Clinical Practice Guideline for the Treatment of Patients with Chronic Obstructive Pulmonary Disease (COPD)

NOTE:

More than 5 years have passed since the publication of this Clinical Practice Guideline, and **its validity has not been reviewed**.

Therefore, **it is unclear whether its recommendations remain valid**; they should therefore be treated with caution and applied in accordance with **clinical judgement and the individual circumstances of each patient**.

CLINICAL PRACTICE GUIDELINTES IN THE NHS
MINISTRY OF HEALTH, SOCIAL SERVICES AND EQUALITY

MINISTERIO DE ECONOMÍA Y COMPETITIVIDAD
MINISTERIO DE SANIDAD, SERVICIOS SOCIALES E IGUALDAD
Plan de Calidad para el Sistema Nacional de Salud
SaludMadrid
Agencia Laín Entralgo para la Formación, Investigación y Estudios Sanitarios
Comunidad de Madrid

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Comunidad de Madrid

This CPG is a healthcare decision aid. It is not mandatory and it is not a substitute for the clinical judgement of healthcare personnel.

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Table of contents

Table of Contents **5**

Presentation **9**

Authorship and Collaborations **11**

Questions to be answered **17**

Levels of evidence and grades of recommendations **19**

Recommendations of the CPG **21**

1. Introduction **25**

2. Scope and objectives **27**

3. Methodology **29**

3.1. Creation of the guideline development group 29

3.2. Formulation of clinical questions 30

3.3. Bibliographic search 30

3.4. Formulation of recommendations via the GRADE system 31

3.5. Patients' perspective 32

3.6. External Review 32

3.7. Update 32

4. Epidemiology of COPD **33**

4.1. Prevalence 33

4.2. Impact of COPD 34

5. Definition, phenotypes, risk factors and natural history of COPD **37**

5.1. Definition of COPD 37

5.2. Phenotypic traits of COPD 37

5.3. Characterisation of the COPD phenotype 39

5.4. Aetiology of COPD 42

5.5. Risk factors for the development of COPD 43

5.6. Comorbidities of COPD 45

6. Treatment of COPD in stable phase **49**

6.1. Sustained-action bronchodilators at onset of treatment in monotherapy 50

6.2. Combined therapy (IC/LABA) opposed to dual bronchodilator therapy (LABA+LAMA) 59

More than 5 years have passed since the publication of this Clinical Practice Guideline, and its validity has not been reviewed

6.3. Use of roflumilast instead of inhaled corticoids as additional therapy to the maintenance treatment with bronchodilators in patients with COPD 62

6.4. Mucolytics in the maintenance treatment of COPD 65

7. Treatment of exacerbation in patients with COPD 75

7.1. Definition and impact of the exacerbation 75

7.2. Severity of the exacerbation 78

7.3. Systemic corticoids in moderate or mild exacerbation of COPD 79

7.4. Pulmonary rehabilitation in the context of an exacerbation 84

8. Treatment of tobacco dependence in smoking patients, diagnosed with COPD 89

8.1. Medical/psychological counselling 90

8.2. Pharmacological treatment 92

8.3. Patients' values and preferences 93

9. Treatment of anxiety and depression in patients with COPD 97

9.1. Pharmacological treatment 97

9.2. Psychological interventions 99

9.3. Pulmonary rehabilitation 100

9.4. Patients' values and preferences 101

9.5. Economic evaluation 102

10. Perspective of patients with COPD 103

10.1. Survey and discussion group with patients with COPD and their caregivers 103

10.2. Health skills and competences (health literacy) of patients with COPD 104

11. Dissemination and implementation 109

11.1. Dissemination and implementation strategy 109

11.2. Indicator proposal 110

12. Future research lines 113

12.1. Combined therapy (IC/LABA) opposed to dual bronchodilator therapy (LABA+LAMA) for the treatment of stable phase COPD 113

12.2. Use of roflumilast instead of inhaled corticoids as additional therapy to the maintenance treatment with bronchodilators in patients with COPD 113

12.3. N-Acetylcysteine in the maintenance treatment of COPD 114

12.4. Systemic corticoids in moderate exacerbation or flare-ups of COPD 114

12.5. Systemic corticoids in mild exacerbation or flare-ups of COPD 115

More than 5 years have passed since the publication of this Clinical Practice Guideline, and its validity has not been reviewed

Appendixes **117**

Appendix 1. Information for patients 117

Appendix 2. Acronyms 155

Appendix 3. Declaration of interest 157

Bibliography **159**

More than 5 years have passed since the publication of this Clinical Practice Guideline, and its validity has not been reviewed

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Presentation

Documenting the variability of clinical practice, analysing it causes and adopting strategies aimed at eliminating them, have proved to be initiatives that foster effective and safe patient-centred decision making by health practitioners. Among this strategies is the development of clinical practice guidelines (CPG), a series of "*statements that include recommendations intended to optimize patient care that are informed by a systematic review of evidence and an assessment of the benefits and harms of alternative care options"*.

The Quality Plan for the National Health System (SNS) try to answer the challenges set out by the SNS, increasing the cohesion of the system, guaranteeing people health care equity, regardless of where they live and ensuring that this care is of maximum quality. Its objectives include promoting the development and use of CPGs, consolidating and extending the Guía-Salud Project.

On the other hand, since the approval in June 2009 by the Interterritorial Council of the SNS of the COPD Strategy, the scientific societies involved, the associations of patients and the health administrations have worked together to try to improve the prevention and approach to COPD in the entire SNS as well as to foster research in this field. The publication of this **CPG for the Treatment of Patients with Chronic Obstructive Pulmonary Disease (COPD)** is framed within this context.

This CPG emerges as an initiative of the "GesEPOC" project, which is a project that has been started up and is shared by different scientific societies involved in the care of patients with COPD and the Spanish Patient Forum (FEP) with the aim of raising awareness about the impact of this disease on the people that suffer from it, on their surroundings and on society in general. It also aims to foster the improvement of health care quality in all areas, engaging the actual patients and their caregivers.

The guideline has been developed by a multidisciplinary team, made up of medical practitioners and nurses from primary care, pneumonology, internal medicine, rehabilitation, physiotherapy and epidemiologists. The patients' viewpoint has been taken into account through the participation of the FEP.

We, at the Directorate General of Public Health, Quality and Innovation, would like to thank all of those who have worked on the guideline and congratulate them for this CPG, which will undoubtedly help improve the quality of life of patients with COPD and their caregivers.

M. MERCEDES VINUESA SEBASTIÁN
Director General of Public Health, Quality and Innovation

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Spanish Society of Family and Community Medicine (semFYC)

Spanish Society of Primary Care Physicians (SEMERGEN)

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Spanish Society of Internal Medicine (SEMI)

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Declaration of interest: All the members of the Development Group, as well as the people who have participated as expert collaborators and external reviewers, have made the declaration of interest presented in Appendix 3.

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Questions to be answered

TREATMENT OF STABLE PHASE COPD

1. Is there evidence to advise a specific type of sustained action bronchodilator in mono-therapy at the onset of treatments of stable phase COPD?

2. What are the benefits of combined therapy (inhaled corticoids/long acting beta agonists) compared with dual bronchodilator therapy?

3. Can roflumilast be an alternative to the use of inhaled corticoids as additional therapy to the maintenance treatment with bronchodilators in patients with COPD?

4. Is the use of the antioxidant and mucolytic, N-acetylcysteine, justified in patients with COPD?

5. Is the use of the mucolytic, carbosyteine, justified in patients with COPD?

TREATMENT OF EXACERBATION IN PATIENTS WITH COPD

6. Must systemic corticoids be used in moderate exacerbation of COPD?

7. Must systemic corticoids be used in mild exacerbation of COPD?

8. Is pulmonary rehabilitation beneficial in the context of an exacerbation?

TREATMENT OF TOBACCO DEPENDENCE IN PATIENTS WITH COPD WHO SMOKE

9. What is the most adequate treatment to make patients with COPD give up smoking?

TREATMENT OF ANXIETY AND DEPRESSION IN PATIENTS WITH COPD

10. What is the most adequate treatment to treat anxiety and depression in patients with COPD?

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Levels of evidence and Grading of Recommendation

Classification of evidence quality with GRADE system

Quality of scientific evidence	Study design	Quality reduced if	Quality increased if
HIGH	RCT	Design limitation: Significant (-1) Very significant (-2) Inconsistency (-1) Direct evidence: Some uncertainty (-1) Great uncertainty as to whether evidence is direct (-2) Inaccurate data (-1) Publication bias: High probability of (-1)	Association: scientific evidence of strong association (RR > 2 or < 0.5 based on observational studies without confounding factors) (+1) Scientific evidence of a very strong association (RR>5 or <0.2 based on studies with no possibilities of bias) (+2) Dose-response grade (+1) All the possible confounding factors may have reduced the effect observed (+1)
MODERATE			
LOW	Observational study		
VERY LOW	Other designs		

RCT: randomised controlled trial

Implications of GRADE levels of recommendation

Implications of a strong recommendation:		
Patients	Clinicians	Managers/Planners
The vast majority of people would agree with the action recommended, and only a few would disagree.	The mayority of patients should receive the intervention recommended	The recommendation can be adopted as healthcare policy in most situations.
Implications of a weak recommendation:		
Patients	Clinicians	Managers/Planners
Most people would agree with the action recommended but a significant number would not.	Acknowledges that different options will be appropriate for different patients, and that clinicians must help each patient choose the option most consistent with his/her values and preferences.	Significant debate and stakeholder involvement are needed.

