furthermore, rehabilitation has the potential for smoothing the negative effect of peripheral factors, succeeding even if dyspnoea is not the main factor limiting the physical performance.

Exacerbations usually account for a temporary dramatic worsening of health status, as well as for a small residual permanent loss. Thus, each exacerbation marks a measurable drop in the involution of health status^{30,31}. Accordingly, attempts at detecting and treating

the exacerbations timely and, hopefully, at preventing them would translate in some slowing of health status decline.

Interestingly, patients with undiagnosed bronchial obstruction are characterized by a lesser impairment of health status, and this likely contributes to conceal the disease. Nevertheless, the impairment is clinically important³². Thus, unrecognized COPD is expected to contribute largely to the burden of disability in the elderly. This further stresses the need of performing any effort aimed at easing the diagnosis of COPD in the frail and multimorbid patient.

THE APPROACH TO COPD AS A FUNCTION OF PHYSICIAN'S SPECIALTY

Therapy of COPD encompasses a variety of pharmacological and non pharmacological options, being truly multidimensional in nature (see sections Papi and Pagano). However, these options are variably

Table I. Physician’s approach to COPD problems as a function of specialty (from Paladini et al., 2011³³, mod.).

	Geriatricians	Pulmonologists	Internists
Clinical awareness of the impact dynamic hyperinflation	54	86	61
Multidisciplinary approach	76,5	24	28
Use of indices of specific health status COPD	57	54	45
ADL/IADL evaluation	75	35	39
Phenotypic variability as an intrinsic feature of COPD	6	37	18

used depending upon the awareness of the patient’s needs and the physician’s cultural background. Thus, physician’s specialty qualifies as a determinant of the approach to the elderly patient with COPD. Indeed, by comparing the attitudes of geriatricians, internists and pneumologists towards COPD patients Paladini et al found that the majority of geriatricians perform a comprehensive geriatric assessment and rate ADL/IADL performance and also frequently use disease specific health status instruments³³. However, the awareness of phenotypic variability of COPD and of the important clinical role of dynamic hyperinflation is scarce among geriatricians. On the opposite, such awareness is higher in respiratory physicians, but, on the other hand, comprehensive assessment is out of their cultural patrimony and working habit, and even COPD-specific health status indexes are used slightly less commonly than by geriatricians. Finally, internists are characterized

by a highly variable approach to the COPD patient, without any specialty-specific trait, but with a basically monodimensional assessment (Fig. 4).

The assessment finds the awareness of individual problems and helps the physician to tailor the therapy. Thus, the specialty-specifics gaps suggest that a truly comprehensive and individually tailored therapy is the exception and not the rule for the elderly COPD patient. This is the basis for multispecialty education actions to improve the care of these complex patients.

CONCLUSIONS

COPD is a disease of age, but its clinical presentation also changes with age. As a consequence, physicians should be aware of the many diagnostic keys and pitfalls. They also should be able to translate the variegated clinical picture into a tailored multidimensional therapeutic strategy. Unfortunately, the dominant economic interest has promoted important pharmacological trials, but no trials testing comprehensive therapeutic strategies. Thus, reports about selected strategies of home care focus on a single domain, e.g nurse based assistance or maintenance home rehabilitation, but they never tested an approach featuring the classical comprehensive geriatric assessment. Given that pharmacological trials could not improve survival, but only bronchial obstruction and health status, the time is ripe for such an effort being jointly sustained by geriatricians, internists and respiratory physicians.

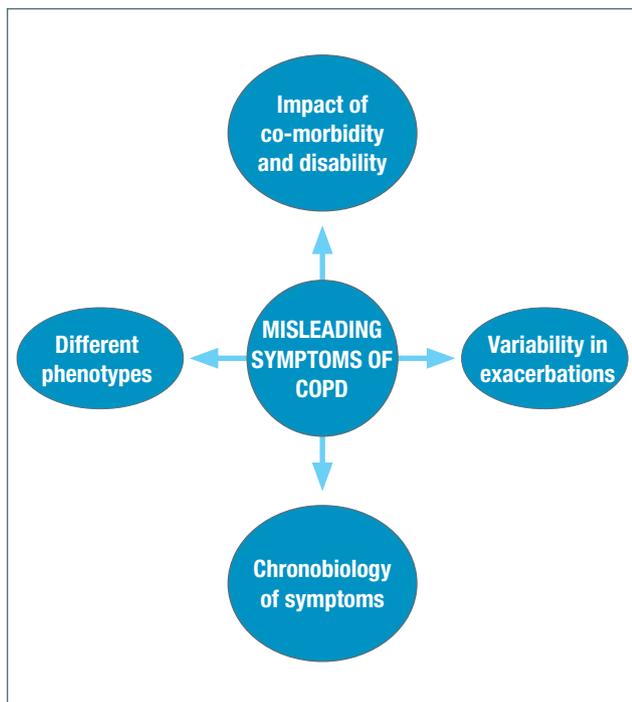


Figure 4. A tentative synthesis of determinants of variant symptoms in elderly COPD patients.

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Comorbidities of COPD as a function of age: evidence and practical recommendations

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Chronic obstructive pulmonary disease (COPD) is a highly prevalent chronic condition with a dramatic impact on the health status that is evident even in milder stages of the disease. However, deaths due to respiratory causes account for only a fraction of mortality in COPD. Thus, comorbid conditions as potential co-determinants of the effects of COPD on both health status and survival have received much attention in the last years. COPD is almost invariably associated with other diseases, and three mechanisms most likely underpin this association. First, COPD is an age-related disease, and as such tends to be associated with other age-related diseases. Second, COPD shares its most important risk factor – cigarette smoking – with several other diseases, in particular cardiovascular diseases. Third, COPD, or COPD treatment, may impact other systems or organs, as is the case of COPD-associated anemia or osteoporosis. The aim of this article is to provide an overview on the comorbidities of COPD that are most relevant for the elderly, providing information relevant for patients' management. COPD is a highly prevalent chronic condition, the only one whose prevalence is steadily rising in western countries¹. Currently the sixth, it is expected to rank the third cause of death by 2020². Furthermore, it dramatically impacts the health status and the personal independence³. However, deaths due to respiratory causes account for only a fraction of mortality in COPD⁴, whereas health status is frequently impaired even in the milder stages of the disease⁵. This fact has switched the attention to comorbid conditions as potential co-determinants of the effects of COPD on both health status and survival.

Key words: Chronic obstructive pulmonary disease, Comorbidity, Aged, Aged 80 and over, Frail elderly

The original concept of comorbidity refers to diseases coexisting with the “main” disease. In elderly people, this is an elusive concept as the main disease may change over time and may be difficult to recognize. Indeed, in the majority of elderly people several chronic conditions contribute in a comparable manner to impair the health status. This is especially true of COPD patients: coexisting cardiac, skeletal, cognitive and affective problems are frequently responsible for impaired health status in a comparable way. To overcome the conceptual limitation of the classical definition of comorbidity, the concept of multimorbidity has been proposed, which refers to the coexistence of multiple conditions with no implicit separation between a “principal” disease and associated diseases. The concept of multimorbidity goes beyond this, however, because it has been shown that some chronic diseases tend to cluster in the population. In a sample of people with 75 years or more, COPD

clustered with coronary artery disease and thyroid dysfunction and, less strictly, with hypertension, congestive heart failure, atrial fibrillation and other cardiovascular diseases⁶. Studies based on the classic concept of comorbidity (usually performed in younger populations) have shown that compared with people without COPD, people with COPD have about a four-fold increase in risk for cardiovascular diseases, and increases in risk between 50% and 100% of having infective, psychiatric, renal, neurological, gastro-intestinal, and metabolic diseases⁷. Thus, COPD is almost invariably associated with other diseases, and three mechanisms most likely underpin this association. First, COPD is an age-related disease, and as such tends to be associated with other age-related diseases. Second, COPD shares its most important risk factor – cigarette smoking – with several other diseases, in particular cardiovascular diseases. Third, COPD, or COPD treatment, may impact other

systems or organs, as is the case of COPD-associated anemia or osteoporosis.

The exposure to cigarette smoking is an important risk factor for cardiovascular and cerebrovascular diseases as well as for female osteoporosis⁸⁻¹⁰. Furthermore, systemic inflammation and a prothrombotic state are highly prevalent in COPD and might promote atherosclerosis¹¹⁻¹². The rapid decline of physical capabilities and, then, daily physical activity secondary mainly to dyspnoea makes the COPD patient at risk of sarcopenia, osteoporosis and fractures besides having unfavourable metabolic and cardiovascular effects¹³⁻¹⁴. Further complicating the issue of comorbidity in COPD is the possibility that bronchodilating and topical anti-inflammatory therapy cause arrhythmias/myocardial hypertrophy and osteoporosis respectively¹⁵⁻¹⁶.

It has been suggested that systemic inflammation may be the link between COPD and comorbidities¹⁷. However, two alternative theories about the origin of that inflammation have been produced: for many authors the lung is still the centre of the disease with some systemic “spill-over” of disruptive and reparatory inflammatory mediators, for some others the pulmonary manifestations are one expression of an originally systemic inflammatory state and must be considered within a multiple organ disease¹⁸.

Some of typical comorbidities of COPD are of particular importance for the elderly and deserve special attention because they are relevant for disease management in these patients.

As previously stated, heart disease is frequently associated with COPD, mainly due to the effect of smoking of both the lungs and the heart. Indeed, the linear association between FEV1 and cardiovascular events is more evident in smokers compared with non-smokers¹⁹. The presence of cardiovascular disease has important prognostic implication, as cardiovascular events are the major cause of death in COPD patients⁴, and ECG signs of ischemic heart disease or right ventricular hypertrophy or overload are significantly associated with mortality²⁰. The coexistence of heart disease and COPD makes the interpretation of dyspnea difficult, as this symptom is the hallmark of both conditions. The BNP essay may be of help for the differential diagnosis, as even in people with pre-existing heart failure its concentration does not increase during COPD exacerbations²¹. However, many different conditions including renal failure, that is frequently associated with COPD, may cause an increase of BNP and reduce its diagnostic value²².

Renal insufficiency is frequently associated with COPD. Once again, cigarette smoking seems to play an important role in this association, as it is associated with worsening renal function and faster course of glomerulopathies²³. Heavy metals (especially lead, strontium

and cadmium) and aromatic hydrocarbons contained in smoke can promote oxidative stress which damages the glomerulus and proximal tubule, and cause proteinuria and immuno-mediated glomerulonephritis²⁴⁻²⁵. Furthermore, nicotine may induce renal fibrosis²⁶ and contribute to mesangial proliferation and extracellular matrix deposition²⁷⁻²⁸. The Extrapulmonary Consequences of COPD in the Elderly (ECCE) study showed that the prevalence of GFR < 60 ml/min/1.73 m² with or without increased serum creatinine was 43% in COPD patients over 64 years and 23.8% among non-COPD controls²⁹. Other studies, however, have reported lower prevalence (9.6% in females and 5.1% in males)³⁰. Differences in age and COPD severity of the study populations and in methods for diagnosing renal insufficiency are the most likely explanation of this discrepancy. It has been shown that the association between COPD and reduced GFR is especially evident in the emphysematous phenotype of COPD³¹. This is of particular importance because this phenotype is associated with loss of muscle mass, and therefore with reduced creatinine production. In this situation, the serum concentration of creatinine may be normal even in presence of reduced GFR, a condition referred to as “concealed” renal failure. In COPD patients, this condition is present in about 20% of patients, that is the same prevalence of overt renal insufficiency in the same population²⁹. In other words, for each COPD patient with abnormal concentration of serum creatinine, there is another patient with normal serum creatinine but reduced GFR. The recognition of this condition is of particular importance, as many drugs used to treat COPD or COPD exacerbations (e.g., antibiotics) are cleared by the kidney and may need dose titration in presence of renal insufficiency.

