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EXPERT OPINION

Management of the COPD Patient with Comorbidities: An Experts Recommendation Document

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Background: Chronic obstructive pulmonary disease (COPD) is associated with multiple comorbidities, which impact negatively on patients and are often underdiagnosed, thus lacking a proper management due to the absence of clear guidelines.

Purpose: To elaborate expert recommendations aimed to help healthcare professionals to provide the right care for treating COPD patients with comorbidities.

Methods: A modified RAND-UCLA appropriateness method consisting of nominal groups to draw up consensus recommendations (6 Spanish experts) and 2-Delphi rounds to validate them (23 Spanish experts) was performed.

Results: A panel of Spanish internal medicine experts reached consensus on 73 recommendations and 81 conclusions on the clinical consequences of the presence of comorbidities. In general, the experts reached consensus on the issues raised with regard to cardiovascular comorbidity and metabolic disorders. Consensus was reached on the use of selective serotonin reuptake inhibitors in cases of depression and the usefulness of referring patients with anxiety to respiratory rehabilitation programmes. The results also showed consensus on the usefulness of investigating the quality of sleep, the treatment of pain with opioids and the evaluation of osteoporosis by lateral chest radiography.

Conclusion: This study provides conclusions and recommendations that are intended to improve the management of the complexity of patients with COPD and important comorbidities, usually excluded from clinical trials.

Keywords: chronic obstructive pulmonary disease, COPD, comorbidities, modified RAND-UCLA, Delphi technique

Introduction

Chronic obstructive pulmonary disease (COPD) is a serious health problem that constitutes the fourth cause of mortality worldwide.[1] In Spain, its prevalence among the population between 40 and 80 years of age is 10.2%.[2] COPD is related with multiple associated conditions and comorbidities which often share characteristics and risk factors.[3] The comorbidities most commonly associated with COPD include cardiovascular disease, endocrine and metabolic disorders, neuropsychiatric diseases, anemia, neoplasms (especially lung cancer), and gastrointestinal diseases,[4,5] conditions often linked with smoking, systemic inflammation, airflow limitation, and aging.[3,4,6]

The presence of comorbidities impacts negatively on COPD patients, reducing quality of life and increasing the probability of hospital admission and mortality.[3,4,6]

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Indeed, the presence of more than 1 comorbidity more than doubles the risk of mortality, and many patients with COPD die because of their comorbidities rather than their COPD, particularly in the mild and moderate phases.[4]

The proper management of multimorbidity in patients with COPD involves the early detection and treatment of comorbidities. In this regard, the Global Initiative for Chronic Obstructive Lung Disease (GOLD) guidelines recommend evaluating separately the presence of comorbidities[5] when assessing these patients.

Often, however, comorbidities in COPD are underdiagnosed, because of a lack of a standardized protocol for their determination and difficulties in differentiating comorbidities from severe COPD.[4,7] Moreover, the influence of the different treatments indicated for comorbidities in COPD and vice versa remains unclear. The outcome is failure to treat patients according to their needs.[3,7]

In the absence of clear guidelines on the treatment of patients with COPD and comorbidities, these expert recommendations aim to help healthcare professionals treating these patients to provide the right care.

Methods

This project has been conducted using a qualitative synthesis of the scientific evidence and a modification of the RAND/UCLA appropriateness method,[8] which combines Delphi consensus and nominal group techniques, collecting the agreement of a group of experts taking into account their clinical experience, the scientific evidence, and the collective judgment of the group.

Process Phases

1. Definition of working group and project and preparation of the consensus protocol. Preparation of the document began with the constitution of the team of 2 experts that made up the group coordinator (GC), and the recommendations preparation group (RPG), composed of 4 Spanish experts in internal medicine. All members of the working group (group coordinator and recommendations preparation group) belong to the COPD working group of the Spanish internal medicine society. The GC met in person and then held a kick-off meeting with the RPG to define the objectives and fundamental criteria of the consensus document (justification, objectives, scope, target population, topics, clinical questions to be answered, formulated according the PICO (Problem/Patient/Population, Intervention/Indicator, Comparison, Outcome) structure whenever possible, participants, and methodology) and the working protocol.

The recommendations validation group (RVG) was formed at a later date.

1. Rapid review of the literature. A non-exhaustive systematic review of the literature was conducted to identify the publications that could answer the consensus questions, using a search strategy that included studies published in the Medline database (PubMed) in the previous 5 years. The search was completed with publications relevant to the topic that the experts felt were of interest. Items for review were then selected and prioritized using two strategies, the first of which took into account title and abstract first, and then the complete document, type, and year of publication; the second strategy took into account title and abstract.
2. Critical reading and synthesis of information. The complete text of the selected articles was read critically, and the information was synthesized using templates which included a brief description of the study, design, patients, interventions used, main results, and conclusions. The studies were classified according to the quality of the work, using an adaptation of the Scottish Intercollegiate Guidelines Network developers' handbook[9] and sent to the RPG for reading, analysis, and preparation of recommendations.
3. Formulation of recommendations. After reading and analyzing the information, the RPG formulated the recommendations and conclusions that corresponded to each of the clinical questions, including the level of evidence and grade of recommendation according to the Oxford Centre for Evidence Based Medicine system.[10]
4. Consensus process. The process of debate and drawing up consensus recommendations consisted of an initial in-person consensus session, using nominal group methodology, in which participants defended or modified the recommendations as appropriate, and then voted on their inclusion in or exclusion from the document. The recommendations document subsequently underwent a process of external validation using a 2-round Delphi technique, in which 23 Spanish specialists participated in the first round, and 21 in the second. The panel of experts consisted of specialists in internal medicine from various hospitals

and geographical areas of Spain belonging to the COPD working group of the Spanish society of internal medicine, selected according to the different hospital sizes. (see acknowledgements). Their experience in the clinical management of COPD in their daily practice was taken into account for inclusion in the panel. In each round, the members of the RVG expressed their degree of agreement or disagreement with the recommendations in an online questionnaire on a Likert scale of 1 to 5 (1 being "strongly disagree" and 5 "strongly agree") and provided reasons for their response. Grades 1 and 2 on this scale were considered disagreement, grade 3 was neither agreement nor disagreement, and grades 4 and 5 were taken as agreement. According to this grouping, the recommendation was considered to be unanimously accepted when the entire panel of experts were in 100% agreement; consensus was accepted when at least 80% of the panelists agreed with the recommendation; divergence was defined as less than 80% of the panelists agreeing with the recommendation.