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Recommendations of the CPG

Treatment of stable phase COPD

Sustained action bronchodilators at onset of treatment in monotherapy

Good clinical practice	In patients with stable phase COPD who require sustained action bronchodilators in monotherapy, it is suggested that the final choice of bronchodilator should be based on criteria such as the preferences of the individual patients, the individual response to the drug and/or economic aspects.
Weak	In patients with stable phase COPD who have suffered at least one previous exacerbation that has required hospital admission and/or treatment with systemic glucocorticoids and/or antibiotics during the previous year and who require a sustained action bronchodilator in monotherapy, the use of tiotropium rather than salmeterol is suggested.
Research recommendation	It is recommended the realization of randomised controlled trials to assess the effectiveness and safety of indacaterol rather than tiotropium in patients with stable phase COPD who require sustained action bronchodilators in monotherapy, due to the evidence identified is insufficient to recommend one rather than the other.

Combined therapy (IC/LABA) opposed to dual bronchodilator therapy (LABA+LAMA)

Research recommendation	It is recommended the realization of randomised controlled trials to assess the effectiveness and safety of combined therapy (IC/LAMA or IC/LABA) opposed to dual bronchodilator therapy (LABA+LAMA) in patients with stable phase COPD, due to the evidence identified is insufficient to recommend one of the options rather than the other.

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Use of roflumilast instead of inhaled corticoids as additional therapy to maintenance treatment with bronchodilators in patients with COPD

Research recommendation	In patients with stable phase COPD in maintenance therapy with bronchodilators, additional therapy with roflumilast as an alternative to additional therapy with inhaled corticoids, must only be used in a research context.

Mucolytics in the maintenance treatment of COPD

N-acetylcysteine

Weak	The generalised use of N-Acetylcysteine as maintenance treatment is not suggested in patients with stable phase COPD.

Carbocysteine

Weak	The use of carbocysteine as maintenance treatment of COPD is suggested in patients with stable phase COPD and exacerbated phenotype with chronic bronchitis.

Treatment of exacerbation of COPD

Systemic corticoids in moderate exacerbation

Weak	The oral administration of prednisone for 9 or 10 days is suggested in non-hospitalised patients with COPD to treat moderate exacerbation.

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Systemic corticoids in mild exacerbation

Research recommendation	The use of systemic corticoids is only suggested to treat mild exacerbation in non-hospitalised patients with COPD in a research context.

Early pulmonary rehabilitation in the context of an exacerbation

Strong	In patients with COPD who have suffered an exacerbation, it is recommended start pulmonary rehabilitation immediately after finishing the treatment of the exacerbation or during the following three weeks.

Treatment of tobacco dependence in smoking patients, diagnosed with COPD

Strong	Offering anti-smoking medical/psychological counselling is recommended in smoking patients with COPD.
Weak	The use of medical/psychological counselling, accompanied by pharmacological therapy, is suggested in smoking patients with COPD who have little motivation to stop smoking.

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Treatment of anxiety and depression in patients with COPD

Good clinical practice	In patients with COPD, anxiety and depression must be treated in the traditional manner, although patients' age, adverse effects of the drugs and pharmacological interactions must be taken into account, especially in polymedicated patients.
Weak	In patients with COPD with symptoms of anxiety and/or depression and who are poor predisposed to follow pharmacological treatments, it is suggested to offer psychological treatment based on cognitive-behavioural therapy principles.
Weak	In patients with COPD and subsidiary anxiety and/or depression symptoms of pulmonary rehabilitation, a multi-disciplinary pulmonary rehabilitation programme is suggested.

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1. Introduction

Chronic obstructive pulmonary disease (COPD) is essentially characterised by chronic airflow limitation, which is practically irreversible and mainly associated with tobacco smoke. It is an under-diagnosed disease with high morbidity and mortality and it represents an extremely important public health problem. It is the fifth cause of death in countries of our environment and its prevalence is predicted to continue growing. It represents a high healthcare cost[1].

COPD is a complex and multi-component disease. The main symptoms are dyspnoea, coughing and expectoration. Its clinical presentation is very heterogeneous and, within what we call COPD today, different phenotypes can be defined with clinical, prognostic and therapeutic repercussion[2]. Although COPD is not a curable disease, smoking cessation is the most effective measure to prevent and stop its progression[3].

Since 2009, the Ministry of Health, Social Services and Equality, through the Quality Plan of the National Health System (SNS) and the COPD Strategy, has been working to identify the way of improving the care and quality of life of people with COPD and to reduce the number of people with COPD. The multi-disciplinary team of the COPD Strategy[4] has promoted the development of a clinical guideline with the participation of all the agents involved in the Strategy. This guideline for the treatment of COPD emerges within this context.

On a global level, the recommendations of the Global Initiative for Obstructive Lung Diseases (GOLD) for the diagnosis and treatment of COPD, published for the first time in 2001 and reviewed every year, have been the most commonly used[5]. In Spain, the reference guidelines have been developed by SEPAR together with other scientific societies[6,7]. The many advances that have been made over the last few years require the updating of the contents of these guidelines.

The guideline, which all the scientific societies involved in the care of patients with COPD have participated in, aims to respond to some of the questions posed in the care of patients with COPD. It pursues the effective care of patients with COPD based on coordinated and multidisciplinary work with the participation of representatives from the different healthcare levels.

This document is the full version of the CPG for the Treatment of Patients with Chronic Obstructive Pulmonary Disease (COPD). The CPG is organised into chapters, where answers are given to the questions that appear at the beginning. The summary of the evidence and recommendations are presented at the end of each chapter.

The material described in the GRADE methodology (The Grading of Recommendations Assessment, Development and Evaluation)[8,9], applied in the CPG (search strategy for each clinical question, evidence tables, justification of recommendations, etc) is available both on the *GuiaSalud* website (www.guiasalud.es) and on the website of the Health Technology Assessment Unit (UETS) of the Lain Entralgo Agency (www.madrid.org/lainentralgo).

On these websites, you can also consult the *CPG development methodology manual* which includes the general methodology used[10]. There is also an *summarize* version of the CPG, which is shorter in length and with the main appendices of the full version, and a *quick version* with the main recommendations and algorithms, both in printed edition and on the aforementioned websites. There is also a version with *information for patients* on the aforementioned websites (UETS, Guiasalud).

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2. Scope and objectives

The main objective of the guideline is to provide health practitioners, who are responsible for attending to COPD patients, with a tool that will enable them to take the best decisions regarding some of the problems posed by their care.

The guideline includes aspects on the treatment of patients with exacerbated and stable COPD, and other treatments related to smoking cessation, as well as anxiety and depression of patients with COPD. It also includes the description of those attributes of the disease which, on their own or combined, describe the differences between individuals with COPD (phenotypes).

This guideline's target audience are family practitioners, nursing professionals in primary and specialised care, neumologist, internists and other specialists that care for patients with COPD and also all patients that suffer COPD. This guideline also provides educational material for patients and families affected by the disease, and it also includes dissemination and implementation strategies to inform about the reality of COPD and the people that suffer from it, and thus facilitate the implementation of the guideline.

As the guideline has a national approach, it does not address organisational issues, but it does propose explicit recommendations to facilitate the implementation of the guidelines.

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3. Methodology

This CPG for the treatment of patients with COPD emerges as an initiative of the "GesEPOC (Spanish guideline for COPD)" project, which is a project that was started up and is shared by different scientific societies involved in the care of patients with COPD and the Spanish Patient Forum, in order to stimulate quality in the care of patients with COPD, who come to the practices of primary and specialised care professionals. The GESEPOC project is the result of an initiative by the Spanish Society of neumology and Thoracic Surgery (SEPAR) and with the collaboration of SemFYC (Spanish Society of Family and Community Medicine), SEMERGEN (Spanish Society of Primary Care Physicians), SEMG (Spanish Society of General and Family Practitioners), GRAP (Primary Care Respiratory Society), SEMI (Spanish Society of Internal Medicine), SEMES (Spanish Society of Accident and Emergency Medicine), SERMEF (Spanish Society of Rehabilitation and Physical Medicine), SORECAR (Spanish Society of Cardiopulmonary Rehabilitation), as well as the National Committee for the Prevention of Nicotine dependence (CNPT).