Osteoporosis and fractures are associated with COPD, regardless of sex, and the risk for spine or hip fractures in these patients is increased by about tenfold³². A review based on 13 clinical studies³³ reported a prevalence of osteoporosis in COPD ranging from 9 to 69%, with difference mostly due to different definitions of osteoporosis. In this study, the major correlates of osteoporosis were forced expiratory volume in the first second (FEV1), fat-free mass, and body mass index (BMI). Beside the role of systemic corticosteroids, the relationship between COPD and osteoporosis may also be mediated by low physical activity, as it has been shown that the bone mineral density is directly correlated with daily physical activity and inversely correlated with the COPD Assessment Tool (CAT) score³⁴. Since vertebral fractures may not only worsen quality of life of these patients, but also respiratory functions³⁵, a screening for osteoporosis using DeXA is probably warranted in all COPD patients. Furthermore, all patients

with COPD should be referred to a physical rehabilitation program, that is effective in reducing the risk of falls and fractures, improves quality of life and functional status. With respect to pharmacological prevention and treatment of COPD-associated osteoporosis, it has not been specifically studied, and the same strategy used for corticosteroid-induced osteoporosis is usually suggested: bisphosphonates and teriparatide as first-line, and denosumab as a second-line choice.

Hypoxemic COPD is an important cause of polyglobulia. Anemia, however, is a more frequent comorbidity of COPD. Its prevalence has been estimated to be about 13% in a population with a mean FEV1 of 37%³⁶, and even in a population with hypoxemic COPD it is still 12%³⁷. Different mechanisms may explain such a high prevalence of anemia in COPD. Chronic inflammation causes increased concentration of IL-1 and TNF-alpha which, in turn, decrease the lifespan of red blood cells and induce resistance to erythropoietin³⁸. Recently, the role of hepcidin in regulating iron metabolisms has come to light. It is a 25-amino acid peptide produced by the hepatocytes, and it is an inhibitor of iron absorption in the small intestine and iron release from macrophages³⁹. It has been shown that its production is stimulated by inflammatory cytokines such as IL-6, but not by the aforementioned IL1 and TNF-alpha⁴⁰. Hepcidin concentration was found to be increased in COPD patients with a mean age of 71 years compared to controls of the same age, and it has been hypothesized that systemic inflammation and elevated values of IL-6 present in exacerbations and stable COPD might be responsible for the increased hepcidin level⁴¹. Interestingly, in a younger population (mean age 60 years) the serum concentration of hepcidin was found to be reduced in participants with moderate or severe COPD compared to controls⁴². Thus, age seems to play a role in the complex interplay between COPD, systemic inflammation, and anemia.

Malnutrition, defined as a BMI below 21 kg/m² or fat-free mass index below 15 kg/m² (in women) or 16 kg/m² (in men), affects about one out of four patients with moderate to severe COPD⁴³. There are several mechanisms that may explain this high prevalence of undernutrition. A decreased energy intake has been described in COPD patients due to dietary problems (including anorexia), and is associated with lower fat-free mass⁴⁴. At the same time, COPD patients tend to have an increased resting energy expenditure, and this increase is associated with weight loss⁴⁵. Beside this imbalance between energy intake and expenditure, an increased production of inflammatory cytokines and an altered secretion of adipokines such as leptin or adiponectin also play an important role in the development of malnutrition in COPD⁴⁶. In front of this evidence, several

attempts have been made to improve the health status of COPD patients using nutritional supplements. A Cochrane review has shown that use of nutritional supplements in malnourished COPD patients may increase weight and fat-free mass, and may improve functional capacity and quality of life⁴⁷.

Neuropsychological problems, mainly cognitive impairment and depression, are a common comorbidity of COPD. Estimates of prevalence of depression in COPD vary according to the screening instrument used, and range between 10% and 42%⁴⁸. Patients with COPD have a 7-fold increase of having depression⁴⁹, and the presence of depression is associated with higher mortality and worse quality of life, as measured by the Saint George Respiratory Questionnaire⁵⁰. Patients with coexisting COPD and depression are less likely to adhere to pulmonary rehabilitation treatments, this fact, however, should not discourage the referral of patients to this treatment. In fact, in patients with severe COPD it has been shown that rehabilitation can improve depressive symptoms independently of its effects on dyspnea and quality of life⁵¹. Cognitive impairment, as measured by the Mini-mental State Examination (MMSE), is 2.5 times more common in patients with COPD compared to non-COPD patients. Among the different measures of COPD severity, such as FEV1 reduction or BODE index, hypoxemia shows the strongest association (OR: 5.45) with cognitive impairment⁵². It must be noted that the association between COPD and cognitive impairment may be even stronger. In fact, it has been shown that the MMSE has a poor sensitivity (55%) in detecting cognitive impairment compared to a complete neuropsychological assessment⁵³. This is probably due to the fact that hypoxemic COPD patients have a peculiar pattern of impaired cognitive functions compared to other forms of dementia common in the elderly, with prevalent involvement of verbal memory and other frontal functions that are not adequately explored by the MMSE⁵⁴. Thus, the screening for cognitive impairment in these patients should also include a tool sensitive to abnormalities in frontal functions (e.g., executive function) such as the clock drawing test. Such a screening may also be useful for prognostic purposes, since the impairment in executive function is associated with increased mortality in hypoxemic COPD patients⁵⁵.

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GOLD is not “GOLD”: applicability of guidelines in the complex elderly patient

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COPD is a common chronic respiratory disease, and its prevalence is steadily increasing worldwide. The main symptom of the disease is exertional dyspnea, which tends to worsen with increasing severity of the disease. The main pathogenetic mechanism of dyspnea is lung hyperinflation, which is caused by structural alterations of the peripheral airways and of the lung connective tissue. Therefore, a comprehensive lung function assessment is mandatory to characterize the functional abnormalities associated with the disease, and to monitor the progression of the disease and the response to treatment. However, as stated by the GOLD recommendations, the occurrence of comorbid condition is frequent in individuals affected by COPD, and these should be treated independently. Indeed, comorbidities may interfere with the management of the disease, and complicate its course. It follows that the main target of treatment are represented by chronic airway inflammation and airway obstruction on one hand, and by the concomitant diseases on the other hand.

Key words: Dyspnea, Lung hyperinflation, Comorbidities, Inhaled device, Adherence

International guidelines on the management of COPD recommend that both lung function and health status, by means of respiratory symptoms and risk of exacerbations, are regularly assessed to properly manage the disease¹. Individuals with COPD mostly complain of limitation of their daily activities, mainly because of dyspnea. The underlying pathophysiological mechanism of dyspnea lies not just in breathing through “narrow tubes”, but rather breathing at “higher volumes” due to early closure of the peripheral airways during exercise, which poses an elastic load to the respiratory system that eventually leads to inspiratory muscle weakness and fatigue. In other words, obstructive patients have difficulty expelling air as a result of air-flow limitation on exhalation, and as a consequence the lungs hyperinflate. This condition has been termed “dynamic hyperinflation”, as opposed to “static” hyperinflation that occurs at rest, and has become a target for current treatment. Physicians should be aware that dynamic hyperinflation can occur in the majority of patients with COPD, especially in the most severe stages of the disease, and may greatly contribute to breathlessness. The blunted exercise ability translates into limitations in daily-life activities, such as walking,

dressings or even eating. This has obviously enormous consequences on health-related quality of life. It follows that the lung functional assessment alone may not be sufficient to fully describe the complex general impairment associated with the disease, and the response to treatment can be unveiled by monitoring changes in the impact of COPD on a patient’s health status rather than demonstrating improvements in conventional lung function. In individuals suffering from COPD, lung hyperinflation can be suspected on a chest x-ray and is confirmed by the plethysmographic evaluation of lung volumes. The diagnosis of dynamic hyperinflation is posed in the pulmonary function or exercise laboratory, where the inspiratory capacity is measured during cardio-pulmonary exercise tests. For study purposes, dynamic hyperinflation has also been assessed with Metronome-Paced Tachypnea (MPT), which has been shown to be a simple, reliable alternative for cardio-pulmonary exercise test. Whether dynamic hyperinflation as measured in laboratory settings reflects that occurring during activities in daily life is still a matter of debate. Lahajje and colleagues² demonstrated that up to one third of the subjects with mild COPD experience hyperinflation during ADL. This is of great importance

because it suggests that early impairment in lung function may be detected in the early stages of the disease, and implies the need for early treatment, when the decline in lung function is also demonstrated to be steeper than in the more advanced stages of the disease.

The steadily increasing prevalence of COPD worldwide, with the parallel burden of morbidity and mortality and the consequent socio-economical impact on health system, advocate for therapeutic strategies that could optimize the clinical management of COPD patients. The pharmacological approach to COPD is evidence-based and relies on the results of randomised controlled trials (RCTs). If, on one hand, the results of RCTs have the highest level of evidence and consequently the highest level of recommendation in clinical practice (grade of recommendation A), the general assumption that the relationship between treatment and efficacy will hold validity in the general population is not always true. RCTs are conducted in “controlled” conditions to exclude potential confounding factors that may affect the internal validity of the study. To achieve this goal, the study population of RCTs is chosen on the basis of highly selective inclusion/exclusion criteria, and is therefore not fully representative of general (unselected) patient populations; indeed, the GOLD recommendations state that *it is important to recognize that all clinical trials recruit restricted groups of patients; this limits their generalizability*¹. In this scenario, it is plausible to assume that the majority of subjects with COPD are currently treated with a therapeutic *armamentarium* that has been tested on different populations (those of RCTs). Herland and colleagues³ and Travers and colleagues⁴ showed that, by applying the inclusion criteria for RCTs to small study populations of individuals with COPD, only the minority would have been eligible for RCTs on COPD. In particular, in the study conducted by Travers and colleagues⁴, the percentage of eligible subjects for a RCT trial for COPD was 5%, whereas in the study conducted by Herland and colleagues³, the percentage of eligible patients was equal to 3.3%. One of the most frequent exclusion criterion is the occurrence of concomitant diseases, which inevitably excludes a large proportion of individuals with COPD, especially in the most advanced ages^{5,6}. This is emphasized by the common observation that real-life populations are much older than study populations. This has been recently confirmed by Scichilone and colleagues⁷, who performed an observational study in a larger population of outpatients with an established diagnosis of COPD aiming at exploring to what extent the RCT evidence applies to individual patients. The authors clearly showed that less than one out of five patients would be eligible for the RCTs; indeed, 83% of the whole group missed at least one of the inclusion

criteria. Lung diseases other than COPD (occurring in 30% of the study population, mostly bronchiectasis), long-term oxygen therapy (31%), FEV₁ (19%), age (14%), extra-pulmonary comorbidities such as cognitive impairment (14%), arrhythmias (17%), and congestive heart disease (13%) would have been the most frequent causes for exclusion from RCTs. It should be outlined that elderly patients often present with conditions that affect adherence to treatment (arthritis, cognitive impairment, changes in the mood state, polypharmacy). Taken together, these findings suggest the need for complementary studies with a pragmatic design. Pragmatic studies are clinical trials designed to assess the efficacy of a therapeutic intervention in conditions that mimic everyday clinical practice⁸. The main purpose is to address the question of how the drug works in real life. To do so, the design of the study should be simplified (using the smallest number of selection criteria), and patient-centred outcomes should be incorporated. On the other hand, pragmatic studies suffer by the limitation of extrapolating the recorded observation outside the local geographic context.

