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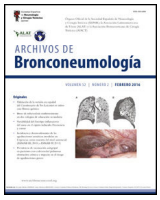

SEPAR's Voice

[Translated article] Spanish COPD Guideline (GesEPOC) Update: Comorbidities, Self-Management and Palliative Care

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ABSTRACT

The current health care models described in GesEPOC indicate the best way to make a correct diagnosis, the categorization of patients, the appropriate selection of the therapeutic strategy and the management and prevention of exacerbations. In addition, COPD involves several aspects that are crucial in an integrated approach to the health care of these patients. The evaluation of comorbidities in COPD patients represents a healthcare challenge. As part of a comprehensive assessment, the presence of comorbidities related to the clinical presentation, to some diagnostic technique or to some COPD-related treatments should be studied. Likewise, interventions on healthy lifestyle habits, adherence to complex treatments, developing skills to recognize the signs and symptoms of exacerbation, knowing what to do to prevent them and treat them within the framework of a self-management plan are also necessary. Finally, palliative care is one of the pillars in the comprehensive treatment of the COPD patient, seeking to prevent or treat the symptoms of a disease, the side effects of treatment, and the physical, psychological and social problems of patients and their caregivers. Therefore, the main objective of this palliative care is not to prolong life expectancy, but to improve its quality. This chapter of GesEPOC 2021 presents an update on the most important comorbidities, self-management strategies, and palliative care in COPD, and includes a recommendation on the use of opioids for the treatment of refractory dyspnea in COPD.

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Actualización de la Guía Española de la EPOC (GesEPOC): comorbilidades, automanejo y cuidados paliativos

Palabras clave:
EPOC
GesEPOC
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Atención integrada
Automanejo
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R E S U M E N

Los modelos de atención sanitaria actuales descritos en GesEPOC indican la mejor manera de hacer un diagnóstico correcto, la categorización de los pacientes, la adecuada selección de la estrategia terapéutica y el manejo y la prevención de las agudizaciones. Además, en la EPOC concurren diversos aspectos que resultan cruciales en una aproximación integrada de la atención sanitaria a estos pacientes. La evaluación de las comorbilidades en el paciente con EPOC representa un reto asistencial. Dentro de una valoración integral debe estudiarse la presencia de comorbilidades que tengan relación con la presentación clínica, con alguna técnica diagnóstica o con algunos tratamientos relacionados con la EPOC. Asimismo, son necesarias intervenciones en hábitos de vida saludables, la adhesión a tratamientos complejos, desarrollar capacidades para poder reconocer los signos y síntomas de la exacerbación, saber qué hacer para prevenirlos y tratarlos enmarcados en un plan de automanejo. Finalmente, los cuidados paliativos constituyen uno de los pilares en el tratamiento integral del paciente con EPOC, con los que se buscan prevenir o tratar los síntomas de una enfermedad, los efectos secundarios del tratamiento, y los problemas físicos, psicológicos y sociales de los pacientes y sus cuidadores. Por tanto, el objetivo principal de estos cuidados paliativos no es prolongar la esperanza de vida, sino mejorar su calidad. En este capítulo de GesEPOC 2021 se presenta una actualización sobre las comorbilidades más importantes, las estrategias de automanejo y los cuidados paliativos en la EPOC, y se incluye una recomendación sobre el uso de opiáceos para el tratamiento de la disnea refractaria en la EPOC.

Introduction

The recommendations of the Spanish COPD guidelines (GesEPOC) should not be limited to reaching the correct diagnosis, classifying patients, selecting the appropriate therapeutic strategy, and managing and preventing exacerbations.[1] Several other areas of chronic obstructive pulmonary disease (COPD) are essential for implementing a more integrated approach to healthcare for these patients. For a start, the high prevalence of chronic diseases constitutes a heavy burden on healthcare systems and on patients. Furthermore, in a chronic, persistent disease such as COPD, the active involvement of the patient is a key component in disease management. Finally, healthcare services must be active in guiding patient decisions and assisting family support in the most advanced phases of the disease in order to offer the best palliative care strategies. The aim of this article is to update GesEPOC 2021 with recommendations on comorbidities, self-management strategies, and palliative care that should be integrated into the existing COPD guidelines for patient care. The methodology used to develop the recommendations included in this article is described in the latest update of the Spanish COPD Guidelines (GesEPOC 2021).[1]