Professionals representing the different scientific societies mentioned and methodologists specialised in developing CPGs have participated in the development of the CPG. The methodology used is described in detail in the Methodology Manual for the development of clinical practice guidelines of the National Health System[10]. The material is available at the GuiaSalud portal (www.guiasalud.es), as well as on the website of the UETS (www.madrid.org/lainentralgo), where the information is presented in detail, together with the methodological process followed to develop the CPG (applying the GRADE system) as well as the methodology used with the patients (survey and discussion group).

The steps below have been followed:

3.1 Creation of the guideline development group

Integrated by professionals who were mainly contacted through the different Scientific Societies related to the topic of the Guideline. The Development Group was constituted by specialists in neumology, internal medicine, family medicine, emergency care, physical medicine and rehabilitation, preventive medicine and public health, psychology and physiotherapy.

There have also been patient's representatives (Spanish Patient Forum) in the Development Group of this CPG.

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3.2 Formulation of clinical questions

The members of the Development Group defined the clinical questions that the Guideline should answer. The PICO format has been followed in all the questions: Patient, Intervention, Comparison and Outcome (or result variable).

3.3 Bibliographic search

Firstly, a search was made for other Clinical Practice Guidelines (CPG) that might address the sections defined in a similar manner. To this end, CPGs were identified in the following sources:

TRIP database and Clinical Excellence

NHS National Library of Guidelines of the United Kingdom

National Guideline Clearinghouse of the United States

GuíaSalud of Spain

NICE (National Institute for Health and Clinical Excellence of the United Kingdom)

SIGN (Scottish International Guidelines Network)

NHMRC (National Health and Medical Research Council of Australia)

After reading the identified CPGs, the main systematic reviews underpinning their recommendations were identified. Furthermore, searches were designed to identify systematic reviews and health technology assessment reports published after the CPGs. Thus, the following electronic databases were consulted:

TRIP database and Clinical Excellence

Cochrane Database of Systematic Reviews (The Cochrane Library)

Database of Abstracts of Reviews of Effects (DARE)

Health Technology Assessment (HTA) Database

NHS Economic Evaluation Database (NHS EED)

MEDLINE (via PubMed)

EMBASE (Embase.com)

Finally, the searches for the relevant systematic reviews that had been identified to answer the different questions of the guideline were updated. The main aim was to identify randomised clinical trials (RCT). Whenever possible, the original search strategy for the relative systematic review was respected. When this strategy was not available, specific strategies were designed for the respective question. At this phase, the following electronic databases were consulted: The Cochrane Central Register of Controlled Trials (CENTRAL) (The Cochrane Library), MEDLINE (accessed via PubMed) and EMBASE (Embase.com).

No limit was established regarding the publication language in the searches made, but studies in Spanish, English and French have been considered. The deadline for the last search was February 2012.

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3.4 Formulation of recommendations via the GRADE system

The guidelines of the GRADE task force (Grading of Recommendations Assessment, Development and Evaluation)[8] were followed to classify the quality of evidence and grade the strength of recommendations related to the questions of the CPGs.

3.4.1 Classification of the relative importance of the outcome variables

The outcome variables of interest for each question were explicitly established at this stage. They were classified according to their relative importance, based on the following nine point scale:

- 1 to 3: Outcome variable not important for decision making, that do not play an important role in the formulation of recommendations.
- 4 to 6: Important outcome variable but not critical for decision making.
- 7 to 9: Critical outcome variable for decision making.

3.4.2 Scientific evidence quality assessment

Assessing the quality of evidence means determining the degree of confidence that the estimation of the effect of the interventions can have. The quality is assessed for each one of the outcome variables selected.

The GRADE system proposes a series of factors that may reduce the quality of the clinical trials (which are considered of high quality as a starting point) and other factors that may increase the quality of the observational studies (which are considered of low quality as a starting point). The quality of evidence is classified as high, moderate, low or very low. After determining the quality of evidence for each one of the variables considered, the critical or key clinical variables are the ones that determine the global evidence quality.

3.4.3 Grading of the strength of the recommendations

The GRADE system proposes a simple system to grade the strength of the recommendations into strong or weak. A strong recommendation is formulated in favour of the intervention when the beneficial effects of an intervention are expected to exceed the damage or opposing strength in the reverse situation, where the damage exceeded the advantages of an intervention. Weak recommendations, both in favour and against an intervention, are formulated when there are no conclusive tests regarding the effects of an intervention. Finally, this guideline also contemplates other types of recommendations: "Good clinical practice" when, despite not having conclusive scientific tests, the start-up of an intervention is considered a good clinical practice action; and "Research recommendation" when, due to the absence of good quality evidence, the balance between benefits and risks is uncertain or there is no agreement. In these cases, it may not be appropriate to formulate a recommendation for the clinical practice in favour or against the intervention. If this occurs, it may be advisable to start up specific research that will provide the necessary evidence to establish a recommendation for the practice[9].

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The following factors were taken into consideration during the grading process of the strength of the recommendations;

- Quality of scientific evidence: Before making a recommendation, the certainty about the estimation of the effect observed must be known. If the quality of the scientific evidence is not high, despite the magnitude being important, the confidence should be reduced, and therefore, the strength with which a recommendation is made.

- Balance between benefits and risks: To carry out an adequate evaluation of the balance between benefits and risks, it is necessary to bear in mind the basal risk of the population that the recommendation addresses and the effect, both in relative and absolute terms.

- Values and preferences: The uncertainty regarding the values and preferences of the target population of the intervention will be another of the factors to be taken into account. Health practitioners, the group of patients or society in general must see that their values and preferences have been reflected and these must have an influence on the grading of each one of the recommendations.

- Costs: Unlike other outcome variables, costs are much more changing in time, in different geographical areas and depending on different implications. Thus, although a high cost reduces the probability of grading a recommendation as strong, the context will be critical in the final evaluation.

3.5 Patient's perspective

The patients' perspective has been incorporated into the framework of GesEPOC and of the CPG presented, through their participation in the taskforce (Spanish Patient Forum). Furthermore, a survey has been carried out with patients diagnosed with COPD at different hospitals and an organised debate session in which 12 patients with COPD and caregivers have participated. The material, with detailed information about the methodological process used, is available at www.guiasalud.es.

3.6 External Review

The members of the Guideline Development Group proposed a multidisciplinary group of external reviewers, integrated by professionals with experience in the field of COPD, which appears in the "Authors and collaborations" section. The final version of the guideline text has been reviewed and approved by the group of authors.

3.7 Update

The scientific literature available recommends updating the recommendations of a CPG every three years (time interval that is taken as reference[10]), or earlier if new scientific evidence that may modify any of the recommendations offered in this guideline appears. The updates will be carried out on the electronic version of the CPG, available at the URL: http://www.guiasalud.es

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4. Epidemiology of COPD

4.1 Prevalence

Key points about the prevalence of COPD in Spain

The prevalence of COPD in adults aged from 40 to 80 years old in Spain is estimated at 10.25% (15.1% in men and 5.7% in women), although this varies a great deal depending on geographic areas.

The prevalence of COPD has increased due to population ageing and above all, to the increase of the prevalence among the smoking female population.

There is a high degree of under-diagnosis of COPD.

A reduction of under-treatment of COPD has been noticed.

The WHO estimates that there are 210 million people suffering from COPD in the world today[11]. In The Global Burden of Disease study, published in 1996, the WHO estimates the global prevalence rates of COPD in 1990 to be 9.3 cases per 1000 inhabitants in men, and 7.3 cases per 1000 inhabitants in women[12]. A systematic review estimates that the prevalence of COPD in the general population is around 1% in all age ranges, increasing to 8-10% or more in adults aged 40 or over[13]. The prevalence in Europe, according to results of a systematic review, varies between 2.1% and 26.1%, depending on the country, the different methods used to estimate the prevalence in terms of definition, severity scales and population groups[14].

Until not very long ago, in Spain, the only national-based prevalence study of COPD available was the IBERPOC study, carried out in 1997 to measure prevalence and variation of the distribution of COPD in seven geographical areas: Burgos, Caceres, Madrid (La Paz), Manlleu (Barcelona), Oviedo, Seville and the Basque Country. The prevalence of COPD in IBERPOC (defined according to former criteria of the European Respiratory Society as post-bronchodilator quotient FEV1/FVC <88% of the theoretic rate in men and <89% in women) was 9.1% (14.3% in men and 3.9% in women)[15]. Depending on the smoking habit, the prevalence was 15% in smokers, 12.8% in ex-smokers and 4.1% in non-smokers. The IBERPOC study also found very important differences depending on the geographical area, from just 4.9% in Caceres to 18% in Manlleu, possibly related to environmental or labour factors not studied. In this sense, the excess of cases detected in some geographical areas usually corresponded to women over 55, non-smokers, with a past history of respiratory diseases in childhood and who did not suffer from expectoration or wheezing symptoms[16]. A very important aspect of the results of the IBERPOC study was the high degree of under-diagnosis, as 78.2% of the cases confirmed by spirometer had not been previously diagnosed with COPD. IBERPOC estimated that in Spain 1,228,000 people between the ages of 40 and 69 suffered from COPD.