As discussed, COPD patients are commonly affected by several other comorbid conditions, which are interrelated and often shared the same risk factors. Amongst them, malnutrition is very common but at the same time not properly assessed in real life. Its prevalence has been demonstrated to increase with the severity of the disease⁹, as well as with aging, and it has been recognized as a risk factor for mortality¹⁰, suggesting that prevention and treatment of body functionality deterioration should be the main objective of nutritional interventions in these patients. Living alone, not living in one's own home, requiring daily community service are all associated with being malnourished¹¹, implying that the approach to malnutrition should also attempt to solve social issues.

Comorbidities can be distinguished in those sharing common pathways, complicating comorbidities, co-incident comorbidities, and inter-current comorbidities. Current GOLD recommendations¹ focus on the need to treat them independently of COPD, rather than on assessing their pathogenesis. As a general concept, the prevalence of comorbidities tends to increase with severity of COPD. Divo and colleagues¹² proposed an attempt to describe comorbidities with higher prevalence in patients with COPD, identifying those that are risk factors for increased mortality in COPD. In a recent investigation, Battaglia and collaborators¹³ found that, in patients with COPD some comorbid conditions such as chronic heart failure, systemic hypertension and nutritional problems seem to be influenced by the severity of the disease, whereas the occurrence of other comorbidities (coronary arterial disease, chronic renal

failure, arrhythmias, chronic liver diseases, cerebrovascular disease, depression, and diabetes) is independent from the disease. These observations could contribute to distinguish those comorbidities that are merely a consequence of COPD from those that share common pathogenetic pathways with COPD. From a clinical standpoint, proper management of COPD cannot exclude parallel treatment of comorbid conditions. The failure to do so will eventually negatively affect the natural course of the disease.

The goal of COPD therapy is to control the respiratory symptoms and to reduce the future risk of exacerbation and lung function decline. As a chronic disease, COPD requires regular treatment. Chronic airway inflammation and persistent (and progressive) bronchial obstruction represent the targets for current treatment, which is modulated on the basis of the severity of the disease. This is obtained by delivering the correct drug dosage to the site of structural and functional alterations of the lung. Inhalation is the preferred route of administration, because it optimises the delivery of active compounds to the targeted site to reduce inflammation and to relieve obstruction, while minimising side effects from systemic distribution. Therefore, the inhaler plays a crucial role in the comprehensive management of COPD, and choosing the proper device can make a difference in terms of treatment efficacy. In *real life* settings, patient training and verification of inhalation technique are necessary steps that need to be incorporated in the conventional management of the disease, as they contribute to reduce the mistakes associated with the activation of the inhalation and to improve the distribution of the drugs in the lung. This aspect is often neglected in daily practice and can negatively influence clinical outcomes. Unfortunately, guidelines are not always evidence-based regarding criteria for choosing inhaler devices, especially for elderly patients, which is therefore often based on the physician's attitude rather than the patient's preference. Probably, priority should be given to the choice of the appropriate device, based on patient needs and expectations, followed by the choice of the drug, based on the disease and its severity. A variety of inhalation devices have been introduced in clinical practice over the last decade, each differing in terms of technical characteristics, making the choice of the proper inhaler a difficult task. A consensus statement by the task force of the European Respiratory Society (ERS) and the International Society for Aerosols in Medicine (ISAM) strongly suggests to take into consideration the patients characteristics, such as patient's actuation-inhalation coordination, level of inspiratory flow, and other clinical conditions when making clinical decisions¹⁴. As an example, some inhalers require strong inspiratory force, which may not be possible in

emergency situations or in children and elderly. Ideally, each patient should have his own device, which has been demonstrated to be the most suitable, and use it for all of his inhaled therapies; this would certainly decrease the chances of making critical errors thus rendering the treatment inefficient. Differences in efficacy among devices are indeed of limited importance when correct inhalation technique is in place.

In this regard, treatment effectiveness is determined by adherence to therapy. Adherence is influenced by several factors, and the choice of the proper inhaler is among them. A device that is simple to use, easy to carry and to check can help to overcome most of the issues associated with the lack of adherence. Adherence must be distinguished from *compliance*, the difference being in the patient's willingness to accept therapy¹⁵. “Non-compliant” patients ignore prescriptions, whereas “non-adherent” patients fail to do so despite their willingness and acceptance of therapy. The unwitting non-adherence that occurs when a patient does not know the proper inhaler technique or does not understand the difference between a rescue and controller medication is common in *real life*. On the other hand, age influences unintentional non-adherence. Elderly patients with COPD often suffer from cognitive impairments, hearing or visual problems or other physical disabilities (e.g., arthritis, tremors and poor coordination) that negatively influence their ability to comply with treatments. In addition, elderly patients with COPD are characterized by a condition of multi-morbidity with consequent poly-pharmacy, and treatment complexity becomes an important contributor to low adherence. As mentioned above, the availability of several inhalers can be confusing for the patient, especially for elderly. Switching between different inhalers further negatively impacts on health care, as inhalers may considerably differ in the activation and inhalation techniques¹⁶.

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COPD pharmacological treatment: efficacy and tolerability profiles in the elderly patient. Focus on acclidinium bromide

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Chronic obstructive pulmonary disease (COPD) is expected to become the third cause of death due to continued exposure to risk factors for COPD such as cigarette smoke, to the reduction in all cause mortality and to an ageing world population. The ageing of airways and of lungs lead to structural alterations that are similar to those observed in COPD, for instance the progressive reduction in the thorax wall compliance, the reduction in respiratory muscle strength and the anatomical changes of pulmonary parenchyma and peripheral airways that in the end lead to lung hyperinflation. All these different aspects cause relevant symptoms that have a critical impact on patient's quality of life related to the health status. In this context the pharmacological treatment choice has to take into account the effectiveness in symptoms control during the most critical part of the day, such as in the morning, the capability to reduce lung hyperinflation, breaking down a vicious circle that starting from dyspnoea lead to muscle deconditioning and to an augment in exacerbation rates, with a worse prognosis. Among the new bronchodilators, acclidinium owing to its pharmacological properties and the well documented efficacy and safety profile.

Key words: COPD, Ageing, Symptoms, Quality of Life, Acclidinium, Effectiveness, Safety

INTRODUCTION

Chronic obstructive pulmonary disease (COPD) is nowadays the fourth cause of death worldwide ¹ but according to the Global Burden of Disease Study, COPD that ranked sixth as cause of death in 1990, is expected to become the third leading cause of death by 2020 ². This mortality increase is linked to the continued exposure to risk factors for COPD such as cigarette smoke, to a decrease in mortality for all causes (for instance coronary artery disease and infectious diseases) and to an ageing world population ³.

Ageing per se is a risk factor for COPD and ageing of airways and of lung lead to structural alterations that are similar to those observed in this chronic respiratory disease ⁴. In general, these changes include a progressive reduction in the thorax wall compliance, a reduction in respiratory musculature strength and anatomical alterations of pulmonary parenchyma e peripheral airways ⁵. From a clinical perspective these aspects turn into the development of a relevant symptomatic burden that

has a critical impact on Health Related Quality of Life (HRQL), compromising daily activities ⁶.

The results of ECLIPSE study (Evaluation of COPD Longitudinally to Identify Predictive Surrogate Endpoints) have shown a huge variability both in progression of FEV1 decline and in symptoms burden increase linked to functional decline (especially as regards symptoms characteristics) ⁷.

Considering this evidences, it is of paramount importance a multidimensional evaluation of COPD patients, that beyond symptoms perception takes into account physical activity reduction, pulmonary function decline and exacerbations frequency ⁶. An accurate evaluation of symptoms and their variability represents a crucial aspect in order to implement an adequate therapeutic strategy ⁶.

DAILY VARIABILITY OF COPD SYMPTOMS

Along with ageing lung residual volume increases while reserve volumes (inspiratory and expiratory) decrease

owing to a progressive loss of elastic recoil of lung tissue⁸. Typically, COPD is characterized by an increase in residual volume and a reduction in inspiratory capacity. Airflow limitation is the common denominator of this respiratory disease. The narrowing of peripheral airways reduces air flow during expiration (FEV₁)⁹. Progressive obstruction of distal airways entraps the air during expiration causing hyperinflation, which in turn decreases inspiratory capacity and increases residual functional capacity especially during physical exercise depicting a picture of dynamic hyperinflation.

In airways, parenchyma and lung blood vessels it is possible to observe typical anatomic-pathological alterations in the lung that include chronic inflammation with an increased presence of inflammatory cells (polymorphonuclear neutrophils, macrophages, CD8+ and CD4+ T cells, B cells and follicle reach lymphoid aggregates) and structural alterations caused by a process characterized by repeated damages and repairing attempts¹⁰⁻¹².

Anatomic-pathological alterations are related to a symptoms burden characterized by circadian variability. A cross-sectional, observational pan-European study that involved 2441 COPD patients in 17 Countries recruited through telephone interviews and aimed to evaluate symptoms variability in every day life during a 7 days observation period, has shown that the majority of patients (92.5%) has at least one COPD-related symptom most frequently dyspnoea reported by 72.5% of patients, followed by phlegm, cough, wheezing or chest tightness¹³ (Fig. 1).

In the study by Kessler and colleagues, 62.7% of symptomatic patients overall reported a daily or weekly perceived symptoms variability, pointing at dyspnoea as the most variable symptom during the week or during the same day. Patients reported a higher symptoms perception in the first morning hours. As a whole, the percentage of patients who reported troublesome symptoms at awakening in the morning and during the day was 45.4% as regards breathlessness, 60.1% as concerns cough, 70.9% for fatigue, 45.4% for chest tightness and 43.4% for wheezing. Night time as well has been indicated as a troublesome period for symptoms that have compromised sleep quality in 26.5% of patients¹³.

These observations confirm the results of the study by Partridge and coworkers conducted through a web survey on 803 European and American COPD patients (289 patients suffered from severe COPD). This study has shown that the morning is the worst period of the day for symptomatology onset, especially for patients with severe COPD. Breathlessness has been the most frequent symptom reported, strictly associated with morning activities limitation¹⁴.