Comorbidities

Establishing recommendations for the management of comorbidities in COPD can be complicated for several reasons. Firstly, the COPD-comorbidity relationship is two-way, so it may be just as necessary to establish an approach to the management of COPD in patients with a particular comorbidity as it is to determine the management of a comorbidity in a patient with COPD. Secondly, in the case of comorbidities that appear before COPD, the temporal relationship may not be clearly established, and there may be a complex interaction between the two.[2] Thirdly, it is sometimes difficult to judge from the available data if the association between COPD and other comorbidities has any etiopathogenic relationship or whether it is a simple coincidence, given the relative cardiovascular of these diseases in the population.[3,4] Fourthly, the available evidence is derived mainly from the description of adverse effects in clinical trials listed as secondary outcomes, from post hoc analysis and sub-analysis of pooled data, and from observational studies.[5] Therefore, prevalence data or their prognostic impact are limited by the quality of the available data. In order to make clinically relevant recommendations, we will evaluate the management of COPD in the presence of comorbidities that are related to 3 aspects: clinical presentation, diagnostic techniques, and COPD treatments, and we will evaluate the frequency and prognostic impact of each comorbidity to put their importance in perspective. Table 1 shows the key points of the recommendations, that are summarized by body systems in Table 2.

Table 1
Comorbidity key points.

- The clinical presentation of poorly controlled COPD patients may be influenced by various comorbidities
- The main comorbidities to study in an initial examination of COPD patients with high-impact disease despite treatment are cardiovascular diseases, gastroesophageal reflux, muscle dysfunction, respiratory comorbidity, osteoporosis, and psychiatric and nutritional disorders
- The main comorbidities that can affect inhaled treatments for COPD are benign prostatic hyperplasia, osteoporosis, and ocular hypertension
- Some type of protocol or algorithm must be established to address these comorbidities in the high-risk COPD patient

COPD: chronic obstructive pulmonary disease.

Cardiovascular system

The relationship between COPD and cardiovascular disease is clearly relevant, since it affects the clinical presentation of COPD, alters diagnostic tests, and has therapeutic implications. The main cardiological diseases associated with COPD are heart failure of different etiologies, rhythm disorders, primarily atrial fibrillation, ischemic heart disease, systemic arterial hypertension, sudden death, peripheral arterial disease, and cerebrovascular disease.[6]

In terms of the impact of cardiovascular disease on the clinical presentation of COPD, whether stable phase disease or exacerbations, when the primary clinical expression is dyspnea, concomitant cardiovascular disease must be considered in a patient who is persistently poorly controlled despite correct inhaled treatment (Table 2).[7] In these cases, an electrocardiogram and echocardiography are recommended as a first approach, while a exercise test should be considered if the contribution of each organ to exercise tolerance needs to be determined. Furthermore, COPD patients who attend the emergency department for dyspnea often

Table 2
Summary of recommendations for the management of COPD in patients with comorbidities.

	COPD symptoms	COPD diagnosis	COPD treatment
Cardiovascular	• Increased symptoms and poor symptom control	• Study spirometric restriction	• Avoid high-dose SABA and SAMA • Use cardioselective beta-blockers • Avoid prolonged high-dose systemic corticosteroids
Periodontal disease	• Rule out in persistent exacerbators		
Gastroesophageal reflux	• Rule out in persistent exacerbators	• Increased bronchial hyperresponsiveness	
Benign prostatic hyperplasia			• Assess worsening at the start of treatment with LAMA • Avoid the SAMA-LAMA combination
Osteoporosis	• Worse lung function • Increased impact of COPD • Worse quality of life		• Evaluate closely the indication of inhaled corticosteroids • Reduce the dose of inhaled corticosteroids
Muscle dysfunction	• Exercise capacity limitation and increased impact	• Perform exercise test, dynamometer	• Pulmonary rehabilitation programs
Sexual dysfunction	• Assess sexual dysfunction in high-risk patients		
Asthma	• Increases respiratory symptoms • Increases the risk of exacerbations	• Assess bronchodilator reversibility • Assess bronchial hyperresponsiveness • Assess the role of FeNO • Assess atopy and etiology	• Treat as asthma
Obstructive sleep apnea	• Worsening quality of life • Greater impact	• Decreased FVC if associated with obesity	• Treatment of SAHS
Bronchiectasis	• Increased symptoms • Increased exacerbations	• Confirm with high-resolution computed tomography • Associated FVC decrease • Determination of sputum cultures	• Treatment of chronic bronchial infection
Pulmonary hypertension	• Greater impact • Worsening of prognosis	• Bilateral hilar increase in X-ray • DLCO changes	
Lung cancer	• Hemoptysis • Constitutional syndrome	• Suggestive lesions on imaging tests • Assess CT screening according to current recommendations	
Thoracic cage abnormalities	• Increased symptoms • Overall respiratory failure	• Restrictive component • Respiratory failure in blood gases	• Pulmonary rehabilitation
Pulmonary fibrosis	• Increased symptoms • Worse prognosis	• Associated restrictive component • Earlier respiratory failure	• Possible future role of antifibrotics
Chronic rhinitis	• Increased symptoms	• Relationship to obstruction	• Assessment of nasal corticosteroids
Vitamin D deficiency	• Increased symptoms • Increased risk of exacerbations	• Progression of obstruction	• Supplements if severe deficiency
Cognitive impairment	• Impact on quality of life		• Select a suitable inhaler
Ocular hypertension	• Some eye drops may produce a bronchospasm reaction		• Assess discontinuation of timolol or benzalkonium chloride • Try to avoid nebulized antimuscarinic agents • Wash hands thoroughly after use of dry powder inhalers with LAMA
Anxiety, depression	• Increased perception of dyspnea • Association with quality of life • Association with prognosis		• Ensure adequate adherence and inhalation technique • Adequately treat psychiatric disorders
Obesity	• Increased symptoms	• Restrictive component • Association with chronic global respiratory failure • Association with increased bronchial hyperresponsiveness	• Initiate ICS if bronchial hyperresponsiveness
Sarcopenia	• Increased impact on clinical presentation • Association with quality of life • Association with prognosis		• Pulmonary rehabilitation
Anemia	• Increased perception of dyspnea		