5. Preparation of the recommendations document. A document was prepared that contained the recommendations and conclusions of the RPG, together with the percentage of final agreement reached after the external validation rounds, which was validated by the GC and the RPG. Three recommendations/conclusions were deleted after inconsistencies were detected.

The different phases of the process are shown in Figure 1.

Evidence Summary and Recommendations

This document contains a total of 73 recommendations and 81 conclusions (Supplementary Tables 1–5) on the management of patients with COPD and comorbidities, which were agreed among the expert members of the RVG. These conclusions and recommendations are grouped for each comorbidity by a) clinical consequences of the different comorbidities in the COPD patient and b) the appropriate treatment of patients with COPD and each of the comorbidities assessed.

COPD as a Disease with Extrapulmonary Manifestations and Comorbidities

The RVG achieved unanimity for conclusion C1 (Supplementary Table 1), based on the evidence that the systemic inflammation present in COPD, probably caused by the inflammatory process that develops in the airway, the parenchyma, and pulmonary circulation of COPD patients,[11] has been flagged as a possible etiopathogenic mechanism[12] common to other clinical manifestations, such as weight loss, muscle dysfunction, osteoporosis, and depression.[3]

Cardiovascular Risk Factors

Obesity

The prevalence of obesity in COPD patients is between 29.1% and 43%,[13] depending on the region, field of study, and disease stage.[14] Obesity causes respiratory function

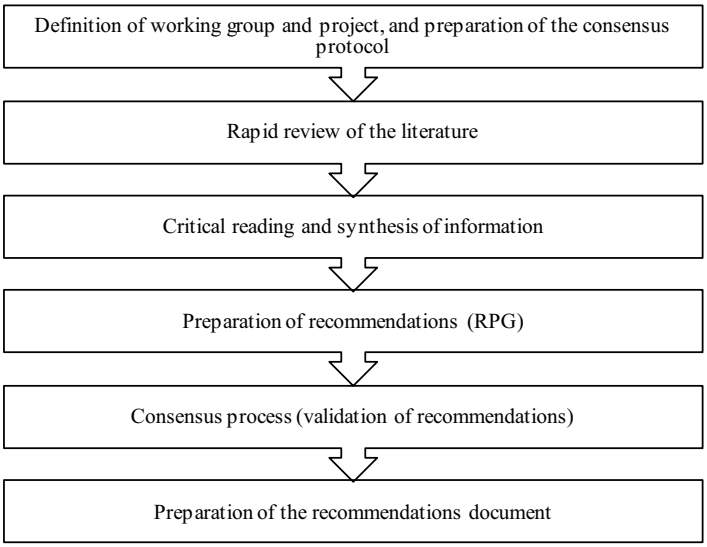

Figure 1 Process followed for the preparation of the consensus document.

changes[15] that lead to a reduction in patients' quality of life and exercise tolerance[13,16] and an increase in the use of health resources.[17] Patients with COPD and obesity should receive recommendations on nutrition and physical activity (Supplementary Table 2A).

Regarding the treatment of patients with COPD and obesity, the use of systemic corticosteroids can contribute to weight gain,[18] while roflumilast can cause weight loss.[19] Moreover, rehabilitation programs have been shown to produce equivalent improvements in obese and non-obese patients,[20,21] so these programs are recommended in patients with COPD and obesity. In overweight or obese patients, a higher fat-free mass index is associated with greater exercise tolerance, so weight loss treatment for reducing weight while preserving lean body mass should be considered[22] (Supplementary Table 2A).

Arterial Hypertension

Arterial hypertension (AHT) is the most common comorbidity in COPD patients[23] It is associated with a greater degree of dyspnea, lower tolerance for physical activity,[24] and airflow obstruction,[25] and correlates inversely with lung function.[26] Although AHT per se does not influence the natural history of COPD, it is a vascular risk factor for the development of cardiovascular disease.[5] Thus, in patients with COPD, AHT can promote the onset of heart failure (HF), ischemic heart disease (IHD), or chronic kidney disease, which worsen the prognosis of COPD.[4,27] A comprehensive examination must therefore be performed to detect the risk factors associated with COPD and AHT in all patients with both diseases (Supplementary Table 2B).

With regard to the appropriate treatment of patients with COPD and AHT, 2 conclusions and 4 recommendations were formulated (Supplementary Table 2B). Although no definitive conclusions can be made regarding the influence of long-acting bronchodilators (formoterol, salmeterol, indacaterol, tiotropium) and anti-inflammatory drugs (roflumilast, inhaled corticosteroids)[28–30] on the control of AHT, it can be concluded that bronchodilators (LAMA and LABA) are safe and well tolerated in hypertensive patients with COPD.[3]

According to evidence on the treatment of AHT in patients with COPD, calcium antagonists have no significant clinical effect on COPD,[31] while both renin-angiotensin-aldosterone system inhibitors and beta-blockers (BBs) may provide a benefit.[32,33] The use of cardioselective BBs is preferable if the patient has COPD and AHT, ICD, HF, or arrhythmias.[34,35] Retrospective and observational studies have also shown that the use of BB in patients hospitalized for COPD exacerbations was well tolerated and associated with a 40% reduction in mortality,[36] and a lower mortality rate and risk of exacerbation, respectively.[37] Patients receiving diuretics and atenolol must be closely monitored, and treatment with potassium supplements or potassium-sparing diuretics in the first case,[38] and reduction of doses of atenolol in the second,[4] may be considered.

