

Managing comorbidities in COPD

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Abstract: Chronic obstructive pulmonary disease (COPD) is a leading cause of morbidity and mortality worldwide. Age and smoking are common risk factors for COPD and other illnesses, often leading COPD patients to demonstrate multiple coexisting comorbidities. COPD exacerbations and comorbidities contribute to the overall severity in individual patients. Clinical trials investigating the treatment of COPD routinely exclude patients with multiple comorbidities or advanced age. Clinical practice guidelines for a specific disease do not usually address comorbidities in their recommendations. However, the management and the medical intervention in COPD patients with comorbidities need a holistic approach that is not clearly established worldwide. This holistic approach should include the specific burden of each comorbidity in the COPD severity classification scale. Further, the pharmacological and nonpharmacological management should also include optimal interventions and risk factor modifications simultaneously for all diseases. All health care specialists in COPD management need to work together with professionals specialized in the management of the other major chronic diseases in order to provide a multidisciplinary approach to COPD patients with multiple diseases. In this review, we focus on the major comorbidities that affect COPD patients. We present an overview of the problems faced, the reasons and risk factors for the most commonly encountered comorbidities, and the burden on health care costs. We also provide a rationale for approaching the therapeutic options of the COPD patient afflicted by comorbidity.

Keywords: chronic obstructive pulmonary disease, comorbid major diseases, management, treatment, health care costs

Introduction

Chronic obstructive pulmonary disease (COPD) is a leading cause of morbidity and mortality worldwide, especially among smokers over 40 years of age and individuals exposed to biomass smoke.¹ The World Health Organization estimates that COPD will be the third most common worldwide cause of death and disability by 2030, from its current fifth ranking.² Despite worldwide medical research, health care efforts, and health care costs, COPD statistics reveal a continuing upward trend in mortality, in contrast with other major causes of death like cancer and cardiovascular disease.² A major factor that complicates therapeutic approaches to the management of COPD is that COPD is rarely the only chronic illness a patient has to contend with. Age and smoking are the major risk factors for COPD and a number of other illnesses, often leading to COPD patients demonstrating multiple coexisting comorbidities.^{3,4}

The presence of comorbidities is so strongly associated with the management of COPD that the need for thorough attention to them is emphasized even in the

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COPD definition by GOLD (Global Initiative for Chronic Obstructive Lung Disease) guidelines:⁵ “Chronic obstructive pulmonary disease, a common preventable and treatable disease, is characterized by 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.” Comorbidities are most often responsible for impairing quality of life for early-stage patients,⁶ for increasing mortality in end-stage patients, for increasing the burden of COPD management on health care costs, and creating therapeutic dilemmas for health care providers.⁵

COPD comorbidities is a rather broad heterogeneous term, including diseases that independently coexist with COPD with no other causation, diseases that share common risk factors and pathogenetic pathways with COPD, diseases that are complicated by the interaction with the lung, and systemic manifestations of COPD, and vice versa. This heterogeneity has given rise in recent years to a conceptual discussion about the appropriateness of the term “comorbidities”, in an attempt to establish an agreement over its meaning. No universal definition has yet been accepted. Terminology issues though should not shift our focus from the fact that COPD patients with multiple diseases often have poorer outcomes and are in need of a more complex, tailored therapeutic intervention approach^{7,8} in order to optimize and achieve better outcomes.

For this review, we consider as common comorbidities all previously described diseases that frequently coexist with COPD, without discriminating between those directly related and those not. The underlying causes of multimorbidity in COPD are not yet fully recognized. There is an increasing abundance of evidence that associates COPD with other age-driven diseases and diseases that share common risk factors (smoking) or etiological pathways.³ This view is supported by the widely accepted hypothesis that COPD sustains systematic inflammation.⁹ Most commonly COPD is associated with lung cancer and other cancers, asthma, obstructive sleep apnea syndrome, hypertension, cardiovascular disease, diabetes, metabolic syndrome, dysfunctional skeletal myopathies, osteoporosis, and mental disorders. Although these associations are part of our established knowledge about the disease, precise prevalence numbers differ in the published epidemiological studies (see Table 1).³ There is a need to identify from the extensive pool of comorbidities those which are more strongly associated with a significantly increased risk of death in COPD individuals. Divo et al in a

Table 1 Prevalence of the most common COPD comorbidities (%)

Study	Cancer	CVD	HTN	DM	Mental disorders*
Anechino et al ¹⁷⁵	–	68	–	12	8
Cazzola et al ⁶⁶	2	–	–	19	42
Koskela et al ⁶	6	27	41	18	45
Frei et al ¹⁵³	14	20	42	16	25
Fumagalli et al ¹⁴⁷	13	–	52	11	13 (F)
Mapel et al ¹³⁹	18	65	45	12	–
Miyazaki et al ¹⁵⁰	25	32	36	15	17
Sidney et al ³⁵	–	18	18	2	–
Soriano et al ¹²	4	22	–	–	–
Lopez Varela et al ¹⁷⁶	8	41	37	8	–
van Manen et al ¹⁷⁷	–	13	23	5	25

Note: *Mental disorders include anxiety and depression.