Recently, new data are available related to the current distribution of COPD in Spain, provided by the EPI-SCAN study[17]. The participating areas were Barcelona, Burgos, Cordoba, Huesca, Madrid, Oviedo, Seville, Requena (Valencia), Vic (Barcelona) and Vigo (Pontevedra). The current prevalence of COPD in the 40 to 80 year-old population, defined by the GOLD criterion as post-bronchodilator quotient FEV1/FVC <0.70, was 10.2% (15.1% in men and 5.7% in women). Compared with the IBERPOC study, the under-diagnosis of COPD in Spain had only dropped slightly, from 78% to 73%, although a considerable reduction of the under-treatment of COPD in Spain was noticed within this 10-year frame, from 81% to 54% ($p<0.05$)[18].

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Today, and according to EPI-SCAN, it is estimated that 2,185,764 Spaniards suffer from COPD out of the 2.14 million people aged between 40 and 80. By sexes, the figures correspond to 1,571,868 men and 628,102 women. And as 73% have still not been diagnosed, it can be said that more than 1,595,000 Spaniards still do not know and therefore receive no treatment for their COPD.

4.2 Impact of COPD

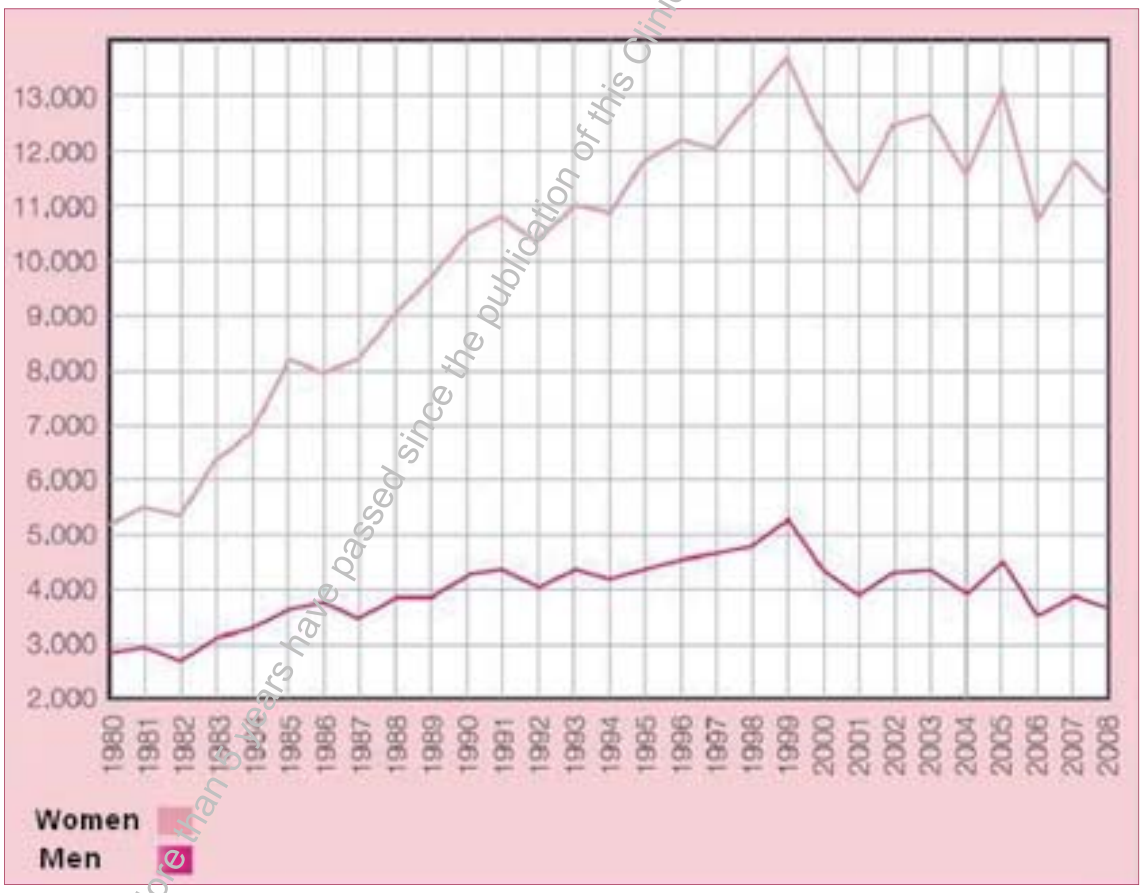
4.2.1 Mortality of COPD

COPD is currently the fourth cause of death in the world and the WHO estimates that by the year 2030, it will be the third[19].

In 2008 in Spain, chronic diseases of the lower respiratory tracts represented the fourth cause of death (responsible for 11.4% of total deaths), after cancer (26.1%), heart diseases (20.8%) and cerebrovascular diseases (18.2%)[20].

The mortality rate per 100,000 inhabitants due to COPD, adjusted for the world population, was 449.22 in men and 238.47 in women in 2008[21]. In men, these rates ranged between 399.13 in Navarra and 526.57 in Ceuta. In women, between 205.36 in Navarra and 310.53 in Ceuta. The mortality rates increase significantly, above all in men, from the age of 55 up[21]. COPD mortality rates in Spain, comparing the world population-adjusted rate, show a downward trend during the last decade, both in men and in women (figure 4.1)[21].

Figure 4.1. COPD Mortality rates in Spain (world population adjusted rates)



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4.2.2 Other data on magnitude, cost and burden of disease

According to the General Hospital Discharge Register of the SNS of 2009, 30,621 hospital discharges were recognised (refined) related to COPD episodes in 2009, with an average stay of 6.29 days[22].

Given that it is a chronic and progressive disease, COPD represents a high cost, both in consumption of health resources and in loss of health-related quality of life (HRQOL) of the patients. The costs of COPD in Spain, reviewed in the Strategy for COPD document of the National Health System, of the Ministry of Health, Social Services and Equality, are estimated at 750-1000 million €/year, including direct, indirect and intangible costs[23]. The average direct cost per patient with COPD is estimated at between 1,712 and 3,238€/year. These direct costs are distributed into hospital expenses (40-45%), drugs (35-40%) and visits and diagnostic tests (15-25%)[24].

4.2.3 Organisation and support to people with COPD in the National Health System

According to an ad hoc survey carried out by the Ministry of Health, Social Services and Equality to prepare the National Strategy for COPD, all the Autonomous Communities consider that COPD is a priority health intervention area[4]. However, in the majority of Autonomous Communities, there is no active plan of action for this pathology, or any organisation responsible for planning or advisory board. There are no standards, either, that govern the area of COPD. On the contrary, in the majority of Autonomous Communities there are action plans to combat smoking as well as tobacco withdrawal units[4].

COPD is diagnosed and care is provided mainly by primary care physicians and by referral pulmonologists. The strategy states that in the majority of the Autonomous Communities coordination exists between primary and specialised care, mainly via agreed protocols, improvement committees, clinical sessions and training activities.

The practitioners (primary care, specialised care and emergency) who care for patients with COPD must have competencies in the early diagnosis of the disease, the interpretation of forced spirometry and treatment of the stable phase and of exacerbation[4]. Primary care practitioners must also have competencies in the prevention and treatment of nicotine dependence, in the prevention and management of exacerbation and handling of patients at end-of-life stage (palliative treatment, final decisions, etc.)[4]. Specialised care physicians must have competencies in non-invasive mechanical ventilation and the multi-dimensional evaluation of the patient with COPD[4].

Primary care nursing professionals must have competencies in: Promotion of healthy lifestyles, prevention of nicotine dependence and tobacco withdrawal, early detection of COPD, adequate execution of forced spirometries, evaluation of needs of people with COPD and their families, execution of a care plan, prevention of exacerbation depending on the stage of the COPD and on the comorbidity, and in health education of patients and family members, and the increase of their autonomy[4]. In specialised care, the nursing professionals must also have competencies in: Non-invasive mechanical ventilation, multi-dimensional evaluation, global assessment of complex patients, work plan, coordination, results assessment and management at end-of-life stage (palliative treatment, final decisions, etc.) and in acute situation[4].

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The National Strategy for COPD establishes a series of strategic lines with objectives to be reached and recommendations, which, realistically and depending on the resources available and area of competence of the Autonomous Communities, contribute to improving the quality of the interventions and results in COPD[4].