Diabetes Mellitus

The prevalence of diabetes mellitus (DM) in COPD patients is higher than in the general population, and an estimated 29.4%–37% of COPD patients hospitalized are diabetic.[39,40] Diabetic patients also have an increased risk of COPD (as well as asthma, cystic fibrosis, and pneumonia), due to lung function decline and increased incidence of respiratory infections caused by chronic hyperglycemia.[41]

DM has implications for COPD patients. In the first place, it has been associated with a lower quality of life in several studies,[42–47] which has also been shown in a recent study to be the result of a decline in lung function and the consequent decrease in exercise tolerance.[47] DM in COPD patients reduces time to first hospitalization, prolongs the length of stay, and increases mortality due to exacerbations,[48] as a result of both greater numbers of exacerbations of infectious origin[49] and poorer outcomes with non-invasive mechanical ventilation during these events.[50] Furthermore, in the 24 months after hospitalization of patients with COPD and DM2 for exacerbations, the risk of mortality is twice that of those who do not have DM2[27], and an increase in 5-year mortality has also been reported.[39,51,52] Another study found that DM in COPD increases mortality by 3-fold, regardless of lung function,[53] and it is associated with restrictive changes in respiratory function that can lead to increased dyspnea and a greater predisposition to exacerbations.[54] Based on this evidence, we recommend to rule out DM in COPD patients, and to maintain an optimal degree of glycemic control in COPD patients with DM (Supplementary Table 2C).

No specific recommendations are currently available for the treatment of DM in COPD patients,[4] who can be managed according to standard guidelines,[3–5] as reflected in our recommendation (Supplementary Table 2C). According to the available evidence, the use of systemic corticosteroids for acute COPD exacerbations is associated with an increased risk of hyperglycemia,[55] an effect that does not occur with inhaled corticosteroids (ICS).[56,57] Insufficient evidence is available on the effect of roflumilast on blood glucose.[58] As in diabetic patients without COPD, metformin

is the first choice, and this drug must be suspended in the same situations as in diabetic patients without COPD. The adjustment of antidiabetic treatment and closer monitoring of blood glucose should be evaluated in diabetic patients with COPD[4], (Supplementary Table 2C).

Dyslipidemia

The prevalence of dyslipidemia in patients with chronic obstructive pulmonary disease (COPD) varies widely, depending on the type of study and the criteria selected to establish the dyslipidemia diagnosis. The prevalence in Spain is around 35%[59,60] although studies such as CONSISTE reported rates of up to 48%.[61] According to several studies, COPD patients characteristically present a lipid pattern with similar total cholesterol and low density lipoprotein cholesterol (LDL-C), lower triglycerides (TG), and greater high-density lipoprotein cholesterol (HDL-C) values than the general population.[4,62]

Although the role of dyslipidemia in the clinical course of COPD is still unclear, it must be monitored, as it represents a risk factor for the development of cardiovascular disease in these patients.[3] However, the available evidence is still insufficient to establish specific conclusions (Supplementary Table 2D).

Very few studies have evaluated the effect of the different COPD treatments on dyslipidemia. No significant clinical effects have been described with inhaled anticholinergics, and studies with methylxanthines and inhaled corticosteroids (ICS) point to an increase in total cholesterol and HDL-C with high doses of ICS in healthy patients[4] and an increase in HDL-C in rheumatology patients receiving prednisone[63] and inhaled beta-2 adrenergic agonists, such as terbutaline.[64] The scientific evidence on lipid-lowering treatments in COPD is insufficient to establish solid recommendations on their use, as studies published to date vary widely in terms of statins and doses, and the follow-up period is generally limited.[65,66] Among the effects observed, low-dose pravastatin was found to improve exercise tolerance in non-dyslipidemic patients,[67] and in several studies, treatment with statins reduced the number of exacerbations[68] in COPD patients with pulmonary hypertension[69] and concomitant cardiovascular disease,[70] as well as the number of hospitalizations.[71,72] In 1 study, however, the number of exacerbations and time to first exacerbation did not decrease in patients who received simvastatin.[68] The reduction in respiratory mortality and all-cause mortality does not appear to be due to the lipid-lowering effect of the statin, but rather to its antiinflammatory action.[73] Reductions in respiratory mortality and all-cause mortality of 55% and 21%, respectively, have been reported in patients with COPD who received statins.[74] Another study found no association between statin use, reduction of all-cause mortality, time to first hospitalization for exacerbation, or time to first pneumonia.[75] A meta-analysis of 10 randomized clinical trials studying the effect of statins in COPD patients showed an improvement in exercise tolerance, lung function, and quality of life in COPD patients with a history of cardiovascular disease treated with statins.[76] Given this evidence, our conclusions and recommendations about dyslipidemia in COPD patients are shown in Supplementary Table 2D.

Concomitant Cardiovascular Disease

Heart Failure

The prevalence of heart failure (HF) ranges from 5% to 60% in the general COPD population,[77] and increases in line with COPD severity, being approximately 30% in patients hospitalized for COPD exacerbations and rising to 75% in patients undergoing mechanical ventilation.[78–82] HF and COPD exacerbations share precipitating factors, such as respiratory infections, and the main symptoms of both diseases are similar (increased dyspnea), which can complicate diagnosis. The determination of natriuretic peptides is useful for ruling out the presence of HF in patients with COPD exacerbations[83] and a positive finding is associated with a worse prognosis in both patients hospitalized for COPD exacerbations and in patients with stable phase COPD,[84] (Supplementary Table 3A).