Abbreviations: F, female; CVD, cardiovascular disease; HTN, hypertension; DM, diabetes mellitus; COPD, chronic obstructive pulmonary disease.

recent report concluded that lung, pancreatic, esophageal, and breast cancers (the last only for female patients), pulmonary fibrosis, atrial fibrillation/flutter, congestive heart failure, coronary artery disease, gastric/duodenal ulcers, liver cirrhosis, diabetes with neuropathy, and anxiety are the most significant and frequent comorbidities.¹⁰ Clinical practice guidelines usually mention but seldom address comorbidities practically in their recommendations. Furthermore, clinical trials investigating COPD treatment routinely exclude patients with multiple comorbidities or advanced age;¹¹ the latter enormously affects the external validity and generalizability of the effectiveness of the treatments tested in the large clinical trials.

In this review, we focus on the major comorbidities that affect COPD patients, present an overview of the problems they face, the reasons and risk factors for the most commonly encountered comorbidities (Figure 1), the burden on health care costs, and provide a rationale for approaching the therapeutic options for the COPD patient afflicted by comorbidity.

Respiratory comorbidities

Asthma

Both asthma and COPD are major chronic obstructive airway diseases that involve underlying airway inflammation. COPD is characterized by airflow limitation that is not fully reversible, is usually progressive, and is associated with an abnormal inflammatory response of the lungs to noxious particles or gases. Individuals with asthma who are exposed to noxious agents (particularly cigarette smoking) may develop fixed airflow limitation and a mixture of “asthma-like” inflammation and “COPD-like” inflammation. Thus, even though

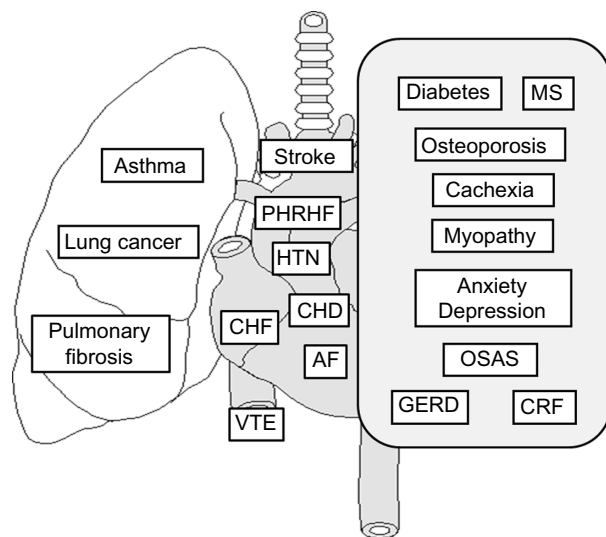


Figure 1 The most common and clinically important comorbidities in patients with COPD.

Abbreviations: PHRF, pulmonary hypertension and right heart failure; HTN, hypertension; CHF, congestive heart failure; CHD, coronary heart disease; AF, atrial fibrillation; VTE, venous thromboembolism; MS, metabolic syndrome; OSAS, obstructive sleep apnea syndrome; GERD, gastroesophageal reflux disease; CRF, chronic renal failure; COPD, Chronic Obstructive Pulmonary Disease.

asthma can usually be distinguished from COPD, in some individuals who develop chronic respiratory symptoms and fixed airflow limitation, it may be difficult to differentiate the two diseases. In some patients with chronic asthma, a clear distinction from COPD is not possible using current imaging and physiological testing techniques, and it is assumed that asthma and COPD coexist in these patients. In these cases, current management includes use of anti-inflammatory drugs, and other therapies need to be individualized. Other potential diagnoses are usually easier to distinguish from COPD.⁵

Coexistence of asthma and COPD in elderly patients is often diagnosed.¹² In some studies, the overlap diagnosis of asthma and COPD exceeds half of the patients examined.^{13,14} The overlap is identified by finding increased variability of airflow in patients with incompletely reversible airway obstruction.¹⁵ The presence of COPD-asthma overlap syndrome is associated with impaired quality of life and more frequent and severe exacerbations compared with COPD only patients.¹⁶

The coexistence of asthma and COPD cannot be excluded even in the study populations of the biggest COPD clinical trials. In UPLIFT, a 4-year trial of tiotropium in COPD, 5,993 patients were enrolled.¹⁷ At visit 2 of the study, prebronchodilator spirometry was performed and the patients then received an enhanced bronchodilation test including four inhalations of ipratropium (80 mg via metered-dose inhaler) followed 60 minutes later by four inhalations of salbutamol (400 mg via

metered-dose inhaler) to ensure maximal or near-maximal bronchodilation. The majority of the study population with moderate-to-very severe COPD demonstrated meaningful increases in lung function following administration of inhaled anticholinergic plus sympathomimetic bronchodilators: 65.6% of the patients met the criterion of a $\geq 15\%$ increase in forced expiratory volume in one second (FEV_1) and 53.9% met the criterion of an increase in FEV_1 of both $\geq 12\%$ and ≥ 200 mL.¹⁸

In ECLIPSE, a large observational study (2,138 COPD patients), researchers tested the hypothesis that there is a frequent-exacerbation phenotype of COPD that is independent of disease severity.¹⁹ The single best predictor of exacerbations, across all GOLD stages, was a history of exacerbations. The second strongest predictor of exacerbations was a history of reflux or heartburn, a common symptom among asthma patients.

Although the overlap syndrome seems to be a common clinical presentation, both the major COPD guidelines (GOLD) and asthma guidelines (GINA, Global Initiative for Asthma) do not give specific recommendations for its combined treatment at the moment.