Currently, the quality of care of people with COPD and the health results are aspects that are difficult to assess. Since the National Strategy, a series of indicators have been proposed that permit compiling and preparing the necessary information to carry out a systematic and continuous assessment[4,25].

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5. Definition, phenotypes, risk factors and natural history of COPD

5.1 Definition of COPD

COPD is defined as a respiratory disease characterised by a limitation to the airflow that is not totally reversible. This limitation of the airflow is usually expressed by way of dyspnoea and, in general, it is progressive. The limitation to the airflow is associated with an abnormal inflammatory response of the lungs to harmful particles and gases, mainly derived from tobacco smoke, which may cause other symptoms such as chronic cough, which may or may not be accompanied by expectoration. COPD is also characterised by the presence of exacerbation and by the frequent presence of comorbidities that may contribute to the severity in some patients.

This definition, which includes spirometric criteria of obstruction to the airflow, pathogenic mechanisms, aetiological aspects and symptomatic expressions, is in agreement with and expands on the definitions proposed by the American Thoracic Society (ATS) and the European Respiratory Society (ERS)[26] and by the Spanish Pneumology and Thoracic Surgery Society (SEPAR)[7]: it recognised that the spirometry on its own cannot be considered as diagnostic, but that it must be used as confirmation proof, if diagnosis is suspected in a patient who has chronic respiratory symptoms and is or has been a smoker. In less frequent cases, we can obtain a history of exposure to other toxic agents inhaled at home or at the workplace.

5.2 Phenotypic traits of COPD

COPD is a very heterogeneous disease and therefore it cannot be categorised just by using the degree of bronchial obstruction determined via forced expiratory volume in the first second (FEV1). The word, phenotype, is used to refer to clinical forms of patients with COPD[27]. An international group of experts has defined the phenotype of COPD as "those attributes of the disease that alone or combined describe the differences between individuals with COPD in relation to parameters that have a clinical meaning (symptoms, exacerbation, response to treatment, speed of progression of the disease, or death)"[27]. Therefore, the phenotype should be able to classify patients into subgroups with prognostic value and that permit determining the most adequate therapy to achieve better clinical results[27,28].

GesEPOC proposes four phenotypes that determine a differentiated treatment: 1. Non-exacerbator with emphysema or chronic bronchitis; 2. Mixed COPD – asthma; 3.

Exacerbator with emphysema; 4. Exacerbator with chronic bronchitis. The characteristics and definition of the basic phenotypes are set out below, which in the case of the exacerbators are combined with chronic bronchitis or emphysema to establish the definite phenotype[29].

Other possible phenotypes have been proposed (rapid decline[29], bronchiectasis[30,31], systemic[32], but their importance related to administering the treatment has not been established, or others which, due to their limited prevalence (alpha-1-antitrypsin deficiency)[33], are not specifically considered in this guideline.

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5.2.1 Definition of exacerbator phenotype

The word "exacerbator" defines any patient with COPD who presents two or more moderate or severe exacerbation a year. These exacerbation must be separated by at least 4 weeks from the resolution of the previous exacerbation or 6 weeks from its onset in cases where they have received no treatment, to differentiate the new event from a prior therapeutic failure[34].

The identification of the exacerbator phenotype is based on clinical history and it has been shown that the diagnosis based on the patient's declaration regarding his or her record of exacerbation is reliable[35]. The exacerbator phenotype underlines the importance of asking about the history of exacerbation in the clinical interview and identifying patients for whom anti-inflammatory treatment is indicated, in addition to bronchodilators. It is important to point out that the type of exacerbation a patient suffers (bacterial, viral or oeosinophilic) usually remains unchanged in successive episodes[36].

Frequent exacerbation may occur in any of the three remaining phenotypes: Emphysema, chronic bronchitis or mixed COPD-asthma. It is important because they will modulate the type and/or intensity of the treatment of all of them. A greater risk of suffering frequent exacerbation has been observed among patients with mixed COPD-asthma phenotype[37]. In these cases, exacerbation usually has an oeosinophilic profile, which suggests a different response to the treatment[36].

5.2.2 Definition of mixed COPD-asthma phenotype

The mixed phenotype in COPD is defined as an airflow obstruction that is not fully reversible, accompanied by symptoms or signs of increased reversibility of the obstruction[38]. To diagnose the mixed phenotype, a group of experts have agreed upon some criteria that are presented in section 5.3 (characterisation of the phenotype).

Within the spectrum of chronic airflow obstruction, there are asthmatic individuals who smoke and develop airflow obstruction that is not fully reversible[39,40] and smokers with no known history of asthma, whose bronchial inflammatory pattern has a preponderance of oeosinophils and is clinically expressed by increased airflow reversibility.

There are epidemiological studies on the incidence of COPD that show that young asthmatic people who develop COPD have a disease that has different characteristics to COPD with not asthmatic history. In the first case, allergic rhinitis, non-specific bronchial hyper-reactivity and the presence of wheezing are more frequent, and the plasmatic concentrations of IgE[41] are greater, thus indicating that it is a combined syndrome between asthma and COPD[42]. In asthmatic patients, the main risk factor of developing an airflow obstruction that is not fully reversible is the consumption of tobacco[40]. So these pathogenic pathways will finally come together to form a patient phenotype with chronic airflow obstruction and increased reversibility, which defines the mixed phenotype.

The prevalence of the mixed phenotype is unknown, but there are different estimations of its importance within the context of COPD. According to the COPDGene study, it is estimated that 13% of patients with COPD share a diagnosis of asthma[37]. Soriano et al[43] estimated that approximately 23% of patients with COPD aged between 50 and 59 could have a mixed phenotype. This figure increased with age, up to 52% of the cases of COPD between the ages of 70 and 79[43].

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5.2.3 Definition of chronic bronchitis phenotype

Chronic bronchitis was defined at the Ciba Symposium in 1958, ratified by the WHO in 1961 and by the ATS one year later, as the presence of a productive cough or expectoration for more than three months a year and for more than two consecutive years[43,44]. The chronic bronchitis phenotype identifies patients with COPD in whom chronic bronchitis is the prevalent syndrome. Bronchial hypersecretion in COPD has been associated with greater inflammation of the airway and a greater risk of respiratory infection[45], which may explain why patients with chronic bronchitis have more frequent exacerbation than patients without chronic expectoration[42,46,47]. A significant number of patients with chronic bronchitis and repeated exacerbation may have bronchiectasis if submitted to examination by high resolution computed tomography (HRCT) of the thorax[30,48].

5.2.4 Definition of the emphysema phenotype

Emphysema is defined as the affection of the lungs, characterised by an increase in size of the air sacs situated beyond the terminal bronchiole and which is accompanied by destructive changes in the walls. Due to the fact that the concept of emphysema is anatomical, the emphysema phenotype diagnosis is a clinical, radiological and functional diagnosis, which expresses the probability of the patient's symptoms and signs being able to be assigned to a morphological state of emphysema.

The emphysema phenotype includes patients with COPD with clinical/radiological/functional diagnosis of emphysema, whose main symptoms are dyspnoea and intolerance to exercise. Patients with emphysema phenotype have a tendency to reduced BMI. The diagnosis of emphysema phenotype must not be confused with the presence of emphysema. Signs of emphysema can be found in any of the phenotypes, and even in smokers without COPD criteria.

This COPD phenotype is characterised by the presence of functional hyperinsufflation[49] data, by the existence of emphysema in the axial high resolution computed tomography (AHRCT), and/or by a diffusion test below the value of reference, measured by the adjusted DLCO/VA quotient for haemoglobin[50]. The execution of these tests at a second healthcare level will enable us to definitely classify the emphysema phenotype.

The emphysema phenotype usually has fewer exacerbation than the chronic bronchitis phenotype, but patients with emphysema may also be exacerbators, especially those with more severe forms of the disease[51] Severe emphysema is also associated with a bad prognosis as it is a predictor of a higher annual drop of FEV1[52].