Health-related quality of life is worse in patients with COPD and concomitant HF (Supplementary Table 3A), These patients present a greater risk of mortality and hospital admission[85] according to a study of 1264 patients with HF and mild or moderate COPD[86] and another study of 7800 patients.[87] On the basis of 2 studies in which it was noted that readmission after hospitalization or COPD exacerbation was more frequent in patients with HF,[88] the latter being the most frequent reason for readmission,[89] and the fact that the presence of HF worsens the short and long-term prognosis of patients hospitalized for COPD exacerbation,[79,90] it was concluded that HF worsens the prognosis of COPD patients in terms of both new exacerbations and hospitalizations and mortality (Supplementary Table 3A). It has also been observed that COPD worsens the prognosis of patients hospitalized with HF,[91,92] and patients with both comorbidities have a higher risk of death and hospital admissions.

Long-acting bronchodilators, ICS, and LABA-LAMA fixed-dose combinations are safe in patients with HF[3,93,94] and do not increase the risk of heart disease.[95,96] Some

treatments for HF (cardioselective BBs, such as carvedilol) were also found to be safe in COPD patients,[33,97,98] and the use of BB was associated with a reduced risk of mortality[99] and COPD exacerbations.[100,101] Therefore, the presence of HF does not require a change in the treatment in patients with COPD.[93,97,102] (Supplementary Table 3A).

Ischemic Heart Disease

According to a systematic review, the prevalence of ischemic heart disease (IHD) in patients with COPD ranges between 7.1% and 31.3%, depending on the study population,[103] while in studies based on administrative databases, this prevalence has been estimated to be between 22% and 33.6%.[104–106] Cohort studies conducted in patients hospitalized for COPD exacerbations have shown a prevalence of IHD of between 17% and 22%.[78,79] The presence of both conditions in conjunction worsens patient prognosis, with COPD patients showing a significantly increased risk of having IHD,[107] a well-recognized cause of mortality in COPD patients.[97] In fact, IHD is one of the most frequent causes of mortality in COPD patients.[108] Several studies have found that quality of life is significantly worse in patients with COPD and concomitant IHD.[109–111] Moreover, the presence of IHD doubles the risk of hospitalization in patients with COPD,[112] and is associated with an increase in 3-month mortality,[79] and after an exacerbation, the risk of a coronary event in the following weeks is more than doubled.[113,114] In this regard, we recommend to rule out the possibility of IHD in all patients with COPD (Supplementary Table 3B).

Concerning the need for prescribing appropriate treatments in patients with COPD and IHD, the conclusions and recommendation are in Supplementary Table 3. In the treatment of COPD, no significant differences were found in mortality for combinations of drugs for COPD and IHD, such as salmeterol/fluticasone[115] or vilanterol/fluticasone.[94] The prognosis after an acute coronary event in COPD patients treated with ICS was better than in those who did not receive ICS.[116] The combination of ICS with LABA or LABA + LAMA also gave rise to lower mortality,[117,118] and LABA and LAMA are safe in patients with COPD and IHD.[29,114,119,120] In the treatment of IHD, statins may have a beneficial effect in COPD, although this was not demonstrated in a clinical trial evaluating the usefulness of statins in reducing COPD exacerbations.[114] The use of statins and angiotensin converting enzyme inhibitors was significantly associated with a decline in 90-day mortality in patients hospitalized for acute exacerbations;[121] BBs decreased mortality in COPD patients after myocardial infarction[99] and the risk of exacerbations in COPD patients with cardiovascular disease.[100] In another retrospective study, continuing treatment with BBs during hospitalization for COPD exacerbations was not associated with an increase in mortality or readmissions at 30 days,[122] while the use of antiplatelet drugs was associated with reduced mortality.[123]

Peripheral Artery Disease

A number of cohort studies have shown a prevalence of peripheral artery disease (PAD) in COPD patients of 8.8%,[124] and between 13% and 16%,[78,79] increasing according to the severity of obstruction.[124] Patients with COPD and PAD have less exercise tolerance and poorer quality of life,[124] and the presence of COPD is associated with a higher readmission rate after PAD is treated with bypass or percutaneous interventions.[125] In patients with stable COPD, a direct relationship was found between an ankle-brachial index of < 1 and an independent increase in 4-year mortality.[126] In hospitalized COPD patients, the presence of PAD was associated with an increase of mortality at 3 months.[79] In view of this evidence, the presence of PAD should be ruled out in COPD patients (Supplementary Table 3C).

Although some studies at the experimental level suggest that treatment with LABA + ICS or LAMA may decrease arterial rigidity (a marker of PAD),[127] in general the treatment of PAD is not affected by COPD treatment. Treatment with statins in patients with PAD and COPD is beneficial and BBs are safe and do not affect quality of life,[128] a finding confirmed in another study focusing on the year after hospitalization.[129] Smoking cessation is also recommended in the clinical practice guidelines for patients with PAD in the lower limbs.[130] (Supplementary Table 3C).