In August 2014, a joint project regarding the diagnosis of diseases of chronic airflow limitation (Asthma, COPD, and Asthma-COPD overlap syndrome [ACOS]) was published by the science committees of GOLD and GINA.²⁰ This document was based on a detailed review of available literature and consensus. It provides an approach to distinguishing between asthma, COPD, and the overlap of asthma and COPD, for which the term ACOS is proposed. A stepwise approach to diagnosis is advised, comprising recognition of the presence of a chronic airways disease, syndromic categorization as asthma, COPD, or ACOS, confirmation by spirometry and, if necessary, referral for specialized investigations.

Lung cancer

COPD patients run an increased risk of developing lung cancer. It is also a factor that contributes to poorer outcomes in lung cancer patients.^{20,21} The prevalence of COPD among patients with lung cancer varies from 40% to 70%.^{22,23} Lung cancer patients tend to have more severe lung function impairment. Several reports confirmed that lung cancer occurs in COPD patients late in the natural course of the disease. The prevalence of moderate-to-very severe disease (GOLD stages II–IV) among lung cancer patients reaches 50%, in contrast with only 8% of smokers without lung cancer.²⁰ The annual incidence of lung cancer is four times higher in COPD patients when compared with the general population.^{20,24}

Both diseases create management difficulties for one another, but therapy for lung cancer is more crucially affected. Mainly due to impaired lung function, patients with COPD often fail to meet the tolerance criteria for undergoing surgical resection of their otherwise operable malignancy. The result is that the overall prognosis for patients with both diseases is worse than each alone. Three-year survival in patients with COPD and lung cancer has been found to be around 15%, compared with 26% for lung cancer patients without COPD.²⁰ Lung cancers, together with cardiovascular comorbidities, are the leading causes of death in COPD patients with mild-to-moderate disease, while respiratory failure due to airway obstruction only becomes predominant in advanced COPD.^{25–27}

Pulmonary fibrosis

Pulmonary fibrosis is more common among smokers, and in coexistence with emphysema it has been classified as a distinct clinical entity (combined pulmonary fibrosis and emphysema syndrome).²⁸ Patients with coexistence of pulmonary interstitial fibrosis and COPD present characteristic lung function tests, with relatively normal spirometry and lung volumes but severely impaired gas exchange. This results from the inverse effect of airway traction of pulmonary fibrosis on bronchus constriction of COPD. Simultaneously, gas exchange is impaired by both thickening of the alveolar membrane in pulmonary fibrosis and reduction of the vascular surface in emphysema. Compared with pulmonary fibrosis or emphysema alone, patients with combined pulmonary fibrosis and emphysema syndrome have more frequent and more severe pulmonary hypertension. Patients with the syndrome face a reduced survival prognosis compared with patients with COPD, with an estimated median survival of 6 years.^{24,29}

Cardiovascular comorbidities

Hypertension

Hypertension is very common in COPD patients, but is not associated with increased mortality.¹⁰ Hypertension is related to the increased systemic inflammation observed in COPD and is correlated with higher Medical Research Council dyspnea scores, reduced capacity for physical activity,³⁰ and airflow obstruction.³¹

Congestive heart failure

Congestive heart failure and COPD share similar risk factors, especially whatever risk factor is associated with smoking, and common pathophysiological mechanisms, which

frequently coexist in the same patient.³² The prevalence of congestive heart failure among COPD patients varies between stable disease and exacerbations. In stable COPD studies report a 3.8% to 16% coexistence compared with exacerbations that reach up to 48%.^{33,34} Congestive heart failure is among the leading causes of hospitalization and death for patients with COPD and worsens their prognosis.³⁵ Simultaneously, COPD is an independent risk factor for death in patients with congestive heart failure.³⁶ Coexistence of COPD and congestive heart failure worsens right ventricular dysfunction, when compared with non-COPD patients.³⁷ Left ventricular dysfunction is present in around 20% of COPD patients, but frequently goes unnoticed.³⁸

Coronary heart disease

COPD and coronary heart disease share a common major risk factor, which is smoking. The coexistence has been reported to be as high as 30% or even higher in COPD patients. Vigilance in recognizing and diagnosing coronary disease signs and symptoms is needed in assessing COPD patients.³⁹ In some studies of the medical records of COPD patients, undiagnosed cases of coronary heart disease reach 70%.⁴⁰ Addressing undiagnosed cases is crucial for improving outcomes, since the coexistence of both diseases worsens the prognosis when compared with each separately. Both diseases are characterized by chronic sustained inflammation and coagulopathy. The key mediator of this sustained inflammation in COPD is probably elevated C-reactive protein levels, which not only maintain bronchial constriction but also increase the risk for coronary disease.^{24,41}

Atrial fibrillation

Atrial fibrillation and COPD are two common morbidities and often coexist.⁴² The presence and severity of COPD are associated with increased risk for atrial fibrillation/atrial flutter and non-sustained ventricular tachycardia. The prevalence of atrial fibrillation and non-sustained ventricular tachycardia among COPD patients has been reported to be as high as 23.3% and 13.0%, respectively.⁴³ Reduced FEV₁ and COPD are associated with a higher incidence of atrial fibrillation after adjustment for confounders.⁴⁴ The prevalence of COPD in patients with atrial fibrillation reaches 18%.⁴⁵ Hospitalization mortality in severe COPD patients with arrhythmia has been reported to be as high as 31%, compared with 8% in non-COPD patients.⁴⁶ Prolonged conduction time in the right atrium and typical atrial flutter are commonly observed in COPD patients with atrial fibrillation.⁴⁷