5.3 Characterisation of the COPD phenotype

Mixed, emphysema and chronic bronchitis phenotypes are excluding and the diagnosis is based on prevalent clinical expressions and compliance with the diagnosis criteria. The exacerbator phenotype coexists with the above three phenotypes, forming 4 phenotype combinations (Figure 5.1)[53,54]:

Type A: Non-exacerbator COPD with emphysema or chronic bronchitis

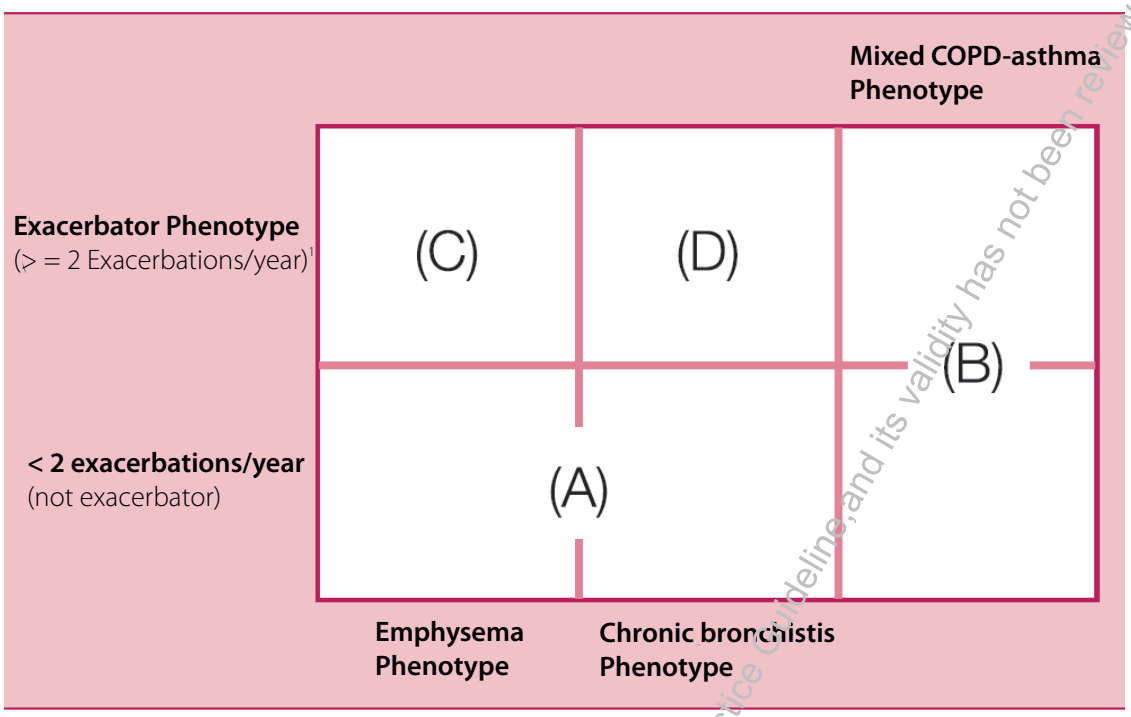
Type B: Mixed COPD with asthma, with or without frequent intensifications

Type C: Exacerbator COPD with emphysema

Type D: Exacerbator COPD with chronic bronchitis

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Figure 5.1. Phenotype combinations according to GESEPOC



The following steps must be followed, according to GesEPOC for the diagnostic identification process of the four phenotypes:

1. Has the patient suffered 2 or more exacerbation of at least moderate severity (which have required treatment with systemic corticosteroids and/or antibiotics) the previous year, and at least one month apart? If the answer is yes, the patient is classified as exacerbator.

2. Has the patient got mixed phenotype characteristics? For a diagnosis of mixed phenotype, at least two major or one major and two minor criteria must be fulfilled, as described below[34]. If the answer is yes, the patient will be classified as mixed, both if he is exacerbator or not.

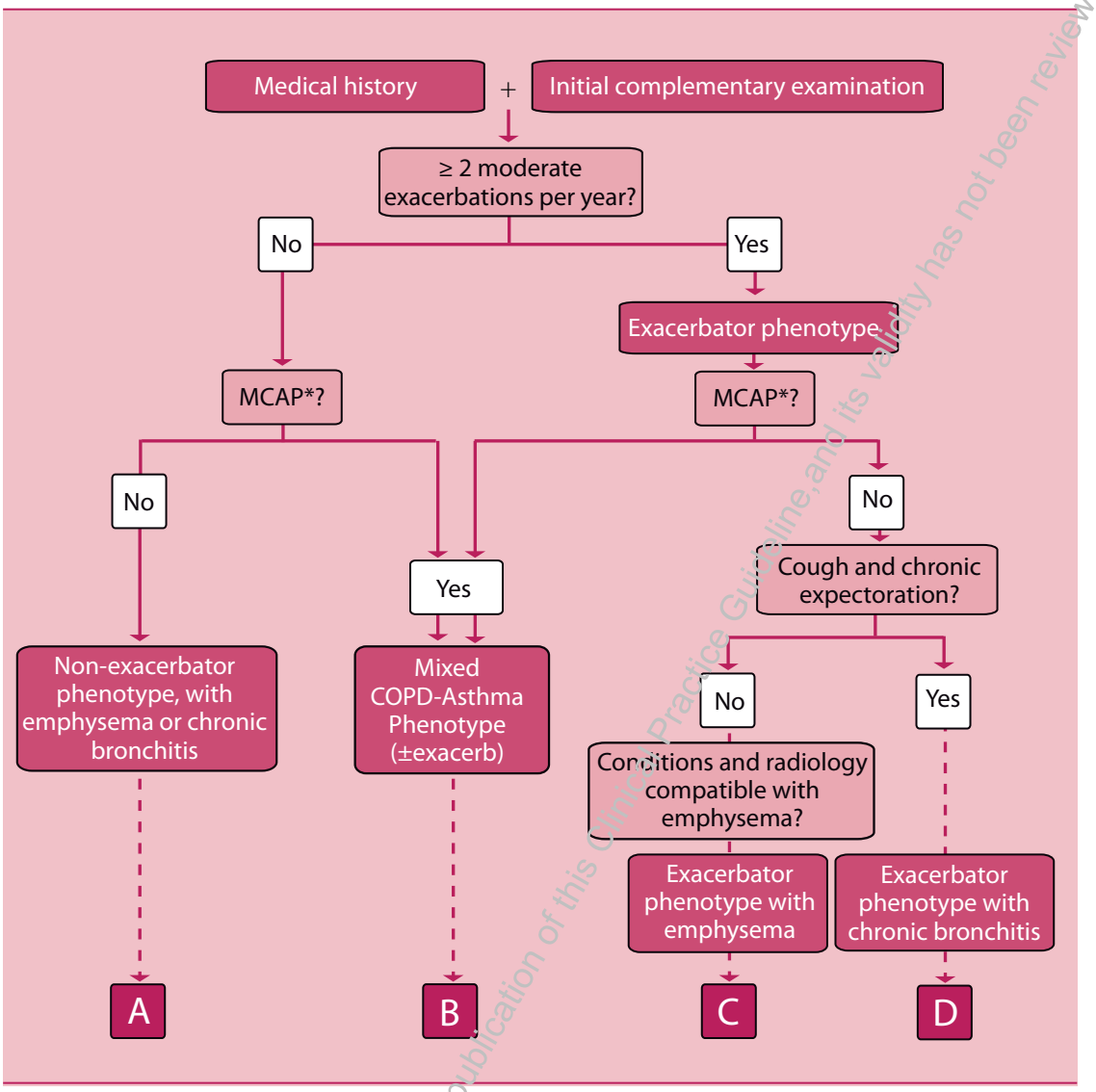
3. Has the patient had a cough and expectoration lasting for at least 3 months a year in two consecutive years? If so, he will be classified as chronic bronchitis phenotype.

4. Does the patient have clinical, radiological and/or functional characteristics typical of lung emphysema? If so, he will be classified as emphysema phenotype. In the majority of these cases, the main symptom in patients is dyspnoea. For confirmation, the demonstration of air entrapment is required (Functional residual capacity –FRC_ >120%, residual volume –RV- >140% of the theoretical rate or quotient, inspiratory capacity/total lung capacity –IC/TLC- <25%), or demonstration of emphysema by imaging techniques (computed tomography) or significant alteration of the diffusing capacity for carbon monoxide corrected by haemoglobin (KCO<80%).

This process is summed up in the figure below (Figure 5.2).

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Figure 5.2. Diagnostic identification process of the four phenotypes according to GesEPOC



*MCAP: mixed COPD-asthma phenotype

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5.4 Aetiology of COPD

5.4.1 Tobacco consumption

Since the 50s, it has been known that tobacco is the most important risk factor for developing COPD[55,56], and its causal relationship has been established through numerous prospective cohort studies, including the study by the British Medical Research Council[57] and by the Framingham Heart Study Offspring[58].

In prospective cohort studies, it is estimated that the absolute risk of smokers developing COPD is between 25 and 30%[59]. It has also been demonstrated that the risk is proportional to accumulated tobacco consumption, so the risk goes from 260% in smokers of 15-30 packets a year to 510% in smokers of more than 30 packets a year[17].

Tobacco consumption, both in industrialised countries and in developing countries, is very wide-spread. In Spain, according to data from the National Health Survey of 2006[17,60], 29.5% of the adult population smoke (26.5% on a regular basis and 3.1% sporadically), with a clear tendency in time towards a decrease in consumption, which is quite noticeable in men (from 42.1 to 31.6% between 1997 and 2006) and less so in women (from 24.8 to 21.5% in the same period). 33% of young people aged between 16 and 24 smoke, meaning that around 1.7 million young Spaniards are smokers. 28% of young people smoke every day and 5% do so on occasions. 34.4% of the girls smoke and 32.1% of the boys. The average age when they start to smoke is around 13.