Atrial Fibrillation

The prevalence of arrhythmias in patients with stable COPD ranges from 5% to 15%, increasing to up to 20%-30% in patients with more severe COPD.[97] In 2 systematic reviews, it ranged from 5% to 29%,[105,107] and atrial fibrillation (AF) occurred in 21% and arrhythmia in 27% of patients hospitalized for COPD exacerbation.[40,78]

The most common arrhythmia in the general population and in patients with COPD is AF, and its presence is inversely associated with FEV_1 values. COPD patients are more likely to develop permanent AF and to relapse following cardioversion.[97] COPD exacerbations can cause AF, which in turn can be the cause of COPD exacerbations.[131]

COPD patients with AF have a worse quality of life, and COPD increases the risk of hospitalization for AF by up to 2-fold,[105,132] while the presence of AF increases mortality in patients hospitalized for COPD exacerbations,[79,133–135] thus worsening prognosis. Both dyspnea and hypercapnia and acidosis may predispose to AF.[136,137]

Several studies have found that treatments for COPD are associated with an increased risk of arrhythmias. The use of short-acting antimuscarinic agents (SAMA), starting treatment with LABA or SAMA in a population study in COPD patients, and oral steroids and theophylline have all been associated with an increased risk of AF and arrhythmias.[138–141] In contrast, no increase in arrhythmias associated with the use of LABA or LAMA has been demonstrated in clinical trials.[29,94] Conflicting results have also been reported with regard to an increase in the number of arrhythmias associated with inhaled SABA beta adrenergic receptor agonists,[140,142] and high doses of prednisone have been associated with an increased risk of AF.[143] Treatments for AF may be used either to reverse AF or to control heart rhythm; propafenone and flecainide should be avoided in patients with COPD, unless the absence of structural heart disease or diastolic dysfunction can be demonstrated.[3]

Neuropsychiatric Comorbidities

Anxiety

The prevalence of pervasive developmental disorders of anxiety in COPD patients ranges from 6% to 33%,[144] and up to 25% in patients with advanced COPD.[3,4,78] COPD patients often present symptoms of anxiety that influence COPD disease course and severity, and similarly, COPD symptoms can also contribute to cause anxiety.

The consequences of anxiety in COPD are shown in Supplementary Table 4A. The coexistence of COPD and anxiety has been associated with lower adherence to treatments and to rehabilitation programs or smoking cessation programs, and with a lower exercise tolerance and greater use of healthcare resources.[144–150] Anxiety is associated with a worse quality of life, greater functional deterioration, and increased mortality, especially among young patients, women, and smokers, and patients with chronic cough, a higher St. George's Respiratory Questionnaire score, or a history of cardiovascular disease.[151–154] When patients were evaluated using the health-related quality of life questionnaires,[155] a correlation was found between the baseline level of anxiety and decline in quality of life at 1-year follow-up.[156] Anxiety in COPD patients also worsens prognosis, with the consequence of higher health spending, increased frequency of readmissions, and worse self-management of the disease,[157–159] and is also associated with earlier hospital admission.[160,161] Moreover, according to a recent meta-analysis, the presence of anxiety increases the likelihood of developing an exacerbation by 31%.[145]

Anxiety also increases mortality rates,[145] emergency department visits, and readmission after exacerbation in the first 30 days after discharge in COPD patients,[145,162] who have discrepancies in terms of lung function, with respect to the effect of anxiety on them. Some studies have shown a decline in FEV1,[151–154] while others have found no correlation.[163] Because some of the symptoms of COPD and anxiety are similar (lack of energy, fatigue, sleep disturbances, or less enjoyment of pleasurable activities), it is very important to assess psychological health using questionnaires or scales validated in these patients.[153]

The concomitant use of pharmacological treatments for anxiety and pulmonary rehabilitation programs may have additive therapeutic effects.[164] Physical exercise, as part of pulmonary rehabilitation programs, has a beneficial effect on anxiety associated with COPD.[165] In respect of treatments for anxiety in patients with COPD, the first line of treatment must be non-pharmacological interventions.[166,167] In this respect, relaxation techniques showed a mildly positive effect on lung function and levels of anxiety, and a greater effect associated with an improvement in perceived quality of life.[168] In terms of pharmacological interventions, antidepressants alter patients' perception of some symptoms, such as dyspnea, and improve quality of life.[85] Selective serotonin reuptake inhibitors have reduced anxiety symptoms in the short term (6 months' follow-up), whereas no significant differences were found with tricyclic antidepressants or azapirones compared to placebo.[169–173] The UK National Institute for Health and Care Excellence guidelines recommend the use of selective serotonin reuptake inhibitors as first-line treatment in patients with associated anxiety.[174] However, drug-drug interactions must be taken into account, as fluvoxamine reduces the metabolism of theophylline derivatives and interacts with roflumilast, so the use of alternative selective serotonin reuptake inhibitors is recommended.[4] The healthcare professional must be aware of and monitor potential interactions between antidepressants and beta-2 adrenergic agonists or anticholinergic bronchodilators.[175] Theophylline may decrease the anxiolytic effect of benzodiazepines, especially diazepam and alprazolam.[4] The recommendations about the therapy of anxiety in COPD patients are shown in Supplementary Table 4A.

Insomnia

Insomnia can affect up to 70% of COPD patients at some point during their disease,[176–178] and COPD is a risk factor for insomnia.[179] The incidence of sleep disorders increases with the presence of respiratory symptoms in all age groups over 45 years.[180]

The main consequences of poor sleep quality are reduced quality of life,[177,181] increased states of anxiety or depression, the uncontrolled and possibly harmful use of hypnotics,[85] and hypoxemia and hypercapnia. The latter two may cause cardiac arrhythmias, pulmonary hypertension, and nocturnal death, especially during acute exacerbations.[182] Insomnia can predict COPD exacerbations, the use of emergency services, and all-cause mortality, which suggests that insomnia may be a significant risk factor for worsening or poor prognosis of COPD.[183] Asking about the quality of sleep in COPD patients is recommended (Supplementary Table 4B).

Insomnia in COPD patients must be treated (Supplementary Table 4B). In the treatment of insomnia, both a non-pharmacological approach[184] and drug treatment are used, principally with hypnotic drugs and benzodiazepines. Epidemiological studies have suggested that hypnotics increase the risk of respiratory adverse events, such as pneumonia, acute exacerbation, acute respiratory failure, and cardiorespiratory arrest in patients with COPD.[185] Benzodiazepines are currently the hypnotics of first choice[184] in these patients, although they may cause respiratory depression.[186,187] The anxiolytic effect of benzodiazepines can be reduced with theophylline,[4] and theophylline levels can increase with the use of St. John's wort, requiring changes in dosing or suspension of the benzodiazepine.[4]

Regarding the interactions between insomnia and COPD, no studies have shown that the treatment of a patient with COPD should differ according to the presence or absence of insomnia, with the exception of possible drug-drug interactions that may occur.