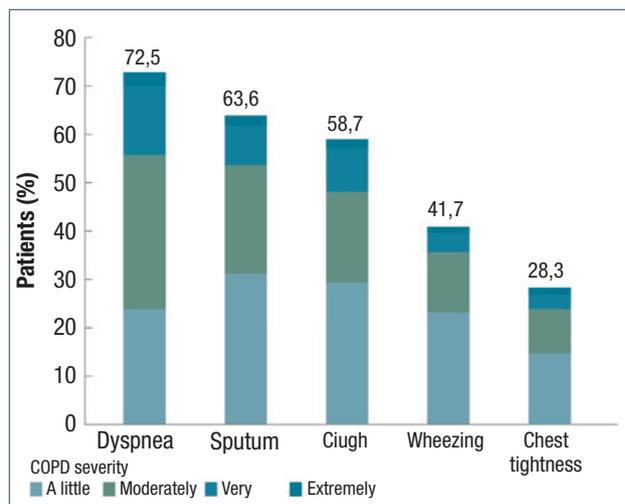


Figure 1. Symptoms variability in COPD patients: observational pan-European study (from Kessler et al., 2011¹³, mod.).

Morning and night time symptoms importance comes to light also from the results of a trial conducted in 85 centers in various European countries, that has evaluated prevalence and severity of night time, morning and day time symptoms in patients receiving treatment for stable COPD¹⁵. The study has included 727 patients (65.8% males, mean age 67.2 years, FEV₁ 52.8% of predicted). In each analyzed moment of the day (night, morning, day) more than 60% of patients reported one or more symptoms in the previous week, with a higher frequency during the morning (81.4%) and during the day (82.7%). In the week before the inclusion in the trial, 90.5% of patients suffered some symptoms at least in one part of the day; in more than half of the patients (56.7%) symptoms were present early in the morning, during the day and the night time periods while only 10.6% of the patients was symptomatic solely in one period during 24 hours.

A significant relationship ($p < 0.001$) has been shown between night, morning and day time symptoms and dyspnoea severity, sleep disturbs, anxiety or depression severity and health status.

Dyspnoea greatly contributes to the disease burden and to the poor quality of life reported by patients^{16,17}. Breathing difficulty is a consequence of a reduced respiratory capacity linked to the reduction in the lung elastic recoil, to the narrowing of airways lumen and to the increase in airflow resistance, to the expiratory flow-limitation and to the consequent static and dynamic hyperinflation. This implies a reduction in physical exercise capability and muscular deconditioning in a vicious circle¹⁸.

The dyspnoea severity is, anyway, scarcely related to FEV₁ modifications¹⁹ and this is clearly shown also by

the efficacy of bronchodilator drugs, that are able to reduce pulmonary hyperinflation, even in presence of moderately altered FEV₁ values. FEV₁ poorly correlates to quality of life, as shown by basal values of St. George Respiratory Questionnaire (SGRQ) and FV1 in 800 patients included in ISOLDE trial²⁰.

Quality of life is on the contrary strongly influenced by symptoms variability. A study in which a specific questionnaire aimed to evaluate the impact of symptoms on morning activities has been applied, showed that morning symptoms have the strongest impact on common living activities²¹, a result suggesting that treatment capable of influencing symptoms perception can potentially ameliorate HRQL²².

EXACERBATIONS AND QUALITY OF LIFE

COPD exacerbations prevention is one of the main goals of the treatment of this respiratory disease²³. Exacerbations have a heavy impact on QoL of patients as well on natural history of the disease, as clearly demonstrated in a trial by Seemungal and coworkers²⁴. In this study, 70 COPD patients (52 males, mean age 67.5 ± 8.3 years, FEV₁ 1.06 ± 0.45L, FVC 2.48 ± 0.82 L, FEV₁/FVC 44 ± 15%, FEV₁ reversibility 6.7 +/- 9.1%, PaO₂ 8.8 +/- 1.1 kPa) were followed for one year during which peak expiratory flow (PEF) was measured on a daily base. Sixtyone patients (87%) experienced 190 exacerbation overall (3 exacerbation/patient as a mean) during observation period. Each exacerbation was associated with an average fall in PEF of 6.6 l/min (p = 0.0003). Dividing the patients on the basis of exacerbations number into frequent (3-8 events) or infrequent (0-2 events) exacerbators, the Authors showed that the SGRQ total and component scores were significantly worse in the group that had frequent exacerbations: SGRQ total score (mean difference = 14.8, p < 0.001), symptoms (23.1, p < 0.001), activities (12.2, p = 0.003), impacts (13.9, p = 0.002). Factors considered predictive of frequent exacerbations were daily cough (p = 0.018), wheeze (p = 0.011), and cough and sputum (p = 0.009) and frequent exacerbations in the previous year (p = 0.001). These findings suggest that patient QoL is related to COPD exacerbation frequency. Exacerbation onset, on the other hand, is a crucial moment per se because it modifies the disease course and it is associated with a worse prognosis. Soler-Cataluna and colleagues have shown that mortality rate increases with the increase in exacerbations frequency, especially when a hospitalization is needed²⁵. The Spanish prospective study was performed in a cohort of 304 male patients with stable COPD, mean age 71 ± 9 years. The frequent exacerbators (3

or more exacerbations/year) requiring hospitalization were those with the higher mortality rate (p < 0.001) with a risk of death 4.30 times greater (95% CI 2.62 to 7.02) than that for patients not needing hospital management. The patients with 2 or less exacerbations per year had also a 2.20 times (95% CI 1.45 to 3.33) higher risk of death than those not hospitalized. Even patients with only one hospital admission had worse survival than those with no acute exacerbations of COPD (HR 2.94, 95% CI 1.82 to 4.72) (Fig. 2). The lowest survival rate was observed in patients requiring hospital readmission (HR 4.31, 95% CI 2.70 to 6.88). The observed increase in mortality following severe exacerbations requiring hospitalization is probably related to baseline severity of the disease which is linked to risk factors such as advanced patient age, hypoxaemia, hypercapnia, BMI, comorbidity, cor pulmonale, or sustained oral corticosteroid treatment.

Exacerbations are also related to lung function reduction: in patients affected by severe COPD it has been demonstrated that frequent exacerbators have a faster decline in respiratory function parameters than those who have less exacerbations during a year²⁶. A study by Donaldson and colleagues conducted on 109 COPD patients, mean age 68.1 years (63-74 years), has shown that those with frequent exacerbations (> 1.5/year) had a significant faster decline of FEV₁ and PEF of -40.1 ml/year and -2.9 l/min/year respectively compared to infrequent exacerbators (< 1.5 exacerbations/year), who experienced reduction in FEV₁ of -32 ml/year (n = 162) and in PEF of -0.7 l/min/year (n = 63) (p < 0.05 and p < 0.001 respectively).

Exacerbation that sprinkle natural course of COPD are associated with an increased risk of myocardial infarction (MI) and stroke. Donaldson and coworkers have analyzed the data of 25,857 patients included in The

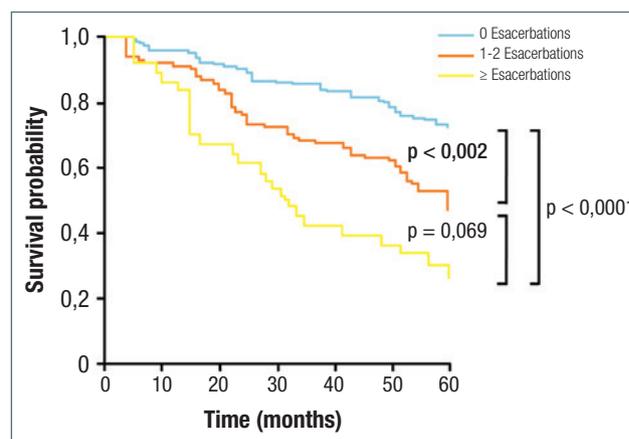


Figure 2. Correlation between exacerbations rate and risk of death in COPD patients (from Soler-Cataluna et al., 2005²⁵, mod.).

Health Improvement Network database, finding that MI risk after 1 to 5 days from an exacerbation event increased 2.27 times (95% CI, 1.1-4.7, $p = 0.03$) and stroke risk after 1 to 49 days from an exacerbation increased 1.26 times (95% CI, 1.0-1.6, $p = 0.05$)²⁷. This study proves that after exacerbation patients are at particular risk of cerebral and cardiovascular events and this aspect can have implications on COPD therapy.

Another study by McAllister and colleagues on 242 COPD patients (mean age 69 ± 9 years) hospitalized for an exacerbation showed that 1 out of 12 patients had symptoms or signs suggestive of MI²⁸.

Exacerbations repercussion on cardiovascular system springs also out from a study showing that patients with frequent moderate exacerbations have a more pronounced arterial stiffness than infrequent exacerbators; during exacerbation arterial stiffness has been shown to increase particularly in presence of airways infections²⁹. Arterial stiffness increase is also related to inflammation degree and regresses slowly in several weeks.

A more pronounced arterial stiffness increases myocardial workload requested to overcome high systolic aortic pressure and decreases coronary blood flow. The mechanism that links together airways infections, airways and systemic inflammation, arterial stiffness increase and myocardial damage has not yet been clearly defined but it may include sympathetic system hyperactivity, nitric oxide availability and endothelial dysfunction.

Airways infections play anyway a crucial role in exacerbations onset. As Papi and colleagues have demonstrated in a clinical trial conducted on 64 patients hospitalized for a COPD exacerbation, respiratory infections are associated with COPD exacerbations majority and seriousness, especially in case of viral and bacterial co-infection, present in 25% of patients, whereas an isolated viral infection has been demonstrated in 24% of patients and a bacterial infection in 30%³⁰. In an experimental model, rhinovirus infection in COPD patients has been shown to induce symptoms and lung function modifications usually observed in case of exacerbation, pointing out an evidence of a causal relationship³¹.

COPD course implies a rapid health status decline after the second severe exacerbation and a high mortality in the weeks following each severe exacerbation. Mortality related to the second severe exacerbation has been shown to be 1.9 times higher than that related to the first exacerbation and mortality related to the tenth exacerbation has been demonstrated to be 5 times higher than the first³². Two strategic goals of COPD management should therefore include the delay in severe exacerbation onset and the improvement in exacerbations treatment in order to reduce early mortality.

THERAPEUTIC MANAGEMENT OF ELDERLY PATIENT

According to the Global Initiative for Chronic Obstructive Lung Disease (GOLD) recommendations in order to properly define the influence of COPD in each patient it is necessary to implement a combined evaluation approach that put together symptoms burden with spirometric results and/or exacerbation risk²³. This approach, along with the evaluation of potential comorbidities, reflects COPD complexity in a better way than a monodimensional analysis such as the airflow limitation previously used to stage the disease and lays the foundations for a tailored treatment choice.

COPD pharmacologic therapy has the goals to reduce symptoms burden, exacerbation frequency and severity, to ameliorate patient's global health status and tolerance to physical strain²³.