Pulmonary artery hypertension and subsequent right heart failure

Pulmonary artery hypertension and subsequent right heart failure are observed in COPD patients as a consequence of pulmonary artery remodeling. This remodeling occurs in COPD due to endothelial dysfunction, clotting abnormalities, hypoxic vasoconstriction, destruction of the pulmonary capillary bed, inflammatory infiltration of the vascular wall, and shear stress due to blood flow redistribution.⁴⁸ Reports estimate that the prevalence of pulmonary artery hypertension in COPD patients is as high as 40%.⁴⁹ When COPD patients develop pulmonary artery hypertension, they experience more intense shortness of breath, greater desaturation during exercise, and more profound limitation of physical activity. The coexistence of COPD and pulmonary artery hypertension is associated with higher mortality.⁵⁰ Signs and symptoms of right ventricular dysfunction should be recognized, although diagnosis of pulmonary artery hypertension does not improve management outcomes in COPD. Addition of long-term oxygen therapy has a stabilizing effect in some patients.^{24,51}

Venous thromboembolism

The prevalence of venous thromboembolism in COPD patients during an exacerbation has been reported to be as high as 29%.^{52,53} The prevalence of pulmonary embolism in COPD patients is also documented to be higher than in non-COPD patients and increases with age.⁵⁴ The risk of venous thromboembolism is higher in patients with COPD and other comorbidities like hypertension, coronary artery disease, or cancer, or with previous surgery. Venous thromboembolism prolongs hospitalization by 4.4 days and increases one-year mortality by 30%.⁵³ If not diagnosed and treated adequately, the risk of death during hospitalization for exacerbations is increased by 25%. COPD not only shares certain common risk factors with venous thromboembolism, like smoking, but also systemic inflammation due to COPD induces pulmonary⁵⁵ and systemic endothelial dysfunction⁵⁶ and coagulopathy.^{24,57,58}

Stroke

COPD patients present an increased risk for ischemic stroke, as a result of common risk factors, like age and smoking, and the systemic inflammation and coagulopathy caused by COPD.^{59,60} There is a linear correlation between stroke risk and airflow obstruction.⁶¹ Almost 8% of all COPD patients have a history of stroke.⁶² About 4% of all deaths in COPD patients are related to an incident of ischemic stroke.⁶³

Metabolic comorbidities

Diabetes and metabolic syndrome

Diabetes has been reported in several studies to be a frequent COPD comorbidity, with a prevalence as high as 18.7% among COPD patients.^{64,65} The prevalence of metabolic syndrome is reported to be up to 22.5% in COPD patients. COPD patients have a relatively increased risk of developing diabetes,^{66,67} but also diabetes often presents before diagnosis of COPD, and diabetic patients have an increased risk of developing COPD.⁶⁸ This side-by-side development of both diseases is a result of common risk factors, like smoking, and also the synergic effect of systemic inflammation mediated by common cytokines.^{69–71} Diabetes worsens the outcomes of COPD by affecting a number of parameters:^{66,72,73} shortening time to first hospitalization and increasing hospitalization time and risk of death during exacerbations,⁷⁴ increasing Medical Research Council dyspnea scores, and reducing six-minute walking distance.³⁰ Diabetes worsens 5-year mortality in COPD patients.^{24,66}

Osteoporosis

Osteoporosis is another chronic illness that frequently coexists with COPD, even in male patients.^{75,76} The prevalence of osteoporosis among COPD patients ranges up to 69% in some reports, reflecting not only common risk factors, like age and cigarette smoking, but also the harmful effects of COPD due to systemic inflammation, reduced physical activity, and in some cases oral steroid therapy.⁷⁷ At the same time, vertebral fractures due to osteoporosis lead to decreased rib mobility and frequently to kyphosis, which further impairs lung mechanics.⁷⁸ Even asymptomatic vertebral fractures accelerate lung function decline.⁷⁹ Osteoporosis is associated with higher dyspnea scores and reduced six-minute walking distance.³⁰ Patients with COPD and osteoporosis tend to have lower body mass index values and more severe airway obstruction.⁸⁰

Cachexia and myopathy

Loss of fat-free mass (cachexia) and skeletal muscle dysfunction (myopathy) are common comorbidities with COPD. Both are more common in northern countries, compared with the Mediterranean, probably as a result of dietary differences.¹¹ The prevalence of cachexia among COPD patients ranges from 10% to 15% in mild-to-moderate disease to up to 50% in severe disease,⁸¹ even in obese patients.⁸² The prevalence of skeletal muscle weakness has been reported to be as high as 32% among COPD patients.⁸³ Skeletal muscle weakness shares common risk factors with COPD, like age

and smoking, but is also affected by systemic manifestations of COPD, like systemic inflammation, oxidative stress, and physical inactivity.⁸⁴ Skeletal muscle weakness is associated with reduced strength, endurance and exercise capacity, lack of physical activity, impaired quality of life, increased risk for hospital admission after exacerbation, increased health care utilization, and increased risk of death.^{85–87} Early onset of muscle weakness may reflect a more aggressive COPD phenotype.¹¹