Depression

Depression is a common disorder in COPD patients, with a prevalence of around 25%,[188] which increases with COPD severity,[152] affecting between 50% and 90% of patients with advanced COPD. Thus, COPD increases the risk of depression.[145] The quality of life of patients with COPD and depression is reduced,[156,189-191] and exacerbations, admissions and hospital readmissions, emergency room visits, and lengths of hospital stay are higher in these patients.[157,192-194] Depression in COPD patients has also been associated with increased mortality[145,193] and with important clinical consequences, such as greater functional decline,[191] lower exercise tolerance,[195] dyspnea,[196] lower adherence to drug treatment[147] and rehabilitation programs,[197] lower physical activity,[198] and higher healthcare costs in the subsequent 2 years.[157] As a result of this evidence, we recommend that the existence of depression in COPD patients should be ruled out at frequent intervals (Supplementary Table 4C).

The treatment of depression in patients with COPD should be similar to that of the general population,[3,5] although patients with COPD generally do not receive treatment for depression.[151,188] Studies that evaluated drug treatments for depression in COPD patients found that SSRIs improve depression,[199] whereas tricyclic antidepressants gave rise to great heterogeneity and high drop-out rates.[199] Treatment with paroxetine improved anxiety and depression in these patients[171] and nortriptyline improved depression,[173] while paroxetine did not worsen respiratory symptoms.[170] Medicare data between 2006 and 2012 reported that patients with COPD and depression who complied with their antidepressant treatment made fewer visits to the emergency room and had fewer hospitalizations.[200] As for psychological treatment, 3 meta-analyses show that psychological and lifestyle interventions, multicomponent exercise training,[161] and behavioral therapy[201] are associated with a small reduction in depressive symptoms, and that relaxation techniques improved dyspnea and psychological well-being,[202] and also slightly improved respiratory function.[168]

COPD treatment based on respiratory rehabilitation and physical intervention programs also improved depressive symptoms, dyspnea, and quality of life.[203,204]

There may be drug interactions between treatments for COPD and depression. For example, the combined use of beta-adrenergic agonists and antidepressants could prolong the QT interval and promote the emergence of ventricular arrhythmias.[175] Tricyclic antidepressants may also enhance the cardiovascular adverse effects of beta-adrenergic agonists[175] and, moreover, their anticholinergic effect added to that of bronchodilators (such as ipratropium, tiotropium) can lead to adverse effects.[175] Despite these potential interactions, the combination of antidepressants with anticholinergic or beta-adrenergic bronchodilators is not contraindicated,[175] although recommendations have been made in this regard. For example, a type C interaction has been observed between beta-adrenergic bronchodilators and monoamine oxidase inhibitors (MAOIs) and tricyclic

antidepressants,[4] so close monitoring of these patients is recommended. The interaction between roflumilast and fluvoxamine is also type C,[4] while a type D interaction has been reported between roflumilast, theophylline, fluvoxamine and St. John's wort (the combination of these drugs is not recommended and treatment should be modified).[4]

Cognitive Impairment

COPD patients often present cognitive dysfunction; in fact, they are twice as likely to develop cognitive impairment.[205] A systematic review estimated a prevalence of cognitive impairment of 2%-20% in COPD patients.[206] Exacerbations[207] and chronic hypoxemia and hypercapnia in patients with COPD and obstructive sleep apnea syndrome[4,208,209] are associated with a greater cognitive impairment. Cognitive impairment is associated with longer hospital stays among patients hospitalized for acute COPD exacerbation[206] and an increased risk of hospital admission.[210] Patients with COPD and dementia have also shown an increased risk of death at 3 years,[210] and cognitive impairment has been associated independently with mortality at 32 months.[211] In another study, the presence of dementia was a predictor of 3-month mortality in patients hospitalized for COPD exacerbation.[79] Looking for and ruling out the existence of cognitive impairment is recommended in COPD patients (Supplementary Table 4D).

With regard to the treatment of patients with COPD and cognitive impairment, we have formulated several recommendations (Supplementary Table 4D), taking into account the following data. Chronic oxygen therapy in COPD patients with hypoxemia has been associated with a decreased risk of cognitive impairment,[212] and patients who followed pulmonary rehabilitation programs showed improved cognitive function[213] in visual attention, verbal memory and visual-spatial functions[214] and, in patients awaiting lung transplantation, an improved mental summary component of SF-36.[215] In the treatment of cognitive impairment, acetylcholinesterase inhibitors were not associated with more emergency department visits, more hospitalizations, or more exacerbations in patients with COPD and dementia.[216] Regarding the possible drug interactions, since anticholinergics counteract the therapeutic effect of central acetylcholinesterase inhibitors used in the treatment of dementia, the protocol of the Spanish Society of Internal Medicine on diagnostic and therapeutic management of comorbidities in COPD[4] recommend that the therapeutic effect of both groups is monitored during concomitant use.