Bronchodilators are the cornerstone in the pharmacological treatment of COPD³³. These drugs allow pulmonary desufflation, a lung volumes reduction both in static and dynamic conditions, a dyspnoea reduction both at rest and during exercise and an increase in physical exercise tolerance.

A crucial aspect of COPD treatment is exacerbation prevention and this regards it must be said that available pharmacologic options have shown to be effective. In TORCH study, for instance, the combination regimen of salmeterol at a dose of 50 μg plus fluticasone propionate at a dose of 500 μg twice daily administered with a single inhaler in a 3 years period significantly reduced exacerbations frequency compared to placebo and compared to single therapies (from 1.13 to 0.85 exacerbations/patient/year combination regimen vs placebo, $p < 0.001$; from 0.97 to 0.85 exacerbations/patient/year combination regimen vs salmeterol, $p = 0.002$; and from 0.93 to 0.85 exacerbations/patient/year combination regimen vs fluticasone, $p = 0.0024$), though combination regimen did not significantly reduce all cause mortality compared to placebo (95% CI 0.681-1.002, $p = 0.052$)³⁴.

The combination of budesonide/formoterol 160 μg /4.5 μg bid has also demonstrated to reduce the exacerbations number compared to monotherapies and to placebo (all $p < 0.005$) and to stabilize respiratory function³⁵.

In another trial, a combination of an inhaled corticosteroid (ICS) and a long acting beta₂-adrenergic agonist (LABA) reduced by 24% the mean exacerbation number per patient per year compared to placebo and by 23% compared to formoterol, while increased FEV₁ by 15% versus placebo and by 9% versus budesonide³⁶. In both studies the combination regimen has significantly improved the overall symptomatology compared to single therapies, while SGRQ score was reduced more

than 4 points – considered as a cutoff value for a perceived beneficial effect of therapy by patients – only in the study by Calverley (-7.5 points) but not in the one by Szafranski (-3.9 points).

A relevant aspect concerns the onset of adverse events (AE). In TORCH study 41% of patients developed a severe EA, in most of the cases related to an exacerbation. These considerations must be taken into account especially for the treatment of elderly patients, who frequently are included in groups B and D – that is more symptomatic patients – according to combined evaluation criteria of GOLD recommendations. In these patients it is of particular usefulness the administration of bronchodilator agents that allow a good symptoms control along the whole day and especially during the morning, with a good safety profile.

In treatment choice it is important to consider that the faster is the pharmacological effect onset of a therapeutic agent the greater is the impact on morning symptoms, with positive consequences on HRQL⁶. The rapid action onset bronchodilators nowadays available, including LABAs such as formoterol and indacaterol, and LAMAs, such as glycopyrronium and acclidinium, could play a key role in the improvement of morning symptoms control symptoms and HRQL in COPD patients⁶.

Acclidinium, in particular, is a long acting muscarinic antagonist with a new chemistry structure that contains a (3R)-quaternized quinuclidine ester. It is important to remember that the parasympathetic activity in respiratory airways induces smooth muscle cells contraction and mucus secretion. These effects are mediated by the action of acetylcholine (ACh) on M₃-type receptors. By contrast, ACh action on M₂-type receptors inhibits the release of more ACh from nerve endings. This in turn causes a reduction in free ACh available to a link to M₃-type receptors, inhibiting this way smooth muscle cells contraction³⁷.

Acclidinium exerts its effects through a selective antagonism on M₃-type receptors.

This molecule has a long residency half-life at the M₃ receptor; the slow dissociation time prolongs the action of the drug. On the contrary, acclidinium has a short residency half-life at the M₂ receptor, thus showing a kinetic M₃/M₂ selectivity³⁸.

Acclidinium is rapidly hydrolyzed in human plasma with an half-life of 2.4 minutes, where more than 70% of tiotropium or ipratropium are not modified in human plasma after a 60 minutes incubation³⁹. Acclidinium has shown good efficacy and safety profiles in clinical trials. In the double-blind ATTAIN trial, 828 patients with moderate or severe COPD were randomized (1:1:1 ratio) to receive acclidinium 200 µg or 400 µg BID or placebo for 24 weeks⁴⁰. The primary efficacy endpoint was

the change from baseline in morning pre-dose (trough) FEV₁ at week 24.

Acclidinium 200 µg and 400 µg BID significantly improved trough FEV₁ compared with placebo ($p < 0.001$ for both). The magnitudes of the improvements over placebo were 99 mL and 128 mL for the 200 µg and 400 µg doses, respectively (Fig. 3).

Pre-dose morning FEV₁ improvement with both acclidinium dosages was significantly greater compared to placebo in each time interval from Week 1 to Week 24 ($p \leq 0.0001$ for all).

A modification from baseline in mean SGRQ total score during study period was a secondary endpoint. A reduction ≥ 4 units represents a clinical significant improvement. At week 24, the improvement over placebo in baseline-adjusted mean SGRQ total score was -3.8 units for acclidinium 200 mg ($p < 0.001$) and -4.6 units for acclidinium 400 mg ($p < 0.0001$). The most frequently reported AE was exacerbation of COPD ($n = 16$; 1.8%) and the incidence was higher in the placebo group than in the acclidinium 200 µg and 400 µg groups (3.7%, 1.4% and 0.7%, respectively). Potential anticholinergic AEs occurred at a similar low incidence ($< 2.5\%$ of patients) in each treatment group. Acclidinium has shown a favourable cardiovascular safety profile.

In the phase IIa randomized, double blind, crossover LAS-23 trial, 30 patients with moderate to severe COPD received acclidinium 400 µg bid, tiotropium 18 µg once daily, and placebo for 15 days, with a 9 to 15 day wash-out between three treatment sequences⁴¹. On day 1 the variation from baseline in normalized FEV₁ AUC_{0-12/12} was significantly greater with acclidinium 400 µg compared to placebo (230 mL vs 16 mL; $p < 0.0001$). Acclidinium 400 µg induced a significantly greater bronchodilation than placebo in each time sequence considered on day 1 ($p < 0.001$). On day 1 acclidinium 400 µg induced also a significantly greater bronchodilation compared to tiotropium during night time (13-22 hours after morning dose administration) ($p < 0.05$). Difference in FEV₁ AUC_{0-12/12} of acclidinium and tiotropium was 101 ml ($p < 0.01$) on day 1 (Fig. 4).

On day 15 as well the variation from baseline in normalized FEV₁ AUC_{0-12/12} was significantly greater with acclidinium 400 µg compared to placebo (236 mL vs 15 mL; $p < 0.0001$).

Acclidinium 400 µg induced also a significantly greater bronchodilation compared to tiotropium during night time (13-22 hours after morning dose administration) on day 15 ($p < 0.05$).

Difference in FEV₁ AUC_{0-12/12} of acclidinium and tiotropium was 78 ml ($p < 0.05$) on day 15.

It has been shown in different conditions that a poor sleep quality deteriorates health status. A study conducted on 2,848 COPD patients managed in a

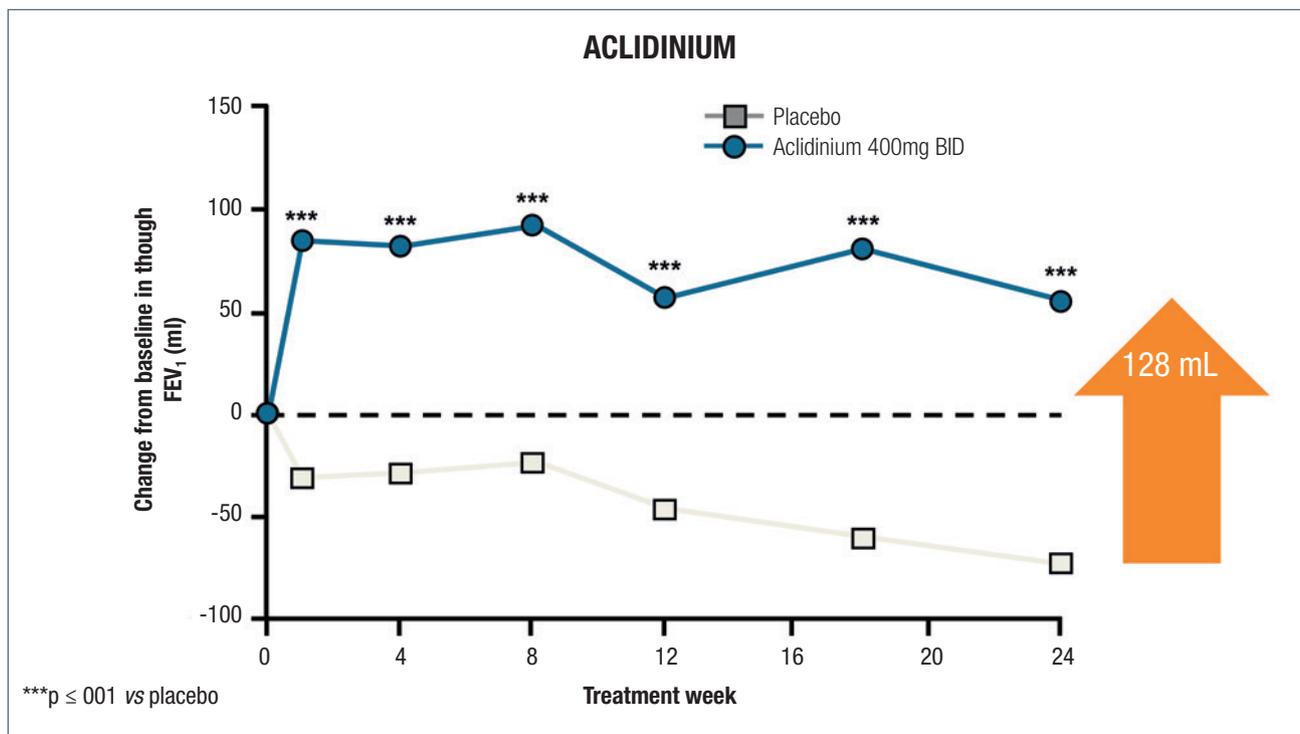


Figure 3. ATTAIN study: FEV₁ improvement due to acclidinium 400 µg (from Jones et al., 2012³⁹, mod.).

primary care setting revealed that 67% of patients had symptoms during the night⁴². The percentage of patients with nocturnal symptoms increased with the worsening of COPD. Patients who experienced symptoms during the night and the morning had a more severe daytime dyspnea and an increased exacerbations rate than patient with only daytime symptoms. Furthermore, patients with both nocturnal and diurnal symptoms needed more maintenance therapies compared to those with only with daytime symptoms. ACCORD COPD1 study has demonstrated that acclidinium improves nocturnal symptomatology⁴³. In this double-blind study, 561 patients were randomized (1:1:1) to receive for 12 weeks acclidinium 200 µg or 400 µg twice daily (BID) or placebo. Primary efficacy endpoint was the variation from baseline in pre-dose morning FEV₁ (trough) on week 12. Acclidinium at both dosages significantly improved pre-dose morning FEV₁ compared to placebo ($p < 0.001$ for both dosages). The improvement amount compared to placebo was 86 ml with 200 µg and 124 ml with 400 µg. Nocturnal and early morning symptoms were registered each morning with COPD nocturnal symptoms questionnaire, filled by patients themselves through an electronic log. On week 12, treatment with acclidinium 200 µg and 400 µg significantly reduced mean daily nocturnal COPD symptoms frequency (night dyspnea, cough, sputum production

and wheezing) compared to placebo ($p < 0.05$, 200 µg and $p < 0.01$, 400 µg). Morning symptoms improved significantly as well (Figg. 5, 6).