5.4.2 Passive smoking

A proportion of cases of COPD occurs in people who have never smoked. Among these non-smoking people61, passive smoking is a risk factor that has been involved in the pathogeny of COPD. Passive smoking, also called environmental tobacco smoke, is the involuntary inhaling of smoke of another person who is smoking tobacco. Although obviously the health risks caused are less than those caused by active smoking, these are not only avoidable but involuntary.

Different observational studies have shown that passive smoking is associated with a greater risk of COPD[62-65]. The most definite study that associates passive smoking has been carried out in Guanzhou, China[65]. This is a study with more than 6,000 non-smoker participants. The majority (89.6%) were women and the average age was 61[65]. More than half the participants stated they were passive smokers, and the duration of the passive smoking turned out to be directly related to the risk of COPD[65].

In our medium, the impact that passive exposure to tobacco has on the pulmonary function of children and adolescents has been assessed[66], concluding that the spirometric parameters were significantly lower among children with a smoker parent. The negative effect of passive smoking on parameters related to the distal airway is greater.

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According to ENS data from 2006, child exposure to tobacco smoke at home is estimated at 24.1% in boys and 21.8% in girls aged 0 to 4, 32.4 and 32.7%, respectively in boys and girls aged 5 to 9, and 39.6 and 42.3% in boys and girls aged 10 to 14[60].

5.4.3 Burning biomass fuel

On a global level, approximately 50% of all homes and 90% of country homes use biomass fuel (wood, vegetal carbon, other plants and manure) and coal as their main domestic energy source[61].

Different systematic reviews have identified biomass and other fuels used for heating or cooking in developing countries as a risk factor of COPD in rural areas[61,67-70]. An example of these results is the systematic review that analyses 15 epidemiological studies (11 cross-sectional studies and 4 cases and controls), and it estimates a higher risk of developing COPD in people exposed to biomass than those not exposed [(OR = 2.44 (95% CI 1.9-3.33)], both in men and in women, in patients with COPD, smokers and non-smokers[67].

An increased risk of hospital admissions has been documented in Spain due to COPD in women, who had been significantly exposed during childhood and youth to wood or coal smoke. This risk was independent from nicotine dependence[71]. The past history of exposure to wood or coal smoke must be questioned, in particular in non-smokers or people who have little exposure to tobacco.

5.5 Risk factors for the development of COPD

5.5.1 Atmospheric pollution

Recent reviews conclude that it is much easier to identify risk factors for developing COPD and that these risk factors also include many other types of exposure, such as occupational or environmental exposure to dust and fumes both in developed countries and in developing countries[61,72]. The specific COPD-related pollutants studied are ozone, suspended particles (PM), carbon monoxide (CO), sulphur dioxide (SO2), nitrogen dioxide (NO2) and other gases[61].

High atmospheric pollution, above all associated with road traffic, is a triggering factor of COPD exacerbation or flare-ups in susceptible individuals[73]. There are controversies with respect to atmospheric pollution being a direct cause of COPD[61] and it is considered that it is quantitatively minimal. A recent study associates long-term exposure at low levels of atmospheric pollution with an increase in the risk of developing severe COPD; this association remained significant when other factors such as nicotine dependence were taken into account[74].

There are several multi-component indicators of the quality of the air we breathe, which combine, according to variable weights, the PM particles (suspended particles in the air) with different gases. Today, it is also possible to carry out continuous monitoring in real time and, in many cases, on a small geographical scale[75], thus providing an alert for COPD-susceptible individuals, the same as occurs with the pollen maps in asthma and rhinitis.

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5.5.2 Occupational exposure

Different cohort studies of workers have identified that occupational exposure to different dust, powders, gases and toxic fumes is associated with a greater risk of COPD, even after bearing in mind confusion factors such as tobacco[61,76]. Those individuals with COPD who are exposed in their workplaces to mineral dust or dust of any type, gases or fumes, have more severe COPD, compared with those whose occupational exposure is not significant[77]. These findings justify the research of occupational exposure in all patients and the establishment of preventive measures in the workplace whenever this is possible.

5.5.3 Pulmonary tuberculosis

Pulmonary tuberculosis is associated with COPD. In a study carried out in China on 8,784 people over the age of 50, patients with chest X-rays that showed they had had pulmonary tuberculosis, were associated with an increase in pulmonary obstruction, regardless of whether they were smokers, exposed to biomass or with a history of asthma[78]. In the COPD epidemiological study performed in Latin America (PLATINO), a past history of tuberculosis was associated with double or four times the risk of developing COPD, regardless of other risk factors, above all nicotine dependence[79].

5.5.4 Genetic factors

Hereditary emphysema, due to alpha-1-antritrypsin deficiency, is the main example of a genetic factor. Congenital alpha-1-antitrypsin deficiency predisposes to an accelerated decrease of the pulmonary function. It is an autosomal recessive expression disease that causes COPD and liver cirrhosis[33,80]. It is estimated that it is responsible for 1% of the cases of COPD and 2-4% of the cases of emphysemas. Early diagnosis is important as there is specific treatment with intravenous infusion of alpha-1-antitrypsin from donor plasma in those cases that satisfy the strict treatment criteria established by national and international regulations[33].

5.5.5 Other factors

Other risks factors that have been described are age, sex, pulmonary ageing, repeated respiratory infections of the child or adult at early ages as well as socio-economic factors[81]. The majority of these factors associated with the development of COPD cannot be modified.

The prevalence of COPD increases with age and it is more frequent in men, but this fact seems to be more related to the cumulative effect of other risk factors that individuals are exposed to throughout their lives rather than with age or sex[81]. The role of the family history is a mixture of genetic and environmental factors.

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In the more underprivileged social classes, there are a greater number of factors that are associated with developing the disease: Greater consumption of alcohol and tobacco, worse living conditions, frequent infections in childhood and fewer health resources[81].

5.6 Comorbidities in COPD

Patients with COPD frequently have extrapulmonary conditions, such as unintentional weight loss, miopathy and an increase of the systemic inflammation parameters. They also present an increase of associated chronic diseases, known as comorbidities, understood as the presence of one or several recognised diseases that coexist with the pathology of interest, which in this case is COPD.

In its 2011 review, the GOLD initiative explicitly recommends assessing COPD by measuring the patient's symptoms, the future risk of exacerbation, the severity of the spirometric abnormality and, for the first time, also by identifying the comorbidities[5].

The causes of this increased prevalence of comorbidities include, among others, nicotine dependence, advanced age, systemic inflammation[82] and, although probably not so important, some not so well-known genetic factors[83].

Noteworthy among the comorbidities most frequently associated with COPD include cardiovascular pathology (ischemic heart disease, cardiac insufficiency or stroke), high blood pressure, diabetes mellitus, renal insufficiency, osteoporosis, psychiatric diseases (anxiety and depression), cognitive impairment, anaemia or neoplasia, especially lung cancer[84] (Table 5.1). Their presence worsens the prognosis of COPD and they are a frequent cause of mortality in this population[85]. Even though some comorbidities are present at the time of the diagnosis[86], their number and severity increase with the evolution of the disease[87], until they are practically the norm in patients with advanced COPD and hospital admissions due to exacerbation[88].

The probability of having ischemic heart disease – myocardial infarction or angina – and the probability of suffering cardiac insufficiency increase two- or four-fold, respectively, in patients with COPD, regardless of other risk factors, including nicotine dependence[89]. In the population aged between 35 and 44, the incidence of myocardial infarction is 10 times greater in patients with COPD and the incidence of having a cerebrovascular accident increases 2.5 times[90]. The incidence of these pathologies increases in the weeks following an exacerbation or flare-up of COPD[91]. The prevalence of cardiac insufficiency also increases with the severity of COPD, reaching 20% in ambulatory patients over 65 and 30% in hospitalised patients due to exacerbation[92]. Patients with both pathologies have less capacity for exertion and greater mortality 3 years after discharge[93,94]. Patients with emphysema and pulmonary hyperinsufflation may present cardiac insufficiency secondary to the difficulty of diastolic filling of the heart[95].

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COPD is a risk factor for lung cancer whose prevalence has increased two- or six-fold, regardless of the history of nicotine dependence[96,97].

Up to 40% of patients with COPD simultaneously present anxiety and/or depression. These patients have worse quality of life, greater functional impairment and higher mortality rates[98,99].