Other Comorbidities

Pain

The prevalence of pain in COPD patients is between 45% and 60%,[217,218] and reaches 70% in advanced stages of the disease,[219] although its incidence is underdiagnosed in these patients.[217,220] Despite its importance, few clinical trials or meta-analysis have focused on pain associated with COPD[217,218,221-223] and pain management is barely mentioned in the national and international COPD guidelines. Pain is up to 2.6 times more common in COPD patients than in patients with other chronic diseases.[217,223-225]

The presence of pain does not alter lung function in COPD patients, but it is associated with increased dyspnea, worse quality of life, insomnia, fatigue, anxiety, depression, and a poor nutritional status. Pain has not been clearly associated with age, sex, or smoking status.[222,226] No studies have evaluated pain and COPD disease course in terms of exacerbations, hospital admissions, and survival. For a proper evaluation of the intensity of pain associated with COPD and response to different analgesics, pain quantification scales, such as the Brief Pain Inventory,[227] the McGill Pain Questionnaire,[228] or the Visual Analogue Scale (VAS) are useful.[229] Patients with COPD and pain tend to score high in these scales. Thus, Lohne et al found that 38% of patients with severe COPD score over 6 in a numerical scale of 1 to 10,[220] (Supplementary Table 5A). No evidence is available on the influence of COPD treatment on the treatment of pain, although analgesics are widely consumed by patients with COPD, and used more than by patients without COPD.[230] Neither opioids at appropriate doses nor non-steroidal anti-inflammatory drugs confer a higher risk of respiratory depression in COPD patients,[231–233] while NSAIDs induce less drowsiness than opioids.[234] The coadjuvant use of tricyclic antidepressants in the treatment of pain should be closely monitored in patients who use beta-2 agonists.[4] Concerning the interactions between COPD and pain, COPD patients with pain may develop worsening dyspnea, with increased use of bronchodilator medication.[220] Patients following pulmonary rehabilitation programs showed no improvement in pain,[235–237] Supplementary Table 5A presents the recommendation about treatment of patients with COPD and pain.

Anemia

The prevalence of anemia in patients with COPD was estimated at between 7.5% and 34%[238] in a systematic review, rising to 43.9% in other studies,[239–241] being chronic anemia and iron-deficiency anemia the most common in these

patients.[242] Anemia is more common during exacerbations. A systematic review[243] found that the presence of anemia in patients with COPD leads to a reduction in quality of life, and a greater number of hospitalizations and readmissions. These findings have been corroborated in studies on administrative databases, in which more exacerbations, hospitalizations, pneumonia, and admissions in intensive care units were observed.[244,245] Survival of patients with COPD and anemia during hospital admissions is lower,[241,243,245-249] with a mortality rate twice that of patients without anemia.[245] In addition, the presence of anemia in COPD is associated with a lower exercise tolerance,[243] greater dyspnea,[246] higher C-reactive protein values,[241] and greater use of healthcare resources.[243] It is also a risk factor for home oxygen therapy in these patients,[250] (Supplementary Table 5B). Anemia is a modifiable condition and correction of anemia in chronic diseases other than the COPD has been associated with improved health. No clinical trials are currently available on the treatment of anemia in patients with COPD, but it has been observed in case studies that blood transfusion helped in weaning from mechanical ventilation[251] and improved both the minute ventilation and work of breathing.[24] Treatment with intravenous iron and erythropoiesis-stimulating agents improved hemoglobin and dyspnea.[239] In patients with COPD, the etiological treatment of anemia is recommended (Supplementary Table 5B).

Osteoporosis

The prevalence of osteoporosis in patients with COPD ranges between 9% and 69%, depending on the study,[252] being higher in women[253,254] and 2 to 5 times higher than in the general population.[252] Osteoporosis is underdiagnosed and undertreated in COPD patients[255] and has been associated with a lower quality of life.[256,257] Osteoporosis appears to be a risk factor for COPD and vice versa. In several studies, osteoporosis, lower bone density, and vitamin D deficiency in COPD patients were associated with more acute exacerbations and hospitalizations.[258,259] Vertebral fracture, lower bone density, osteoporosis, and vitamin D deficiency have also been associated with more hospitalizations.[258–260] The number of exacerbations has been associated with an increased risk of osteoporosis[261] and a greater decrease in bone mass.[262] The degree of obstruction is also associated with an increased risk of bone fractures.[261] With regard to survival, vertebral fracture in patients with COPD has been associated with higher 2-year mortality.[260] Each vertebral fracture also reduces forced vital capacity by 9%.[263] A systematic review of rehabilitation programs in patients with COPD and osteoporosis found that exercise tolerance improved to a lesser extent than that of patients with other comorbidities.[264] The existence of osteoporosis should be ruled out in COPD patients. We recommended to check the lateral chest X-ray to find vertebral fractures (Supplementary Table 5C).

No specific treatments are available for osteoporosis in COPD patients, but corsets can be used for the treatment of unstable vertebral fractures. Systemic corticosteroids, used for the treatment of COPD exacerbations, increase the risk of osteoporosis[265] and their use has been associated with a higher incidence of fractures.[265] This is also true of ICS,[266] for which the association is dose-dependent.[267] Lung volume reduction surgery[268] led to an improvement in bone density in 40 patients with emphysema,[268] and pulmonary rehabilitation programs have been shown to improve exercise tolerance in patients with COPD and osteoporosis.[264] Bisphosphonates were useful for the treatment of corticosteroid-induced osteoporosis.[269] Patients with COPD and osteoporosis should be referred for rehabilitation (Supplementary Table 5C).

The potential drug-drug interactions between treatments are not of particular importance, and only steroids show a type C interaction (it is recommended that patients receiving denosumab are closely monitored).[4]