Secondary endpoint was the percentage of patient with a clinical significant improvement in SGRQ total score (clinical relevancy for a modification of ≥ 4 units from baseline) on week 4, 8 and 12. Both acclidinium dosages produced a significant improvement from baseline in SGRQ total score on each time point ($p < 0.05$ for all). The treatment was well tolerated. The incidence of anticholinergic AEs was low and similar across groups (dry mouth: 0.5%-1.6%; constipation: 0%-1.1%). Exacerbation onset was observed in 12.4% in placebo group, in 9.2% in acclidinium 200 µg group and in 7.4% in acclidinium 400 µg group.

An effective and persistent bronchodilation is a key point in order to improve dyspnoea and physical performance in COPD patients²³. The combination of LABA and LAMA at low doses can optimize the bronchodilation both in patients with a less severe disease by reducing the risk of adverse events related to single agents at full dose, and in severe COPD patients not controlled by monotherapy⁴⁴.

Fixed dose combinations (FDC) of bronchodilators with different mechanisms of action, administered via the same inhaler allow a higher efficacy not only owing to the optimization of bronchodilation linked to a synergistic

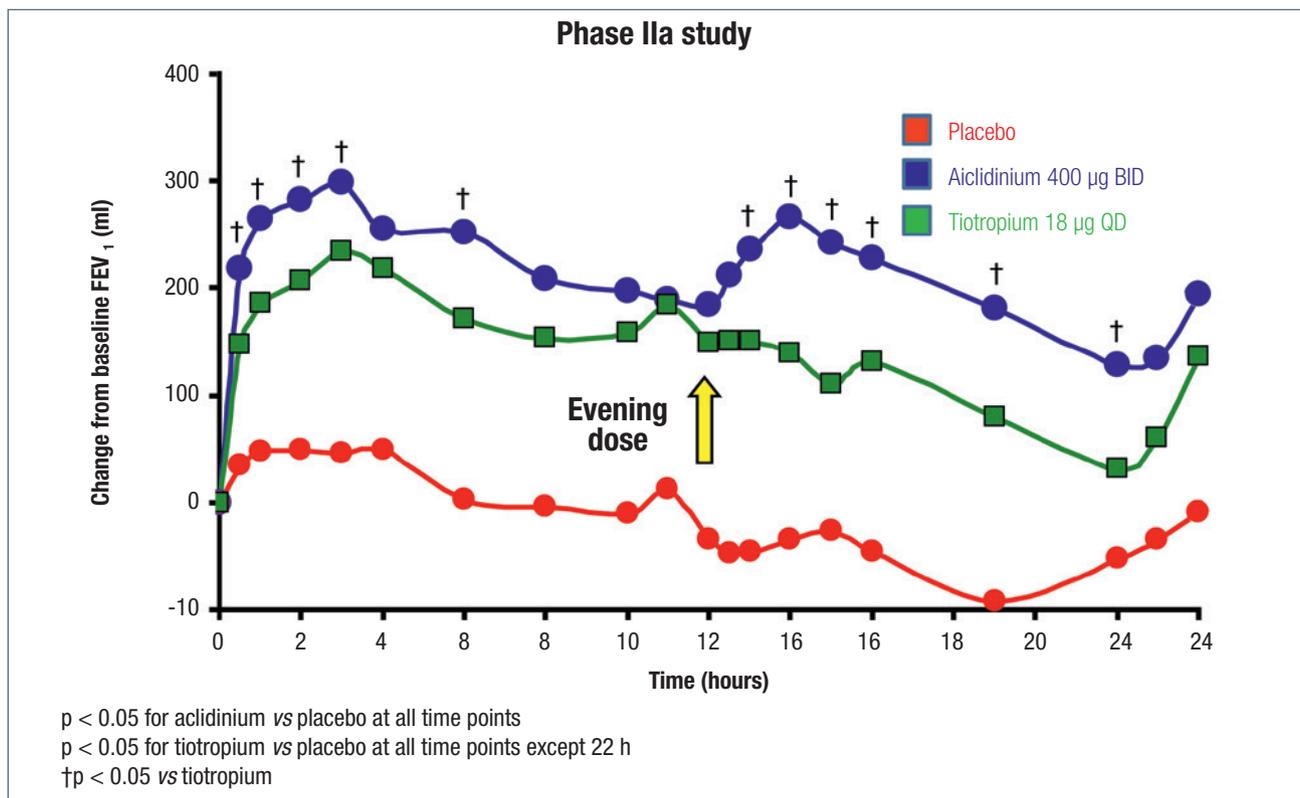


Figure 4. FEV₁ improvement induced by aclidinium compared to tiotropium and placebo on the first day of administration (from Fuhr et al., 2012⁴⁰, mod.).

effect of the single components, but also in the name of a possible enhancement in therapeutic adherence deriving from a simplification in therapy. The pharmacological mechanism that supports an association of more bronchodilators is complex and has to be found in the mutual influences between the cholinergic and the adrenergic systems at pre- and post-synaptic level. This mechanism includes the activation of the β_2 -Adrenergic receptor (β_2 -AR) from β_2 -agonist agents and the blockade of M3 post-synaptic receptors mediated by anticholinergic agents⁴⁵.

The intracellular strictly interconnected cross-talk between β_2 -AR and muscarinic pathway explains the synergistic effects on airways smooth muscle relaxation observed with the combination LABA/LAMA both in ex vivo human bronchi studies and in vivo in COPD patients^{46,47}.

Among the available FDCs, the one between aclidinium bromide and formoterol fumarate administered via the single inhaler Genuair offers numerous advantages compared to single agents separately or simultaneously administered through different inhalers.

Aclidinium bromide and formoterol fumarate act synergistically with a rapid onset of bronchodilation 5 minutes after administration⁴⁷.

The study on interaction between aclidinium and formoterol, in particular, has shown a synergistic interaction that induces a fast effect onset after only 5 minutes after administration ($p < 0.001$) and from 120 to 240 minutes after administration ($p < 0.05$) and an additive interaction in the time interval of 30 to 60 minutes after administration. Compared to the effect of single components, the FDC induced a synergistic effect with a variation in FEV₁ of $+55,14 \pm 14,34\%$ after 5 minutes and a $+32,86 \pm 15,73\%$ between 120 and 240 minutes after administration⁴⁷.

The results of this study show that the combination aclidinium/formoterol produces a synergistic interaction both ex vivo in human bronchi studies where it induced the airways smooth muscle relaxation and in vivo in COPD patients with an increase in FEV₁. The synergistic effect plays an important role in the clinical management of COPD, because it allows the optimization of bronchodilation combining low doses of drugs with different mechanisms of action⁴⁷.

This FDC has to be administered twice daily and this allows the symptoms control in the first morning hours, thus preserving a good quality of life (QoL) of patients, owing to the rapid improvement of FEV₁ after

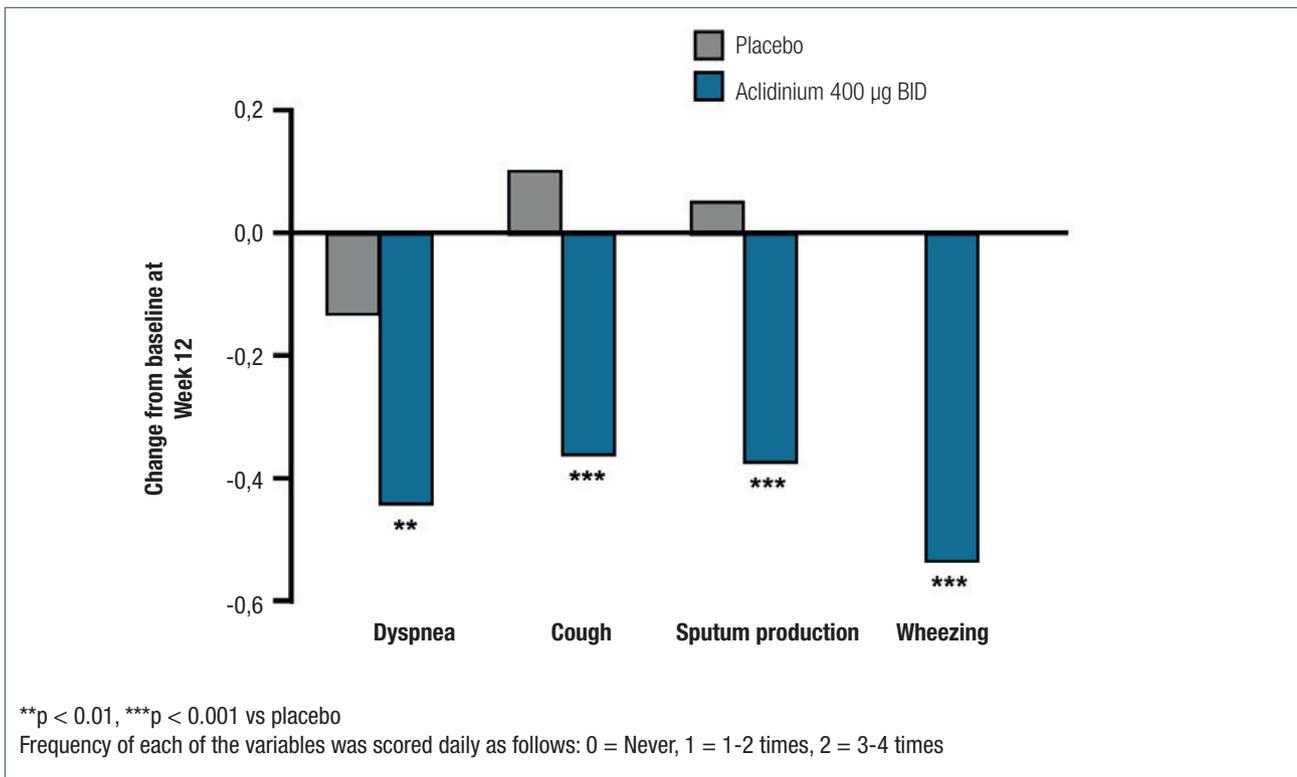


Figure 5. ACCORD COPD 1 Study: improvement induced by acclidinium in nocturnal symptoms (from Kerwin et al., 2012⁴², mod.).