Mental comorbidities

Anxiety and depression frequently accompany certain chronic illnesses.^{88–90} Many COPD patients experience transitory mood symptoms during exacerbations, which improve spontaneously after recovery. Identifying COPD patients with clinical depression and/or anxiety remains a challenge.⁹¹

Anxiety is also more frequent among COPD patients, compared with the general population or patients with other chronic illnesses, with a prevalence reported to be as high as 19%.⁹² Patients with anxiety tend to have their first hospitalization earlier in the natural course of COPD,⁹³ they are earlier and more intensely irritated by their shortness of breath, and have higher rates of mortality and readmission after an exacerbation.⁹⁴ Anxiety is one of the known comorbidities with the highest risk of death, especially among female patients,⁹⁵ that needs adequate attention as it is a potentially treatable condition.⁹⁶

The prevalence of depression in COPD patients receiving long-term oxygen therapy reaches as high as 60%.⁹⁷ Depression reduces physical activity, quality of life scores,^{98,99} and adherence to medical treatment,¹⁰⁰ and is associated with higher rates of COPD exacerbations^{101,102} and increased mortality.¹⁰³ Almost 25% of all COPD patients suffer from depression that eludes diagnosis,¹⁰⁴ and an estimated two thirds of patients with coexistent COPD and depression do not receive any antidepressant treatment.^{88,105}

Other comorbidities

Obstructive sleep apnea syndrome

Obstructive sleep apnea syndrome (OSAS) is no more common in COPD than in the general population, as previously believed. Results from the Sleep Heart Health Study, after stratification for body mass index and age, give a prevalence for OSAS of around 14% among COPD patients 40 years and older.¹⁰⁶ However, the fact that OSAS is a common clinical entity in the general population gives a significant number of cases of coexistence with COPD. The combination leads to increased risk of death^{107,108} due

to more frequent exacerbations and an increased risk for development of cardiovascular comorbidities like pulmonary hypertension and right heart failure.^{24,109}

Gastroesophageal reflux disease

Gastroesophageal reflux disease (GERD) is commonly associated with asthma. Little attention has been paid to symptoms of GERD in COPD patients. Studies show a significant prevalence of GERD in up to 60% of COPD patients,^{110–112} which is correlated more with quality of life scores on the COPD Assessment Test than with airway obstruction¹¹³ and risk for exacerbation.^{19,114} These findings raise more questions as to whether COPD patients are dealing with an independent comorbidity or if there is an unnoticed strong asthma component in their disease.

Chronic renal failure

Renal complications of COPD are common, especially in patients with hypoxemia and hypercapnea.¹¹⁵ The arterial rigidity and endothelial dysfunction caused by COPD frequently lead to a decreased normal renal functional reserve.¹¹⁶ Impairment of renal functional reserve in COPD patients is correlated with more severe airway obstruction and inflammation.¹¹⁶ COPD patients have approximately twice the incidence of acute renal failure, and three times the prevalence of diagnosed chronic renal failure than age-matched and gender-matched controls.¹¹⁵ Renal insufficiency may be present in around 22% of COPD patients.¹¹⁷ Chronic renal failure often goes undiagnosed, and is a particular concern in elderly COPD patients and in COPD patients with cachexia.¹¹⁸ Among COPD patients over 64 years of age, 25% may have chronic renal failure even with normal serum creatinine values.⁹⁷

Links between COPD and comorbidities

COPD comorbidities include clinical conditions that share common risk factors and pathogenetic pathways with COPD, ie, diseases that are consequences of COPD and diseases that just coexist with COPD due to their large prevalence in the general population but affect outcomes such as hospitalization rates and mortality. As our knowledge of COPD and of the pathogenesis of COPD comorbidities is gradually elucidated by basic science data, the more the complexity of the interactions involved becomes apparent. As COPD becomes more and more understood as a systematic inflammatory disease, our focus is shifting from the lungs.¹¹⁹

Smoking and biomass exposure, along with genetic predisposition, are the major risk factors for developing COPD.⁵ Age is also a common risk factor for developing COPD, but should not be overestimated. For example, COPD is often considered to be a disease of the later years, but estimates suggest that 50% of those with COPD are now younger than 65 years of age.¹²⁰

The cause-effect diagram (Figure 2) shows the four ways that comorbidities may complicate COPD. Even if this eye-catching presentation tends to oversimplify the underlying interactions involved, the predominant cause-effect relationships are summarized. Lung cancer and COPD may share certain risk factors, like age, smoking, or genetic predisposition, but bronchial and systemic inflammation due to COPD may also contribute to carcinogenesis, swifiting cancer to dependent comorbidity.^{121,122} The same is evident in several cardiovascular diseases, which also share common risk factors and seem to have a bidirectional inflammatory link with COPD that impairs outcomes for both diseases.^{123,124} Type 2 diabetes has been considered as a coincidental comorbidity, but evidence is accumulating in favor of considering diabetes and metabolic syndrome as dependent comorbidities.¹²⁵

Systemic inflammation is the key for linking COPD and most of its dependent comorbidities.^{119,126} Without overlooking other pathways, like hypoxia and oxidative stress, the mainstream approach is that a variety of inflammatory mediators, including interferon- γ , interleukin-1, C-reactive protein, tumor necrosis factor- α , interleukin-6, interleukin-8, surfactant protein D, fibrinogen, and amyloid protein, from

the peripheral airways enter circulation and affect multiple distal organs.^{24,126,127} The opposite route is also evident, with inflammatory mediators produced in other organs, due to chronic conditions like heart failure or coronary disease, which may contribute to the pathogenesis of COPD structural abnormalities. Some researchers go as far as to propose that COPD is just a manifestation of a systemic inflammatory syndrome.⁷¹