CO: carbon monoxide; COPD: chronic obstructive pulmonary disease; CT: computed axial tomography; FeNO: exhaled fraction of nitric oxide; FVC: forced vital capacity; ICS: inhaled corticosteroids; LAMA: long-acting anticholinergics; SABA: short-acting beta-agonists; SAMA: short-acting anticholinergics.

have heart disease,[8,9] so it would be reasonable to recommend a cardiological clinical evaluation along with the determination of markers of heart failure (pro-BNP) or acute myocardial damage (troponin) as part of the study of acute dyspnea.

From a diagnostic point of view, the presence of hyperinflation has been associated with impaired cardiac function.[10] Heart failure may also be associated with a restrictive component in spirometry.[11] COPD patients should, therefore, be examined for clinical signs of heart failure if spirometry shows a mixed pattern.

From a therapeutic point of view, 3 factors should be taken into consideration. First, although the cardiovascular safety of bronchodilator drugs has been demonstrated,[12] it is also that one of the most common adverse effects is an elevated heart rate, especially with short-acting bronchodilators, seems reasonable to avoid their excessive use and to ensure the correct dosing of long-acting

compounds. Second, if beta-blockers are necessary, cardioselective drugs (acebutolol, atenolol, bisoprolol, celiprolol, metropolol, nebivolol and esmolol)[13] should be used. Third, although systemic corticosteroids are only recommended in COPD exacerbations, we should remember that the main adverse effects of glucocorticoids on the cardiovascular system include dyslipidemia and hypertension. These effects may predispose to coronary artery disease if high doses and prolonged courses are administered.[14]

Digestive system

The relationship of COPD with various gastrointestinal conditions has been discussed in the literature, but 2 comorbidities of particular significance emerge: periodontal disease and gastroesophageal reflux. Several papers have described a higher frequency of periodontal disease in COPD patients.[15] Although COPD patients are at increased risk for periodontal disease, the impact of the disease on clinical presentation, diagnostic techniques, and COPD treatment has not been conclusively demonstrated. Its impact on self-reported quality of life has been noted, but no effect on the frequency of exacerbations has been observed.[16,17] COPD patients should therefore be advised to maintain good oral health, especially if they are symptomatic.

Numerous studies exploring the relationship between gastroesophageal reflux and COPD have consistently shown an increased risk of exacerbations.[18] This relationship has two controversial aspects. The first is that gastroesophageal reflux can be asymptomatic[19] and the effect of asymptomatic reflux on COPD exacerbations has not been sufficiently explored. Secondly, the efficacy of reflux treatment in reducing the risk of exacerbations is under debate.[20–23] Despite these limitations, it seems reasonable to recommend active screening for the presence of gastroesophageal reflux in patients with persistent exacerbations and to start appropriate treatment, if available.

Excretory system

Although the data are conflicting,[24–27] an association has been described between treatment with inhaled antimuscarinic drugs and episodes of urinary retention.[28] The risk may be greater in patients who use both SAMA and LAMA simultaneously[25,29,30] and in subjects with benign prostatic hyperplasia[25,29,31] during the first months of treatment.[25,31] Therefore, urinary symptoms should be monitored in patients with COPD and prostatic hyperplasia during the first few months of treatment, especially if they are receiving a SAMA-LAMA combination.