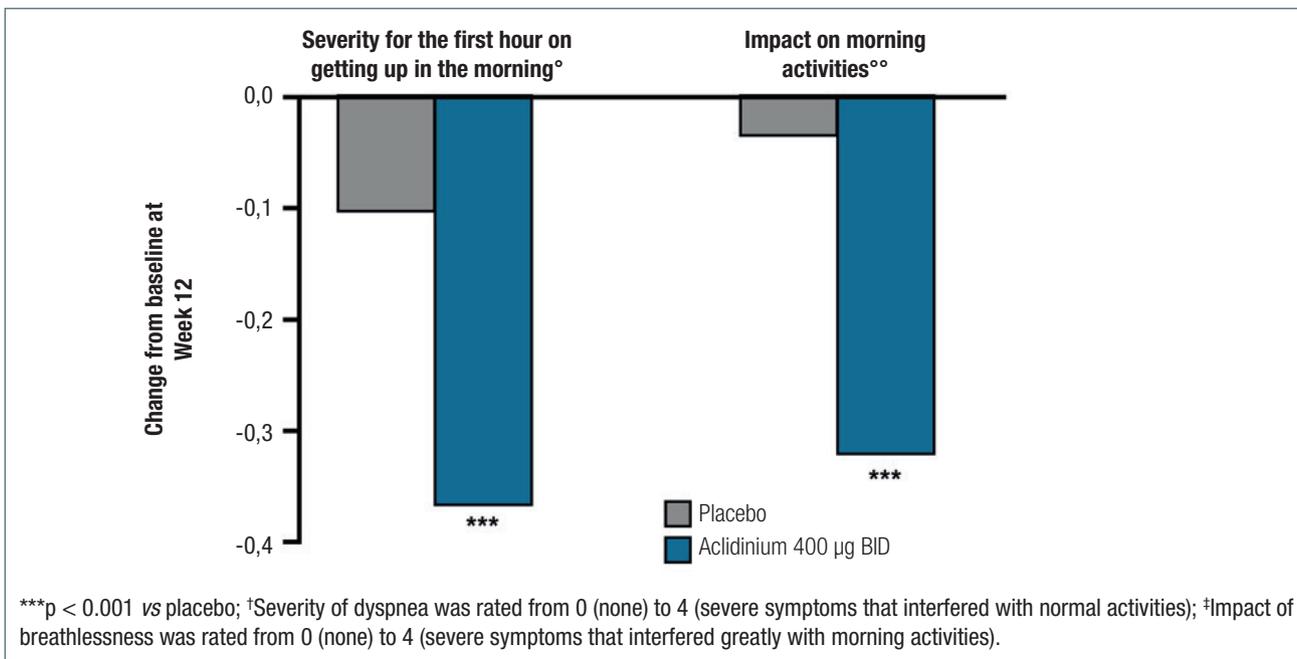


Figure 6. ACCORD COPD 1 Study: improvement induced by acclidinium in morning symptoms (from Kerwin et al., 2012⁴², mod.).

administration⁴⁹. A clinical dose-response study conducted in patients with stable moderate-severe COPD (n = 566) to evaluate efficacy, safety and pharmacokinetic

of three different formoterol dosages (6, 12, e 18 µg) in association with acclidinium bromide 200 µg, in comparison to monotherapy with acclidinium bromide 200

µg, and formoterol 12 µg or placebo has shown better improvements in respiratory parameters with the combination compared to monotherapies or placebo. The differences were significant for all the combinations compared to monotherapies and to placebo ($p < 0.01$)⁴⁹.

Efficacy and safety of acclidinium/formoterol FDC were evaluated in two wide clinical studies, ACLIFORM COPD study (ACLIdinium FORMoterol-COPD)⁵⁰ and AUGMENT COPD study (Acclidinium/formoterol fUmarate combination for investiGative use in the treatment of moderate-to-severe COPD)⁵¹.

As regards efficacy on lung functions, at week 24 acclidinium/formoterol 400/12 mg FDC has produced higher improvements in trough FEV₁ from baseline values than placebo (least mean squares: 143 mL; $p < 0.001$), a clinically significant result because greater than 100 mL. The variation in trough FEV₁ compared to formoterol was 85 mL at each timepoint ($p < 0.001$), which is in the range observed with different LABA/LAMA FDCs (70-95 mL)^{50 51}.

Acclidinium/formoterol 400/12 µg FDC significantly improved peak FEV₁ by 334 mL vs placebo and single agents, with a bronchodilation onset within 5 minutes from first inhalation, statistically significant compared to placebo and to acclidinium ($p < 0.05$) and similar to formoterol^{50 51}.

Acclidinium/formoterol FDC showed a significant efficacy also in dyspnoea (TDI) and QoL (SGRQ). Acclidinium/formoterol 400/12 µg induced a long lasting improvement in TDI of 1.4 units compared to placebo ($p < 0.01$) which is beyond the clinically significant threshold (MCID > 1 unit). At 24 weeks, Acclidinium/formoterol 400/12 µg improved significantly the TDI by 0.4 units vs formoterol ($p < 0.01$) and by 0.44 units vs acclidinium ($p < 0.05$)^{50 51}.

The aggregated data analysis showed that FDC produce a clinically significant improvement in SGRQ of 4.4 units compared to placebo ($p \leq 0.001$)^{50 51}.

The efficacy of FDC on symptoms control during the whole day was evaluated through some questionnaires: the EXacerbations of Chronic obstructive pulmonary disease Tool- Respiratory Symptoms (Exact-RS), the Early Morning Symptoms COPD (EMSCI) and the Nighttime Symptoms of COPD (NeSCI) questionnaire.

Acclidinium/formoterol showed an improvement in daily COPD symptoms (dyspnoea, cough, wheezing and sputum) compared to placebo, acclidinium and formoterol ($p < 0.05$) (evaluated with E.RS total score)^{50 51}.

The FDC produced an improvement in early morning symptoms vs placebo ($p < 0.001$), acclidinium ($p < 0.001$) and formoterol ($p < 0.01$) and in night symptoms vs placebo, acclidinium and formoterol ($p < 0.05$)⁵² in COPD.

The morning symptoms improvement implies a lesser

limitation in daily activities. Acclidinium/formoterol was more effective compared to monotherapies in terms of dyspnoea, morning and night symptoms severity and limitation in daily activities also in less symptomatic patients⁵³.

In a post hoc analysis of registrative trials, acclidinium/formoterol FDC significantly reduced by 29% moderate and severe exacerbations compared to placebo ($p < 0.05$)⁵².

In the AFFIRM study, in which acclidinium/formoterol and Fluticasone/Salmeterol (Flu/Salm) FDCs were compared in a non inferiority secondary endpoint, the LABA/LAMA FDC 400/12 µg produced an improvement in exacerbation rate similar to Flu/Salm (37.8% and 39.5% respectively)⁵⁴.

A crucial aspect in the efficacy of inhalatory therapy is the device used. A systematic review of literature data showed that a lot of patients don't use properly their inhaler due to a miscorrect inhalatory manoeuvre⁵⁵. It is thus necessary not only to develop new inhalers but also to favour an easiness of their use, especially in particular populations of patients, such as the elderly⁵⁶.

The recently developed Genuair[®] inhaler has peculiar technological innovations that improve both performance and safety. The use of the Genuair[®] inhaler was associated with a patients preference (percentage of patients: 79.1% vs 20.9%; $p < 0.0001$) and an overall satisfaction significantly greater compared to HandiHaler[®]⁵⁷.

The percentage of patients that made one or more critical error in the device use was significantly lower with Genuair[®] than with HandiHaler (2.9% vs 19%; $p < 0.0001$)⁵⁸.

The Genuair[®] inhaler is also preferred by patients compared to Breezhaler[®] (percentage of patients: 72.7% vs 27.3%; $p < 0.0001$), with a greater satisfaction (mean score 5.9 vs 5.3; $p < 0.0001$). A lower number of critical errors was observed with Genuair[®] (2.4%) vs Breezhaler[®] (6.5%)⁵⁸.

The Genuair[®] inhaler was considered more practical and easy to handle: in a population of 626 elderly patients, 90% favoured the device after reading the patient information leaflet. This percentage increased to 96% among the patients who already used an inhaler and was 91% among patients with hand arthritis⁵⁹.

CONCLUSIONS

COPD is a heterogeneous and complex disease that affect mainly the elderly, representing one of the most prominent problem globally in health care systems, owing to the progressive ageing of the population. COPD exacerbations implicate the heavier socio-economic burden of this disease.

Frequent exacerbators have higher mortality rate, a worse QoL and a faster decline in pulmonary function compared to not frequent exacerbators. Exacerbations are associated with an increased airways and systemic inflammation and with patho-physiological alterations that cause hyperinflation. These episodes that characterize COPD in a heterogeneous fashion are related to viral and bacterial infections accountable of a worsening of the inflammation. It is thus of paramount importance to delay the most that is possible the exacerbation onset, guaranteeing to the patient a good symptoms control during the whole day, allowing him to stay active and counteracting the vicious circle that from dyspnoea leads to reduced exercise capability and to the muscle deconditioning with a worsening of QoL. An effective, rapid onset and long lasting bronchodilation such as the one obtained with aclidinium bromide as monotherapy and more as fixed dose combination with formoterol can be a valid pharmacologic help to give an adequate answer to the unmet patient need still there nowadays.

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Therapeutic compliance in elderly patients with COPD

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The problems of therapeutic adherence are very frequent in the elderly. Compliance to drug therapy in COPD is much lower than that of other common diseases such as diabetes, osteoporosis, hypertension. Major predictors of poor adherence to medication are presence of psychological problems, presence of cognitive impairment, treatment of asymptomatic disease, inadequate follow-up or discharge planning, side effects of medication, patient's lack of belief in benefit of treatment, patient's lack of insight into the illness, poor provider-patient relationship, presence of barriers to care or medications, missed appointment, complexity of treatment, cost of medication, copayment or both.

Number of daily administration and rapid onset of the effect of the drugs may affect compliance with therapy. Comorbidity can affect adherence to therapy because more factors may interfere with drugs assumption (mental impairment, depression, visual impairment, functional limitations related to arthritis, cerebrovascular disease, parkinsonism).

Polypharmacy can also adversely affect compliance.

Another factor that significantly influences therapeutic compliance is the devices management.

Key words: Compliance, Therapy, COPD, Elderly

Instead of the term compliance that expresses passivity by the patient, today we use the term adherence that implies active involvement of the patient in sharing with the therapeutic choices of his physician.

The problems of therapeutic adherence are very frequent in the elderly. This is also confirmed for COPD (14.3% of adherence to treatment in Italy according to the Report OsMed 2013, against 38.4% for depression, 55.1% for hypertension, 62.1% diabetes mellitus). Compliance to drug therapy in COPD is much lower than that of other common diseases such as diabetes, osteoporosis, hypertension¹.

Data from the international literature shows that adherence to treatment in COPD is less than 50% including drug therapy, O₂-therapy and rehabilitation².

Poor adherence to therapy includes:

- "overuse" (typical of exacerbations);
- "underuse" (typical of mild-moderate COPD in which low intensity of symptoms, besides progressive reduction in physical activity, induces the patient to do without therapy);
- "improper use" (typical of elderly patient and often due to difficulties in devices management).