COPD medications may also contribute to the development or worsening of certain comorbidities.⁸⁸ Bronchodilators are suspected of causing tachyarrhythmias and tremors, but recent randomized clinical trials of long-acting β -agonists suggest that these effects probably do not increase cardiovascular mortality.^{128,129} Inhaled anticholinergics can affect intraocular pressure and bladder function and might have cardiovascular effects.^{130,131} Inhaled corticosteroids may increase the risk for cataracts, skin bruising, osteoporosis, and pneumonia.¹²⁸ Systemic corticosteroids, often overprescribed in COPD patients, could contribute to diabetes, hypertension, osteoporosis, muscle dysfunction, and adrenal insufficiency.⁸⁸ On the other hand, heart, liver, and kidney comorbidities need to be taken into account in terms of pharmacokinetic changes and pharmacodynamic modifications, which may lead to unfavorable side effects with suboptimal treatment.^{4,132}

Burden on health care costs

COPD remains a major health issue with a significant economic impact.¹³³ The prevalence of COPD is rising in developing and developed countries, resulting in increased

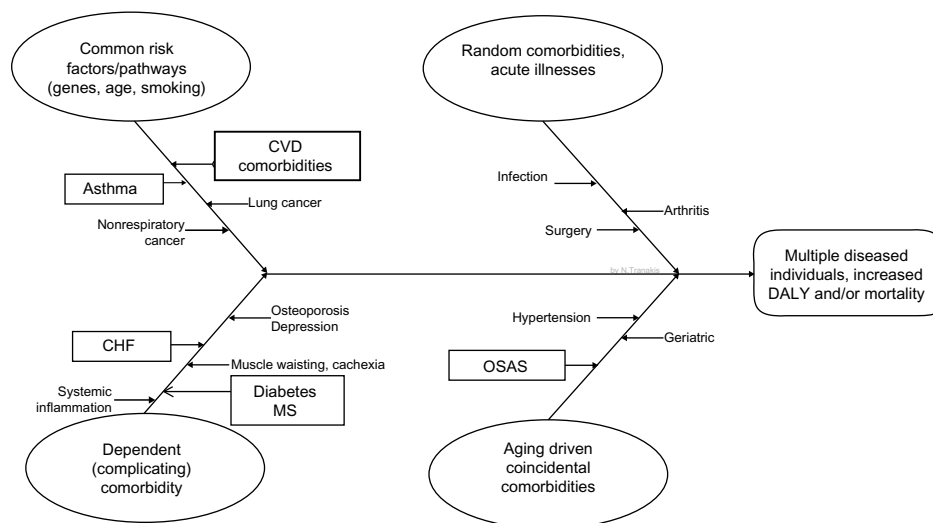


Figure 2 Cause-effect diagram shows the four different ways in which other abnormalities may be linked with COPD, presented in the same individual, the so-called multidiseased COPD patient, and leading in increase morbidity and mortality.

Abbreviations: CVD, cardiovascular disease; CHF, congestive heart failure; MS, metabolic syndrome; OSAS, obstructive sleep apnea syndrome; DALY, disability-adjusted life years; MS, Metabolic Syndrome; COPD, Chronic Obstructive Pulmonary Disease.

direct and indirect costs of COPD to health care systems worldwide.

In the USA, direct costs have escalated from 18 billion dollars in 2002 to 29.5 billion in 2010, the largest part consisting of hospital expenses,¹³⁴ whereas indirect costs accounted for 27%–61% of total costs, with the higher estimates produced by studies of working age populations.^{135,136} Average lifetime earnings losses for COPD patients retiring early have been estimated to be \$316,000 per individual.¹²⁰ In Europe, the total annual cost of COPD is estimated at €38.7 billion.¹³⁷

The total annual direct costs of COPD expenditure are directly associated with the number of comorbidities,¹³⁸ not the severity of airflow obstruction or health-related quality of life indices.¹³⁹ Comorbidities, after age and chronic symptoms, are the factors most predictive of future health care costs.¹⁴⁰ COPD patients with comorbidities have increased risk⁶⁶ and significantly higher mean costs for hospital admissions.¹⁴¹ Hospitalizations are the greatest contributor to total COPD costs, and account for up to 87% of total COPD-related costs.¹⁴² Exacerbations are the leading but not the only cause of hospital admissions, and account for between 40% and 75% of the total health care cost of COPD,^{143,144} despite treatment with maintenance medications.¹³³ Elevated costs in comorbid COPD patients are not only associated with hospitalizations: COPD patients use approximately 50% more cardiovascular agents than age-matched and sex-matched controls, and almost twice as many antibiotics, analgesics, and psychotherapeutic medications.¹³⁸

COPD patients with multiple comorbidities make use of a disproportionately large percentage of the total overall health care expenditure on COPD.^{142,145} The median cost of COPD patients with multiple comorbidities has been found to be 4.7 times higher compared with comorbidity-free COPD patients.¹³⁹ At the same time, compared with non-COPD controls, COPD patients consume 3.4 times more health care resources.¹³⁹

It is obvious that holistic medical interventions are urgently needed for COPD management in order to decrease direct and indirect costs. These interventions must aim to reduce exacerbations of the disease and should emphasize personalized therapy according to different COPD phenotypes.