Musculoskeletal system

The musculoskeletal system includes the joints, bones, and muscles. The most relevant comorbidities to consider are osteoporosis and muscle disorders. There is evidence on the association between COPD and osteoporosis.[32] COPD patients have a higher prevalence of vertebral fractures and a low bone mineral density, which in turn is associated with COPD severity and prognosis.[33] The risk of osteoporosis is multifactorial and appears to be related to treatment with inhaled corticosteroids (ICS), the appearance of emphysema, and a reduction in bone mineral density. However, evidence on the relationship between osteoporosis and ICS is controversial and conflicting. The results of clinical trials with ICS do not show a relationship,[34] while observational studies describe a clear association, probably because most clinical trials have a duration of 1 year, which is insufficient time for the development of osteoporosis.[35,36] Until this relationship is clarified, if ICS treatment is necessary, it is advisable to use the lowest possible dose in patients with a diagnosis of osteoporosis or other risk factors for osteoporosis (greater age, smoking habit, lower body mass index, sarcopenia, low level of physical activity, and vitamin D deficiency, among others).

Muscle dysfunction is a significant systemic consequence of COPD and affects both ventilatory and non-ventilatory muscle groups. This a very important comorbidity associated with poor quality of life and reduced survival.[37] It is the result of a complex combination of functional, metabolic, and anatomical changes that lead to suboptimal muscle force.[38] Muscle function should therefore be evaluated in symptomatic patients, since it can identify patients who have an increased risk of poor clinical outcomes, such as exercise intolerance and premature mortality.[39] In these cases, the recommended therapeutic approach is exercise training. Other therapies, such as neuromuscular electrical stimulation, may be useful in specific cases.

Reproductive system

It has been reported that COPD patients are at increased risk of sexual dysfunction,[40] and that this is associated with poorer quality of life and episodes of depression and other comorbidities,[41] generating a complex spiral of interrelationships between comorbidities and COPD. This is therefore another comorbidity that may need to be explored and treated in patients with a high disease impact.

Respiratory system

Many respiratory comorbidities have been studied in the setting of COPD. The most relevant are bronchial asthma, obstructive sleep apnea syndrome, bronchiectasis, pulmonary hypertension, lung cancer, chest wall disorders, pulmonary fibrosis, and chronic rhinitis (Table 2). These comorbidities have three important repercussions in COPD, affecting the impact of the disease, the risk of exacerbations, and prognosis. The presence of any of these comorbidities should be explored in COPD patients with poor disease control by taking a comprehensive medical history and performing specific complementary tests.

The concomitant presence of bronchial asthma and COPD, known as asthma-COPD overlap (ACO), is currently under debate.[42] It seems reasonable that if a patient is diagnosed with asthma, this comorbidity should guide the pharmacological treatment,[43,44] including the evaluation of biological therapy, where indicated. Other interventions including rehabilitation, roflumilast, or antibiotics, should also be considered as part of an individualized approach for COPD. Because each disease has its own assessment scales and severity criteria, it seems more reasonable to establish both diagnoses, COPD and asthma, and to determine the severity criteria for each one separately.

The presence of bronchiectasis also affects clinical presentation, the risk of exacerbations, and the prognosis. Specific guidelines are available for the diagnosis and treatment of this comorbidity.[45,46]

Pulmonary hypertension is usually mild, but in some cases it has a clear impact on patients' symptoms, on their prognosis, and on the performance of some complementary tests. These patients are defined by a vascular phenotype consisting of less severe airflow limitation, more intense arterial hypoxemia with normocapnia or hypocapnia, very low diffusion capacity, severe dyspnea during exercise, and a cardiovascular exercise limitation pattern.[47] Unfortunately, no specific treatment is currently recommended,[48] but a thorough investigation can help clarify the origin of the symptoms to establish individualized measures in cases of severe pulmonary hypertension.[49]

COPD and lung cancer not only share the main risk factor, smoking, but they also mutually affect the clinical expression and prognosis of each disease. The risk of lung cancer is most common in patients with an emphysema phenotype, irrespective of airflow obstruction.[50] Although the treatment of COPD does not

vary in cancer patients, cancer treatment may vary in the presence of COPD. On the other hand, the clinical challenge lies in cancer screening by computed axial tomography, for which specific guidelines are available.[51]

Chest wall alterations, and in particular kyphoscoliosis, are usually associated with a restrictive component in respiratory function tests and a greater likelihood of developing chronic global respiratory failure with a specific response to pulmonary rehabilitation.[52]

The emphysema-fibrosis complex is a rare combination, but one that has a great impact on clinical presentation and prognosis. Its clinical and functional presentation and progression are marked by the pulmonary fibrosis component.[53] At present, antifibrotic treatment is not indicated in this setting, although some trials are ongoing.