Gastroesophageal Reflux Disease

The prevalence of gastroesophageal reflux disease (GERD) in patients with COPD in Spain has been estimated at 28%-62%,[270–273] higher than in the general population. The severity of GERD symptoms increases with the severity of COPD,[274,275] and COPD patients diagnosed with GERD have poorer lung function.[276] The presence of reflux symptoms in COPD patients is related with more frequent and more severe exacerbations.[277–279] The presence of GERD, then, is an independent risk factor for exacerbations[276] and is associated with a worse quality of life,[280–282] and may result in a COPD patient with an "infrequent exacerbator" phenotype developing a "frequent exacerbator" phenotype.[275] Pulmonary hyperinflation and dyspnea are risk factors associated with the incidence of symptoms of GERD.[283] The influence of GERD on mortality in COPD is not presently known.[271,272,276,284] Supplementary Table 5D, shows the conclusions and recommendations referring to the treatment of patients with COPD and. Beta agonists and theophylline, used in the treatment of COPD, can produce reflux symptoms[285] while tiotropium may reduce the symptoms of GERD.[284,286] Proton pump inhibitors are the most effective

drugs in GERD[287,288] and reduce chronic cough in these patients.[289] It has not been demonstrated that high-dose omeprazole improves the degree of pulmonary obstruction or bronchial hyperresponsiveness.[290] Oral lansoprazole has been effective in preventing exacerbations by inhibiting gastric secretion, reducing reflux, and decreasing levels of inflammatory markers in sputum.[291]

Thromboembolic Disease

In Spain, the estimated prevalence of venous thromboembolism in hospitalized patients with COPD is between 8% and 25%,[292] and the incidence of deep venous thrombosis (DVT) is 10%-12%.[292] COPD patients are more likely to develop a venous thromboembolic event [DVT, pulmonary thromboembolism (PTE)], both during exacerbations[293,294] and in stable phase disease.[295] Clinical manifestations in patients with COPD and thromboembolic disease may be subtle and diagnosis is often delayed, while symptoms of PTE can be confused with a COPD exacerbation. With regard to the influence of thromboembolic disease on quality of life, data from studies vary widely,[296,297] and in the course of COPD, the presence of DVT in patients with COPD exacerbation results in longer hospital stays, increased risk of PTE, a greater number of intensive care unit admissions, and a greater need for mechanical ventilation and placement of filters in the inferior vena cava.[293,294,298] (Supplementary Table 5E), Frequently PTE is the first presentation of thromboembolic disease in COPD patients, and is associated with higher mortality, more frequent hemorrhage, and more recurrence of thrombosis within 3 months.[299,300]

No evidence is available on the influence of COPD treatment on patients with thromboembolic disease. COPD patients present a greater number of major bleeds,[299] so other therapies such as temporary inferior vena cava filters have been used.[299,300] In cases of spontaneous VTE, no significant differences were observed in the duration of anticoagulation therapy between patients with or without COPD.[301] Treatment with low molecular weight heparins during acute COPD exacerbations has proved useful in the prevention of DVT: nandroparine prophylaxis in patients with acute COPD exacerbations reduced the incidence of DVT.[302] The Supplementary Table 5E presents the recommendations about prophylaxis and treatment of venous thromboembolic disease in COPD patients.

Chronic Kidney Disease

The prevalence of chronic kidney disease (CKD) in patients with COPD ranges between 6.5% and 26.2%.[40,78,303,304] Moderate CKD has been detected in 6.5% of the COPD population in Spain[78] and 22% of patients with multiple pathologies associated with COPD.[305] Frequently CKD is an unknown comorbidity.[303] The recommendation is to estimate the glomerular filtration rate (CKD-EPI or MDRD equations can be used) in COPD patients (Supplementary Table 5F). CKD is more common in COPD patients with serious lung function impairment and systemic inflammation,[306] and the risk increases significantly when obstructive sleep apnea syndrome occurs in COPD.[307] No studies have yet evaluated the impact of CKD on quality of life in COPD patients and patient progress. With regard to survival, CKD is an adverse prognostic factor related to short-term mortality in patients with COPD,[308] and moderate and severe COPD associated with CKD and acute CKD correlated with an increase in mortality,[309,310] a finding corroborated in another longitudinal cohort study.[311]

In respect of to the appropriate treatment of patients with COPD and CKD, there is no evidence that COPD treatments influence the treatment of CKD, nor that this comorbidity requires a change in COPD treatment, so it is advisable to follow clinical practice guideline recommendations,[312,313] (Supplementary Table 5F).

Lung Cancer

The prevalence of COPD in patients with lung cancer (LC) is between 50% and 64%[314,315] Moreover, 20%–25% of patients with COPD develop LC, primarily patients with mild or moderate airflow obstruction.[314,315] According to other data, LC develops in around 3.8%–8.0% of COPD patients.[316,317]

Ample evidence is available to demonstrate the association between COPD and LC, the common etiologic factor of which is smoking.[6,318] Also emphysema and airflow limitation are risk factors for LC development.[317] COPD is also an independent risk factor in the development of LC.[319] No studies have assessed the impact of LC on the quality of life of patients with COPD nor have any studies assessed the course of COPD in patients with LC. With regard to survival, various studies show that LC is one of the leading causes of mortality in COPD patients with mild-to-moderate obstruction and that the presence of COPD adversely affects the prognosis of the patient with LC.[6,280]

There is no evidence that the presence of LC requires a change of treatment in patients with COPD and vice versa. It has been suggested that, due to their anti-inflammatory

properties, ICS have a possible protective effect on the development of LC, and high doses of these drugs reduce the LC risk.[320–322] The treatment of LC requires a multidisciplinary approach with additional tests, since the decision to perform resection surgery is more complex due to worse lung function.[323] No drug-drug interactions have been described between treatments for COPD and LC (Supplementary Table 5G). In Supplementary Table 6 we present the recommendations in divergence after the Delphi rounds.

Conclusions

In summary, this document presents conclusions and recommendations on the consequences of various comorbidities in COPD patients and the treatment of these patients, proposed by the recommendations preparation group and validated by a group of experts after 2 Delphi rounds. Consensus was reached (agreement > 80%) for a total of 73 recommendations and 81 conclusions that are intended to be useful in the management of patients with COPD and comorbidities.

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Author Contributions

All the authors of this document made substantial contributions to conception and design, acquisition of data, or analysis and interpretation of data; took part in drafting the article or revising it critically for important intellectual content; gave final approval of the version to be published; and agree to be accountable for all aspects of the work.

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