Multimorbidities and outcomes

Comorbidities seem to be present in the majority of COPD patients. Studies show that up to 94% of COPD patients have at least one comorbid disease and up to 46% have

three or more.¹⁴⁶ Even after correcting outcomes for age, sex, and smoking history, patients with COPD and comorbidities tend to have worse health status and functional impairment.^{30,147} The presence of three or more comorbidities is a better predictor of impaired health status than any other demographic or clinical variable.¹⁴⁸ In mild-to-moderate COPD, lung cancer and cardiovascular comorbidities are the main causes of death and account for up to two thirds of all deaths in these patients, while respiratory failure only becomes predominant in advanced COPD.^{25–27}

The use of health status questionnaires cannot always identify the presence of COPD comorbidities and the risk they pose on affecting outcomes.¹⁴⁹ Attempts have been made to measure the relevant effect of multiple concomitant COPD comorbidities on outcomes, especially mortality, using several indexes or scales, which are not always designed exclusively for COPD patients. In these scales, each comorbidity is addressed separately.¹⁵⁰ These include the Charlson Comorbidity Index, the Cumulative Illness Rating Scale, the Index of Coexisting Disease, and the Kaplan Index.^{10,151}

The COTE index (a COPD-specific comorbidity test) identified 12 comorbidities that predicted death in COPD patients and is suggested as a complementary tool to the BODE (BMI, Obstruction, Dyspnea, Exercise) index.¹⁰ The COMCOLD (COMorbidities in Chronic Obstructive Lung Disease) index addresses the combined effect of COPD comorbidities on mortality and health-related quality of life.¹⁵² The use in clinical practice of multiple comorbidity indexes is a powerful tool for better stratifying COPD patients according to their risk for unfavorable outcomes and identifying high-risk patients that need attention paid to tailor-made treatment.

Treatment and management

The cornerstone of management for COPD and comorbidities is guideline-based treatment. The aim of this review is to focus on highlighting important key issues that complicate management of COPD in patients with comorbidities, in order to provide practical guidance for the pulmonary specialist physician in clinical practice. For this reason, we will not repeat in detail what is already established in the guidelines published for each disease.

The management and treatment of COPD is usually based on GOLD guidelines.⁵ Appropriate treatment (pharmacological and nonpharmacological) can reduce COPD symptoms, reduce the frequency and severity of exacerbations, and improve health status and exercise tolerance.

The main pharmacological regimens are: β_2 -agonists, anticholinergics (short-acting and long-acting, SABA-LABA), anticholinergics (short-acting and long-acting, SAMA-LAMA), combination short-acting β_2 -agonists plus an anticholinergic in one inhaler, combination long-acting β_2 -agonists plus an anticholinergic in one inhaler, methylxanthines, inhaled corticosteroids, combination long-acting β_2 -agonists plus corticosteroids in one inhaler, systemic corticosteroids, and phosphodiesterase-4 inhibitors.

LABA have been associated with increased mortality and hospitalization in patients with heart failure and an increased risk of incident heart failure.¹⁵³ Tiotropium, on the other hand, has been associated with a reduction in the risk of all-cause mortality, cardiovascular mortality, and cardiovascular events.¹⁵⁴ Even if few long-term studies have measured changes in bone mineral density, inhaled steroid use for at least 3 years has not been associated with worsening major clinical features of osteoporosis.¹⁵⁵ On the other hand, oral corticosteroids can potentially worsen coexistent heart failure, and are associated with an increased risk of arrhythmias.¹⁵⁶ If used in COPD, close monitoring for hypertension, diabetes, and osteoporosis is recommended, as they have potentially harmful adverse effects.¹⁵⁷ GOLD guidelines recommend a limited dosage.⁵ Theophylline is also correlated with increased risk for arrhythmias and atrial fibrillation.¹⁵⁸ Each pharmacological treatment regimen needs to be patient-specific, and guided by severity of symptoms, risk of exacerbations, drug availability, and the patient's response. To date, none of the existing COPD medications have been shown conclusively to modify the long-term decline in lung function.

Patients with asthma and COPD seem to benefit from the use of combinations containing drugs with complementary pharmacological actions. The treatment of patients with asthma or COPD has also led to the discovery and development of drugs having two different primary pharmacological actions in the same molecule, which are now called "bifunctional drugs".¹⁵⁹

The joint project recently published by the science committees of GOLD and GINA²⁰ confirms that initial treatment should be selected to ensure that patients with features of asthma receive adequate controller therapy including inhaled corticosteroids but not long-acting bronchodilators alone (as monotherapy), and patients with COPD receive appropriate symptomatic treatment with bronchodilators or combination therapy, but not inhaled corticosteroids alone (as monotherapy).