Few studies have evaluated the COPD-rhinitis association, but all data indicate that this association exists from the early stages of COPD[54] and its presence suggests involvement of the entire airway.[55] Its impact on COPD is associated with bronchial obstruction and respiratory symptoms. Consequently, the diagnosis and treatment concomitant rhinitis should be considered as part of the evaluation of COPD patients.

Endocrine system

Vitamin D deficiency is associated with worse lung function, accelerated deterioration of lung function, and increased COPD exacerbations. Studies have identified 25-OH-vitamin D levels as a potentially useful marker of COPD-related adverse outcomes.[56] It appears that supplementing this vitamin in patients with very severe deficiency (10 ng/ml or 25 nmol/l) might contribute to improving the clinical presentation of COPD patients in this situation.[57,58] Therefore, the recommendation in patients with high clinical impact, especially if they are persistent exacerbators, is to determine 25-OH-vitamin D levels in blood and to correct any deficiency below 10 ng/ml or 25 nmol/l.

Nervous system

The most relevant comorbidity, other than cerebrovascular disease, is cognitive impairment associated with COPD. Although this condition is common and has a clear impact on clinical presentation and quality of life,[59] there is no specific treatment for COPD patients beyond choosing an appropriate inhalation device that the patient can manage correctly.

The most relevant of the sensory organ diseases is ocular hypertension. Although this comorbidity does not affect clinical presentation or diagnostic tests, treatments have a bidirectional impact. For example, it is well known that topical ophthalmic drugs can cause systemic side effects by absorption through the nasal mucosa. Thus, timolol, a beta-blocker commonly used in the treatment of ocular hypertension, can produce bronchospasm.[60] Moreover, the preservatives present in some eye-drops, including benzalkonium chloride, are potent bronchoconstrictors and may cause respiratory compromise in some susceptible patients.[61,62] This interaction should, then, be considered in the evaluation of patients with symptomatic COPD despite treatment. On the other side, anticholinergics may worsen intraocular pressures in patients with ocular hypertension. This association can occur when the anticholinergic drug is deposited directly on the eyeball in two circumstances: during nebulization of the anticholinergic or by touching the eyes after handling dry powder and not washing hands afterwards. Although pressure elevations may not be very marked, they can contribute to a worse control of long-term ocular hypertension. Therefore, patients with COPD and ocular hypertension should be warned of this possible effect and instructed to wash their hands after the use of inhalers with anticholinergics. The effect of ICS on glaucoma has not been consistently demonstrated.[63]

Psychiatric diseases

Although COPD is associated with various psychiatric conditions, the most relevant are probably mood and anxiety disorders, given their frequency and impact on the disease. These syndromes are not only related to the clinical presentation of COPD,[64] but can also impact prognosis.[65] For these reasons, clinicians should know how to identify them and treat them appropriately,[66] since currently available neuropsychiatric drugs at the recommended doses are safe from a respiratory point of view. Extremely simple questionnaires that allow rapid assessment in routine clinical practice are now available.[67]

Nutritional changes

Nutritional changes, obesity, and low body weight should be addressed in the COPD patient. Obesity is related to COPD and other comorbidities and has a greater impact on symptoms and greater functional alteration with a restrictive component or bronchial hyperresponsiveness.[68,69] It may also be associated with obstructive sleep apnea and hypoventilation.[70] This clinical presentation can be corrected by weight loss.[71]

Low body weight associated with sarcopenia has a profound impact on patients with COPD in terms of both clinical presentation and prognosis.[72,73] A particular presentation with a significant impact on COPD is sarcopenic obesity, which must be identified by bioimpedence analysis.[74] Patients with poor COPD control should undergo a nutritional assessment with evaluation of the lean and fatty compartments, at least by bioimpedence, and pulmonary rehabilitation programs should be recommended, if indicated.

Hematology

Anemia is another comorbidity that increases the impact of COPD by increasing symptoms.[75] High-risk patients should undergo a complete blood count to detect this comorbidity, determine its origin, and start appropriate treatment in each case.

Study of comorbidities in poorly controlled COPD patients

From the above sections, it seems clear that concomitant complaints can affect the clinical presentation of poorly controlled COPD patients, so comorbidities should be addressed in a protocolized manner in high-risk patients. The initial diagnostic evaluations to be conducted are summarized in Table 3. This approach will help identify which comorbidities may be at play before a more specialized assessment is made.