Major predictors of poor adherence to medication are presence of psychological problems, presence of cognitive impairment, treatment of asymptomatic disease, inadequate follow-up or discharge planning, side effects of medication, patient's lack of belief in benefit of treatment, patient's lack of insight into the illness, poor provider-patient relationship, presence of barriers to care or medications, missed appointment, complexity of treatment, cost of medication, copayment or both³. It is known as some features of the pharmacokinetics of the drugs may affect compliance with therapy. For example, the number of daily administrations are inversely related to compliance; as well as the rapid onset of effect of the drug is directly related to compliance¹. Another factor that affects compliance is the comorbidity. It is known that there are clusters that characterize the distribution of chronic diseases. Ischemic heart disease and thyroid dysfunction are associated with each other as first aggregation, to COPD as a second aggregation, to arterial hypertension, heart failure, atrial fibrillation and cerebrovascular disease as final cluster⁴. COPD is also associated with other conditions such

as diabetes mellitus, renal failure, osteoporosis, mood disorders, cognitive impairment. Comorbidity can affect adherence to therapy because more factors may interfere with drugs assumption (mental impairment, depression, visual impairment, functional limitations related to arthritis, cerebrovascular disease, parkinsonism). In addition, the presence of cardiovascular comorbidities may limit the prescription long-acting bronchodilators. However the literature have demonstrated the safety of this class of drugs on the cardiovascular profile. Polypharmacy can also adversely affect compliance. It is known in literature as the number of drugs taken can negatively affect compliance regardless of the type of drugs taken. Another factor that significantly influences therapeutic compliance is the devices management. There are two principal types of devices: pressurized Metered Dose Inhalers (pMDI) and Dry Powder Inhalers (DPI).

pMDI have a low cost, are easy to handle and to use but require a good hand-breathe coordination and can cause pharyngeal deposition. When used with spacers require less coordination but have a higher cost, are less transportable and their use is more complex. DPI require less hand-breathe coordination, are easy to handle and to transport, but require high flow (> 30 l/min.), can induce cough and are difficult to preserve in wet weather.

Inhaling techniques are always inadequate also in adult patients. A lot of patients do mistakes using inhalers devices.

Inhaling technique are often wrong even in adult people. A lot of patients do mistakes while using inhalers. Common mistakes in pMDI use include failure to shaking before use, failure to breathe holding by patient at the end of inspiration, lack of coordination between drug delivery and inhalation, inhalation through nose, interruption of the inspiration for "freon effect".

A characteristic of the devices which adversely affects the effectiveness of the inhalation is the internal resistance to the air flow (which has decreasing values from HandiHaler, to Turbohaler, to Diskus, to Breezhaler) ¹.

The factor that most affects the improper use of devices inhalers is cognitive impairment. In a paper published in 2006 the MMSE score (< 24 or > 23) distinguished significantly patients who used an adequate or inadequate inhaler technique ⁵.

Always in this study, the ability to perform correctly the pentagon test discriminated patients able to properly use the inhaler device. In another study a score at the Mental Deterioration Battery less than 4, a test of immediate Rey test below 35, a score of delayed Rey test less than 7, discriminate patients with poor therapeutic adherence ⁶.

When prescribing an inhalation device to an elderly patient there are some questions that should be done:

- Is it easy to take with you? Is it easy to grip?
- Is it easy to hold in your hand while inhaling medication?
- Does it have the right size, making it easy to handle?
- Is the cap covering the mouthpiece easy to take off?
- Is the mouthpiece easy to hold in mouth when you inhale?
- Is it easy the functioning? Is it easy to make the inhalation? Is it easy to load a dose?
- Is the click of drug loading heard clearly? Is it easy to see if the drug was taken correctly?
- Is the cap that covers the mouthpiece easy to reclose after use?

An Italian survey made in 2014 (progetto FARE, SIGG 2014), involving 526 subjects aged more than 65 years, representative of the Italian population, with an additional samples of 100 patients affected by arthritis of the hand, showed how generic is a device simple

Correct step of inhalation technique	Checklist of inhalation technique errors	Errors, % of users
Remove mouthpiece cap	Failure to remove cap	0.15
Shake inhaler (suspensions only)	Not shaking the inhaler	37
Breathe out before firing	No exhalation before actuation	50
Inhaler upright during firing	Not holding the inhaler in the upright position	9
One inhalation for actuation	More actuations for a single inhalation	19
Place mouthpiece between lips and over tongue	Actuation against teeth, lips, or tongue	0.7
Actuation in the first half of inhalation	Actuation in the second half of inspiration	18
Fire while breathing in deeply and slowly and continue until total lung capacity	Actuation after end of inhalation	5
Inhalation by mouth	Stopping inhalation immediately after firing	10
Hold breath for 10 s	Forceful inhalation	52
	Inhalation through nose whilst and after actuation	2
	No or short (less than 2-3 s) breath-holding after inhalation	53

Table II. Step-by-step DPI checklist of proper inhalation technique and errors recorded in our population (from Melani et al., 2011⁸, mod.).

Correct step of inhalation technique	Checklist of inhalation technique errors	Errors, % of HandiHaler/aerolizer [®] use	Errors, % of diskus users	Errors, % of turbuhaler
Remove or turn cover Correctly insert capsule Pierce capsule	Failure to open the device			
	Failure to insert the capsule			
	Failure to pierce the capsule			
Load dose	Failure of loading	0	0,65	0
	Incorrect dose loading	9	NA	NA
Hold inhaler upright	Keep the inhaler inclined no more than 45 from the vertical axis during loading	3	NA	NA
	Exhaling into the device mouthpiece after loading	NA	7,3	14
Breathe out the device mouthpiece	Exhaling into the device mouthpiece after loading	NA	NA	23
	Stopping inhaling prematurely (not inhaling to TLC)	19	22	14
Inhale by mouth	Inhaling by nose	26	29	22
	Not sealing lips around mouthpiece during inhalation	2	1	0
		5	5	4
Forceful and deep inhalation	Slow and not forceful inhalation	24	28	22
	Exhaling into the device mouthpiece after inhalation	19	21	11
Breathe out the device mouthpiece	Exhaling into the device mouthpiece after inhalation	25	32	28
	No breath-holding after inhalation			
Breath-hold	Do not control whether some powder drug rests into the capsule after inhalation	30	NA	NA
Control if capsule is broken and does not contain residual powder				

to be used even by very old people and with hands problems. Genuair is an intuitive device and includes several feedback mechanisms that ensure the patient the correct inhalation of the drug. These elements could be an advantage in improving compliance of the elderly patient to inhalation therapy.

There is now shared documentation that the poor adherence in COPD treatment leads to increased mortality, increased hospitalization and reduction in quality of life. According to data presented at the symposium "Patient's adherence to therapy," held in 2013 in Milan by the company SIMER-SIAIC-AAIYO, failure/incorrect use of inhaled medications involves:

- 20% increase in the likelihood of exacerbations;
- 50% increase in spending on the treatment of COPD (2723 Euros/year/patient).

When prescribing inhaled therapy to elderly patients in real life you have to take into account that he is a frail patients with problems of comorbidity (especially over 75 years of age), polypharmacy, cognitive impairment, mood disorders, osteoporosis/osteoarthritis, sarcopenia, functional limitations, socio-economical difficulties and often with poor hand-eye coordination that limits his ability to press the spray and breathe at the same time. The multidimensional approach in

the management of COPD treatment in the elderly can be useful in terms of quality of life, lung function, reduction of exacerbations and therapeutic compliance⁷. Researchers from the Cochrane Collaboration have recently proposed an updated overview summarizing the findings of 75 systematic reviews published until March 2012 on "Cochrane Database of Systematic Reviews" and "Database of Abstracts of Review of Effect" concerning both acute and chronic diseases in different populations and contexts Overall, the study results suggest that there are many potential paths to optimize the use of drugs, but there is not an effective one for each disease, population or environment. The collaborative approach is likely to have the best results in improving compliance with therapy in the COPD treatment in elderly patient¹.

Three seem the cornerstones for a correct approach to this problem: 1. Simultaneous involvement of the patient, family members, caregivers, pharmacists and general practitioners; 2. Closed follow up to evaluate the adherence to therapy; 3. Counselling. The role of the family members is essential for the adherence to therapy in elderly patient as they remind patient to take his medicine correctly. Equally important is the role of the general practitioner who often manages

Table III. Number of subjects with adequate or inadequate turbobalmer technique when retested the day after training in comparison with their MMSE score (n = 50) (from Board et al., 2006⁵, mod.).

Adequate technique	Inadequate technique		
MMSE < 24	3	13	
MMSE >23	25	9	< 0.0001

Table IV. Relationship Between Medication Adherence and the Main Cognitive Indexes (from Antonelli Incalzi et al., 1997⁶, mod.).

Medication adherence	Good (n = 25)	Poor* (n = 17)	χ^2	p
MDB < 4	7	13	7.7	< 0.006
Immediate recall < 35	11	12	1.91	0.16
Delayed recall < 7	9	14	7	0.008

*Poor medication adherence was diagnosed if the patient forgot to take his or her prescribed medications at least twice in week.

exacerbations without taking into account the underlying disease (COPD) and its treatment. Instead, given the frequent contact with his client, its role is just to verify adherence to therapy, without delay each time to a specialist consultation that would lead to unnecessary losses of resources and time. In the early days after the diagnosis of COPD, the general practitioner should provide for a close follow-up because the benefit of treatment may not be immediately perceived by the patient, and at this stage can arise conflicts between doctor and patient on the necessary lifestyle changes (smoking cessation). All these objectives are realized in a counseling activities directed to the patient and family, the effectiveness of which is proportional to the time spent talking to and listening the patient. A recent systematic review of the researchers of the Cochrane Collaboration has shown promising results from the involvement of pharmacists in the management of drug therapy. In order to increase the patient's adherence to therapy it is necessary: 1. to raise awareness and inform the patient to take consciousness and accept their disease state; 2. to establish a easy regimen of therapy; 3. to educate patient to follow a correct lifestyle, to make the training on the use of the device, to remind him to keep the therapeutic adherence. Because COPD is a disease that in most cases has poor symptoms, the patients should be aware of the importance of being adherent. Approximately 9% of diagnosis of COPD are made when the disease is severe or very severe, and 25-30% when the disease is moderate. It would be, however, desirable that even the less severe patients had knowledge of having a disease that leads to serious consequences both functional and prognostic, like other diseases such as diabetes mellitus and arterial hypertension who need treatment for the whole life. Establishing a simplified regimen of therapy is certainly important, by

eliminating unnecessary drugs. Regimes that provide for the one-two administration are useful. Using programs for self-management therapy including papers, electronic supports, memo packaging can improve therapeutic adherence. Often you need to provide suggestions, seemingly trivial, that enable the patient to enter COPD therapy in their daily routine. At the same time it's necessary a training of the patient for proper use of devices. It would be useful and fruitful to take a few minutes to make sure the patient has really understood the correct use of the device, having the patience to wait for the patient to perform the tests in the presence of the doctor and, when possible, even of the relatives who live with him. It 'also essential adherence to follow-up, making the patient aware about the importance of returning to close controls for the necessary findings of efficacy, tolerability and adherence to treatment. In conclusion, a primary goal of COPD treatment is that it is taken correctly and continuously. As demonstrated by large studies such as the TORCH, this allows to achieve important results in terms of: 1. Quality of life; 2. Reduction of exacerbations; 3. Reduction of hospitalizations; 4. Reduction of costs by the NHS.

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