There is little specific guideline guidance for administering cardiovascular regimens to patients with comorbid

COPD.⁴ As a result, β -blockers are frequently underused in patients with COPD.¹¹ Awareness is needed for patients with congestive heart failure and COPD not to be denied β -blocker treatment.¹⁶⁰ Cardioselective β -blockers improve the prognosis without impairing lung function. Caution is needed because cardioselectivity decreases as the dosage escalates.^{161,162} However, even older nonselective β -blockers are well tolerated in most COPD patients.⁴ Patients with coronary heart disease should also not be denied the protective effects of β -blockers.¹⁶³ GOLD guidelines recommend the use of the general coronary disease guidelines, and especially note the use of selective β_1 -blockers even in patients with severe COPD.^{2,5} The use of angiotensin-converting enzyme (ACE) inhibitors by smokers may protect against a rapid decline in lung function and progression to COPD.¹⁶⁴ Chronic lowering of ACE improves pulmonary inflammation, respiratory muscle function, and peripheral use of oxygen.¹⁶⁵ ACE inhibitors and statins are associated in retrospective studies with reduced cardiovascular mortality, lower respiratory morbidity/mortality, and lower lung cancer risk.¹¹ Statins though should be used with caution because they may worsen myopathy and elevate liver enzymes. All medications that metabolize through the cytochrome P450 system can be affected by administration of a statin.¹⁶⁶

Treatment of OSAS largely does not differ between patients with COPD and those without. Treatment of COPD patients with OSAS is based on the treatment of constituent diseases (for COPD bronchodilators, inhaled steroids when indicated, rehabilitation, nutrition, domiciliary oxygen when indicated, and for OSA weight loss and application of continuous positive airway pressure [CPAP]).^{107,108} The goal of treatment is to maintain adequate oxygenation at all times and to prevent sleep-disordered breathing. CPAP remains the accepted standard treatment for OSA, but CPAP alone may not fully correct hypoxemia, so supplemental oxygen may be required.

The large prevalence of concealed and overt chronic kidney failure in COPD patients, especially the elderly, indicates that awareness is needed for monitoring and addressing adverse effects caused mainly by hydrosoluble drugs, which are cleared by the kidney. Special attention is warranted for drugs like thiazides or digoxin, used in the treatment of cardiovascular comorbidities, but also antibiotics commonly used in acute exacerbations of COPD.^{117,167}

The nonpharmacological treatment of COPD patients includes smoking cessation (counseling plus pharmacotherapy), influenza and pneumococcal vaccination, and pulmonary rehabilitation. Pulmonary rehabilitation,

a nonpharmacological intervention, has the potential to affect a number of comorbidities alongside COPD, through exercise training, emphasis on self-management and behavioral change, and psychological support.³⁷ Physical activity and regular exercise are proven to be beneficial for multiple comorbidities, including cardiovascular disease, diabetes, or musculoskeletal diseases.^{168–171} Smoking cessation is the most cost-effective method for slowing COPD progression, and has proven beneficial effects on the outcomes of most comorbidities, for which smoking is a major risk factor.²⁴ Despite the abundance of data on smoking, only a small percentage of smokers in the USA have received any kind of smoking cessation intervention.^{172,173} Similarly, the percentage of the population that currently receives influenza vaccination is also low.¹⁷²

The harmful and beneficial effects of pharmacological and nonpharmacological treatments underscore the paramount importance of a multidisciplinary approach in order to improve outcomes. Management of COPD needs a systemic holistic approach that does not neglect the nonrespiratory component of treatment.

Given the potential complications of treatment and the interactions between comorbid diseases and COPD, some researchers have started to advocate for an integrated care approach to the management of patients with COPD. There is a need for a chronic care model approach to the management of COPD, including automatic screening for common comorbidities.

In order to truly build such a chronic care model, future research has to be moved in certain directions: including patients with comorbid conditions in clinical trials with appropriate analytic strategies to understand the heterogeneity of the

treatment effect; investigating the development of a method for assessing and scoring comorbidities so that we can provide accurate prognostic information for patients as well as treat in a robust effective manner; evaluating current treatment regimens in patients with different patterns of comorbid conditions; and continuing to study possible pathophysiological connections between COPD and comorbidities.

Conclusion

Management and medical intervention in COPD patients with comorbidities needs a holistic approach (Figure 3), that is not clearly established in guidelines worldwide regarding the management of major chronic diseases. This holistic approach includes COPD management based on pharmacological and nonpharmacological treatment, guideline-based management for specific comorbidities, and modification of the risk factors for COPD and comorbidities.

All health care specialists in COPD management need to work together with professionals specialized in the management of other major chronic diseases in order to provide a multidisciplinary treatment strategy for COPD patients with comorbidities. More studies are needed to clarify and establish a holistic approach to medical intervention in comorbid COPD patients.

Disclosure

The authors report no conflicts of interest in this work.

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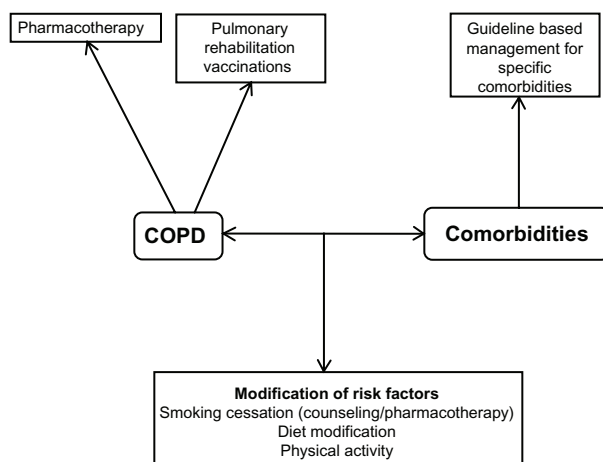


Figure 3 A holistic approach to medical intervention.

Abbreviation: COPD, chronic obstructive pulmonary disease.

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