Self-management

In addition to relieving symptoms, reducing exacerbations, and improving quality of life with the correct administration of medications, healthy lifestyle habits should be adopted to improve COPD care, and interventions should be made to promote adherence to complex treatments and to develop patients' ability to recognize the signs and symptoms of exacerbations and to know what to do to prevent and treat them. In this respect, disease self-management programs provide an opportunity to improve clinical outcomes while giving patients autonomy and confidence in their day-to-day lives, thus potentially improving their quality of life. The goals of self-management are to develop skills, change health behaviors,

Table 3
Initial diagnosis of the main comorbidities associated with COPD.

Comorbidity	Initial assessment
Cardiovascular	Electrocardiogram
	Echocardiogram
	Exercise test
Periodontal disease	Visual assessment of the oral cavity
Gastroesophageal reflux	pH-metry
	Esophageal manometry
Benign prostatic hyperplasia	Clinical assessment
	Prostate ultrasound
Osteoporosis	Densitometry
Muscle dysfunction	Bioimpedance
	Dynamometry
Sexual dysfunction	Clinical assessment
Bronchial asthma	Clinical assessment
	Bronchodilator reversibility test
	Bronchial challenge test
	FeNO
Obstructive sleep apnea	Clinical assessment
	Excessive sleepiness questionnaires
	Polygraphy
Bronchiectasis	HRCT
Pulmonary hypertension	Echocardiography
Lung cancer	CT with contrast
Chest wall abnormalities	Clinical assessment
Pulmonary fibrosis	HRCT
	Lung volumes
	DLCO
Chronic rhinitis	Clinical assessment
Vitamin D deficiency	Analytical determination
Cognitive impairment	Clinical assessment
	Use of questionnaires
Ocular hypertension	Ophthalmological assessment
Anxiety, depression	Clinical assessment
	Use of questionnaires
Obesity	Clinical assessment
	Bioimpedance
Sarcopenia	Clinical assessment
	Bioimpedance
Anemia	Complete blood count

CO: carbon monoxide; COPD: chronic obstructive pulmonary disease; CT: computed tomography; FeNO: exhaled fraction of nitric oxide; HRCT: high-resolution computed tomography; SAHS: sleep apnea–hypopnea syndrome.

and learn how to act when symptoms get worse by implementing action plans.[76]

Who should be included in a self-management program?

A comprehensive COPD treatment strategy must select the appropriate patients who can benefit from self-management programs. However, it is still difficult to find a consensus on the best model for comparing the outcomes of the different studies, patients and interventions, professionals involved, and health models.[77]

What elements should be included in a self-management program?

In the last decade, self-management studies have assessed the multiple COPD components that are essential to achieve integrated care. The main components included in a self-management program should be treatment education programs to proactively promote self-care and health literacy, exercise training, and telemedicine.[78] These components all form part of the multidisciplinary actions that constitute respiratory rehabilitation.[79]

Interestingly, the results of various clinical trials that have evaluated each of these components vary considerably, to the extent that in some cases they are contradictory, most likely due to variations in the intensity, duration, implementation and content of programs, and highly heterogeneous interventions, patient types, follow-up periods,[80–84] and settings.[85,86] For this reason, self-management interventions in COPD must be structured and personalized, they must include multiple components, and be coordinated between levels of care. These integrated healthcare models that are based on interactions between patients and health professionals are useful tools for addressing complex clinical problems,[87–90] but the latest systematic reviews do not yet provide us with clear evidence as to whether self-management interventions with action plans can improve outcomes in COPD.[81,91] This makes it difficult to propose clear recommendations regarding the most effective implementation of self-management plans[92–94] and the most appropriate selection of candidates.

Palliative care

Palliative care is one of the pillars of comprehensive COPD care. The most important aspects are summarized below and Table 4 lists the key points.

What do we mean by palliative care in COPD?

Palliative care seeks to prevent or treat the symptoms of a disease, the side effects of treatment, and the psychological, social, and spiritual problems of patients and their caregivers in the face of a serious or life-threatening disease or its treatment.[95]

The aim of such care is not to prolong life expectancy, but to improve its quality. Unfortunately, palliative care in Spain is wanting and medical training and protocols and strategies for COPD are insufficient,[96] and our patients are less like to receive this specialized attention than cancer patients.[97,98]

When does a COPD patient need palliative care?

It is difficult to establish the point in terms of lung function, physical limitation, or degree of dyspnea at which a palliative care strategy should be established in a COPD patient. We are probably talking about a clinical situation in which a patient who is receiving optimized pharmacological (with 3 or more drugs) and non-pharmacological treatment, perhaps even within a respiratory rehabilitation program, presents persistent symptoms and is not a candidate for surgical therapeutic measures or when this approach has not been effective.

The most prevalent symptoms associated with advanced COPD are dyspnea (present in 97% of patients), fatigue (68%), and pain (43%). Depression can be detected in between 50% to 90% of patients, while the prevalence of anxiety can be as high as 25%.[97] In many cases, symptoms coexist and may go unnoticed if patients do not undergo a targeted interview.[99]

What medical interventions are options in palliative care in COPD patients?

Opioids. For this section of the guidelines, we developed a PICO question (Patient, Intervention, Comparison, and Outcomes) on opioids (Supplement 1).

PICO question: should opioids be prescribed for refractory dyspnea in COPD?

For the analysis, 14 randomized trials (RCTs) using placebo as comparator in a total of 642 patients were selected. The characteristics of the participants and the interventions varied widely. Most included outpatients, except one study that included hospitalized patients[100] and another that studied mixed-type patients.[101] All studies had a crossover design except one that had a parallel group design.[101] In 4 studies, participants had not previously been treated with morphine.[102–105] The endpoint assessment also ranged from

Table 4
Palliative care key points.

- The goal of palliative care in COPD is to prevent or treat the symptoms of the disease, the side effects of treatment, and the psychological problems of patients and their caregivers
- Palliative care alone does not shorten survival and should be progressively introduced over the course of the disease, without waiting for the patient's risk of death to be considered high in the short term
- The candidate patient is one whose symptoms persist and are refractory to the optimized treatment of the disease. The most prevalent symptoms in advanced COPD are dyspnea, psychological disorders, pain, and sleep disorders
- Despite the scant evidence, low-dose opioid use improves refractory dyspnea with preventable side effects, while the use of anxiolytics can be used as a second or third line in selected cases
- The use of oxygen and high-flow nasal therapy may relieve dyspnea. The indication of non-invasive ventilation can be regarded as a ceiling of treatment in patients seeking to relieve symptoms, mainly dyspnea
- The patient's preferences on limiting treatment must be respected and ideally stated in an advance directive document
- Healthcare professionals who care for these patients should be trained in palliative care and a palliative care support team should be on hand

COPD: chronic obstructive pulmonary disease.

1 h to 6 weeks. The variables analyzed were dyspnea (measured with the visual analog scale or the Borg scale), exercise tolerance, and quality of life (using different instruments). To assess dyspnea, 3 secondary analyses were conducted, evaluating route of administration, dyspnea scales, and type of morphine used.

In terms of intensity of dyspnea measured at the end of the trial, opioid therapy showed a significant reduction in the dyspnea score compared to placebo, with a standardized mean difference of −0.27 points (95% confidence interval of −0.50 to −0.04 points) on the visual scale analog or Borg scale (10 RCTs, 302 participants). However, the mean change from baseline in the dyspnea score between the groups was not significant. When both results were analyzed together, the administration of opioids showed a reduction in dyspnea intensity with a standardized mean difference of 0.18 points (95% confidence interval from 0.34 to 0.03; 14 RCTs; 642 participants). Subanalyses according to the type of opioid or route of administration are not useful for making recommendations in this regard. Exercise capacity and quality of life outcomes showed no significant differences, but the studies are limited by heterogeneous measurements and small sample sizes. Adverse effects significantly associated with opioid use were constipation, nausea, vomiting, and drowsiness.

Recommendation: Opioids are suggested for the treatment of refractory dyspnea in COPD (weak recommendation; low quality of evidence).

Specifications: Morphine should be used at low oral or transdermal doses (Table 5). The administration of low-dose opiates does not increase the risk of hospital admission or death, even in patients receiving home oxygen therapy.[106] Analysis by morphine type shows a more marked effect for dihydrocodeine.

Benzodiazepines. Although no strong evidence is available on the use of benzodiazepines,[107] the combination of opioids and anxiolytics is often used to treat end-of-life dyspnea and anxiety as second- or third-line treatment when opioids and other non-pharmacological treatments do not provide adequate control.[107] Compounds that can be added to opioid therapy include oral or sublingual lorazepam (0.5–1 mg), subcutaneous or intravenous midazolam (1.25 mg), or, in very anxious patients, continuous subcutaneous or intravenous infusion of midazolam (10–20 mg in 24 h), if the patient is hospitalized. These doses must be progressively titrated to achieve the desired effect.[108]

Systemic corticosteroids. Corticosteroid use in these patients is justified by the need to reduce airway inflammation and edema. However, efficacy in this clinical setting remains controversial[109–111] and use must be individualized.

What non-pharmacological interventions are options in palliative care in COPD patients?

Continuous standard oxygen therapy. Mechanisms that justify the use of palliative oxygen to relieve dyspnea include reduced respiratory center demand, reduced hypoxemia and serum lactic acid, decreased pulmonary arterial pressure, and stimulation of upper airway receptors that decrease the respiratory impulse and minute ventilation, irrespective of the effect on hypoxemia.[112,113] However, while many COPD patients report improved dyspnea when they receive oxygen, the evidence supporting its use in patients with dyspnea in this clinical setting is inconclusive.[114–116] At present, a supplemental oxygen trial should be performed in these patients, and it should be discontinued if they do not tolerate treatment or do not benefit symptomatically.

High-flow nasal therapy. This consists of a mixture of heated and humidified gas with adjustable FiO_2 from 0.21 to 1.0 that is delivered at flow rates up to 60 L/min through a specially modified soft, loose-fitting nasal cannula. Benefits include reducing labored breathing in patients with respiratory failure.[117,118] Preliminary studies on the use of high-flow nasal therapy in the treatment of dyspnea in terminal patients suggest that it might provide more respite and relief of dyspnea than standard oxygen.[118,119]

Non-invasive mechanical ventilation. Non-invasive ventilation can help reduce breathing difficulty by improving oxygenation, ventilation, respiratory muscle resistive load, dynamic hyperinflation, and labored breathing. It is currently considered a ceiling of treatment in the pursuit of symptomatic relief, primarily of dyspnea.[120] If it is well tolerated, it is a non-aggressive therapy with a patient acceptance rate similar to oxygen therapy. However, due to differences in tolerance and accessibility, oxygen therapy is recommended as the first therapeutic approach in this clinical context.

How should palliative care be implemented?

The prognosis of COPD is uncertain,[121] so palliative care should be incorporated in a stepwise fashion throughout the course of the disease, without waiting for life expectancy to be considered limited in the short term. Planning should be based on a process of communication with the patient, taking into account his or her opinions, preferences, values and beliefs.[122] Unfortunately, communication of this type between healthcare professionals and patients with advanced COPD is not as frequent.[123] Healthcare professionals who care for these patients should be trained in palliative care and a palliative care support team should be at hand.

In summary, the medical treatment of dyspnea should start with a trial of progressive opioid titration, with or without anxiolytics, and patients' responses, side effects, and preferences should be taken into account. Non-pharmacological treatments can include respiratory rehabilitation and oxygen therapy can be attempted. Each case must be evaluated individually to assess the need to escalate to a high-flow system or the use of non-invasive ventilation.

One concern often raised about palliative care is that it can shorten life. However, this possibility is extremely rare at the usually recommended drug doses, and in any case, the use of these

Table 5
Recommended doses of morphine at start of treatment, adjustment, and maintenance.

	Rapid-release oral morphine	Extended-release morphine	Other presentations
Start	2.5–5 mg/4–6 h Double night dose	10 mg/day	Subcutaneous morphine. 3:1 equivalence (30 mg oral morphine corresponds to 10 mg subcutaneous morphine)
Dose adjustment	Increase dose slowly if not well controlled (2.5 mg/4 h)	Increase doses slowly (10 mg/week) to 30 mg/day	Fentanyl patches may be useful in stabilized patients Starting dose: 12–25 mg/3 days (60 mg morphine daily corresponds approximately to a 25 mg fentanyl patch every 3 days)
Maintenance	If patient is controlled, switch to extended-release morphine	If a rescue dose is required, use rapid-release oral morphine	Prevent side effects: • Constipation: laxative • Nausea: haloperidol 10 drops/day Decrease the dose in case of kidney failure or low weight

interventions is ethically justified by the principle of double effect, which dictates that shortening of life is acceptable if the main objective is to alleviate suffering.

Conclusions

COPD requires a more comprehensive and individualized vision, prioritizing problems and selecting therapeutic objectives adapted to the personal circumstances of each patient. Comprehensive assessment will allow us to identify specific needs that can be used as a basis for an individualized treatment plan. In order to achieve these objectives, we will have to devote the time necessary to educate patients and their caregivers in understanding the disease, its symptoms, its implications, and its therapeutic management.

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Annex 1. GesEPOC Task Force 2021

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Appendix B. Supplementary data

Supplementary data associated with this article can be found, in the online version, at doi:10.1016/j.arbres.2021.08.023.

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