Table 5.1. Comorbidities associated with COPD

– Ischaemic cardiopathy
– Cardiac insufficiency
– Arrhythmias
– Pulmonary hypertension
– Lung cancer
– Osteoporosis
– Miopathy
– Cachexia
– Glaucoma/Cataracts
– Psychological disorders (anxiety and depression)
– Cognitive impairment
– High blood pressure
– Diabetes mellitus
– Síndrome metabólico
– Anaemia
– Sleep apnoea syndrome
– Thromboembolic disease

Adapted from: Barnes 2009[100] and Soriano 2005[86]

Natural history

The clinical course of COPD reflects the progressive decrease in time of the pulmonary function. Data referring to the natural history of patients with COPD are based on cohort studies that include the pulmonary function as a variable. The study by the British Medical Research Council (BMRC)[57] shows the different evolution of the pulmonary function depending on the smoking habit and susceptibility to it. Susceptible smoking patients, representing around 25% of the smokers, present a steeper curve in the drop of FEV1 related to age. If these patients stop smoking, their ventilation capacity does not improve, but the impairment curve of their pulmonary function adopts the slope of non-smokers, thus slowing down the evolution of the disease[57].

More recent results from the Framingham Heart Study Offspring cohort[58] and different intervention studies[101,10], suggest that the progression of the disease is not even and that not all patients follow the same progression, although the beneficial effect of smoking cessation is observed constantly in all of them. The Framingham cohort shows that changes in the pulmonary function of non-smokers from adolescence to old age are different in men than in women, but it shows a similar increase in the rate of decline of FEV1 and a greater benefit the sooner the smoking habit is abandoned, especially if this is done before the age of 40[58].

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Patients with COPD symptoms represent a group that is susceptible to an accelerated decrease of the pulmonary function[58]. Mucus hypersecretion and recurrent infections of the low respiratory tracts increase the risk of exacerbation and have, therefore, an impact on the natural history of the disease, favouring the decline of FEV1. Furthermore, patients with frequent exacerbation present a greater decline of FEV1[103,104].

The different phenotypes purport to explain the existence of patients with COPD in whom parenchymal destruction and loss of elasticity (emphysema) or bronchial hyper-reactivity (mixed COPD-asthma) prevail, or exacerbator patients with an accelerated loss of pulmonary function caused by exacerbation. The findings of the ECLIPSE study have shown that the three prognosis factors significantly associated with an accelerated loss of pulmonary function are the ones that identify and characterise three of the phenotypes described in GESEPOC: The presence of emphysema, the positivity of bronchodilator testing and frequent exacerbation[105].

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6. Treatment of COPD in stable phase

Questions to be answered:

- Is there evidence to advise a specific type of sustained action bronchodilator in mono-therapy at the onset of treatments of stable phase COPD?
- What are the benefits of combined therapy (inhaled corticoids/long acting beta agonists) compared with dual bronchodilator therapy?
- Can roflumilast be an alternative to the use of inhaled corticoids as additional therapy to the maintenance treatment with bronchodilators in patients with COPD?
- Is the use of the antioxidant and mucolytic, N-acetylcysteine, justified in patients with COPD?
- Is the use of the mucolytic, carbosyteine, justified in patients with COPD?

Treatment of COPD can be summed up in three general objectives: reduce the chronic symptoms of the disease, decrease the frequency and severity of the exacerbation, and improve the prognosis. Short-term benefits (control of the disease), as well as medium and long-term objectives (risk reduction)[106] must be reached.

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6.1 Sustained action bronchodilators at onset of treatment in monotherapy

After establishing the COPD diagnosis, the first step in the treatment is bronchodilation.

Short-acting muscarinic antagonists (SMA) such as ipratropium bromide and short-acting β2 agonists (SABA) such as salbutamol or terbutaline are effective drugs in the rapid control of symptoms. In patients with occasional symptoms, treatment with short-acting bronchodilators reduces the symptoms and improves tolerance to exertion. These, added to the base treatment, are drugs of choice for treating symptoms on demand, whatever the level of severity of the disease.

When regular treatment with bronchodilators is required, the clinical practice guidelines recommend the use of long-acting bronchodilators, rather than short-acting ones, as the former are more effective[5,107-109]. In general, long-acting bronchodilators are well-tolerated and present few adverse effects. However, the following must be taken into account:

- Long-acting beta-adrenergic agonists (LABA): Fine tremor of arms and legs, muscle cramps, tachycardia, high blood pressure, peripheral vasodilation, headache, hyperglycaemia, hypopotassemia, cough, bronchospasm, oropharyngeal irritation and dyspepsia.

- Long-acting muscarinic antagonists (LAMA): can be associated with dry mouth[110]. Other adverse effects observed include: urine retention, increase of ocular pressure and pharyngeal irritation.

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Long-acting muscarinic antagonists marketed in Spain[5,111]

Active principle	Presentation and dose	Trade names	Duration of the action
Long-acting beta-adrenergic antagonists			
Formoterol	Turbuhaler 9 µg Turbuhaler 4,5 µg	Oxis	+ 12 hours
	Novolizer 12 µg Novolizer 6 µg	Formatris	
	Aerolizer 12 µg	Foradil Broncoral Neblik	
	Inhaler 12 µg	Broncoral Neo Foradil Neo	
	Formoterol 12 µg for inhalation	Formoterol Stada Formotero Aldo-Union	
Salmeterol	Inhaler 25 µg Accuhaler 50	Serevent Beglan Inaspir Betamican	+ 12 hours
Indacaterol	Inhaler 150 µg Inhale 300 µg	Oslif Breezhaler Onbrez Breezhaler Hirobriz Breezhaler	24 hours
Long-acting muscarinic antagonists			
Tiotropium	Handihaler 18 µg Respimat 2,5µg		+ 24 hours

On the other hand, the guidelines do not indicate what type of long-acting bronchodilator is preferable when starting sustained treatment with monotherapy.

It is important to point out that the studies included in the review to answer this question are those where the intervention to be compared exclusively included long-acting bronchodilators, although some studies enable those patients with corticoids and/or inhaled short-acting bronchodilators on demand in their base treatment, to maintain this treatment regardless of the intervention assigned to them. It must also be pointed out that the studies are not long enough so as to be able to assess the mortality associated with each one of the treatments.

6.1.1 Quality of evidence

Tiotropium (LAMA) versus salmeterol/formoterol (LABA)

Studies that compare the effectiveness of tiotropium with respect to other long-acting beta-adrenergic agonists are few.

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Bronchodilation

A systematic review from the year 2007 that assessed the efficacy of tiotropium in the treatment of stable phase COPD, included three studies (N=1.599) where both types of bronchodilators (tiotropium versus salmeterol/formoterol) were compared. The results of the review show higher FEV1 and CVF associated with the use of tiotropium. This result, although statistically significant, is not clinically relevant as the differences were small (30 ml and 80 ml respectively)112. High quality

Exacerbation

According to this review, patients who received tiotropium showed a 20% reduction in the risk of suffering exacerbation with respect to the beta-adrenergic agonists, although statistical significance was not reached for this latter result, probably due to lack of power in the studies. Later on, a larger sized RCT was published (N=7,376) on patients who had suffered at least one exacerbation that required hospital admission and/or treatment with systemic glucocorticoids and/or antibiotics the previous year. This study was specifically designed to detect differences in the risk of suffering exacerbation between patients treated with tiotropium and salmeterol. Results show that tiotropium significantly reduces the risk of suffering at least one exacerbation by 17% compared to salmeterol. It also reduces the risk of suffering exacerbation that require treatment with glucocorticoids by 23%, that require treatment with antibiotics by 15%, and that require treatment with both by 24%. An increase of 42 more days, on average, was noted with respect to the time that elapses until the first exacerbation was suffered, when monitoring patients who received tiotropium[113]. High quality

Dyspnoea, general state of health, use of rescue medication

In other reviews, both dyspnoea and the general state of health, and the use of rescue medication, were also evaluated, not finding important differences between both treatments[114,115]. Moderate quality

Risk of adverse events

The majority of adverse events suffered by patients were slight or moderate. An important increase in dry mouth was observed among those patients who receive tiotropium (OR= 4.72; 95% CI: 2.43 to 9.16)[112]. High quality

When severe adverse effects are compared between tiotropium and salmeterol, a similar incidence is observed in both groups (14.7% of patients who received tiotropium and 16.5% of those who received salmeterol). During the one year period that this study lasted, 64 deaths were registered in the group that received tiotropium and 78 in the group that received salmeterol[113].

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Abandonment due to adverse events

On the other hand, salmeterol appears to be tolerated worse than tiotropium. According to the results of a meta-analysis, a higher percentage of patients abandoned the studies as a result of the adverse effects among those that received salmeterol[114]. In a later RCT, a 12% increase in the risk of dropping out of the study due to an adverse effect was observed in those that received salmeterol, although the differences were not significant[113]. Low quality

Indacaterol opposed to other long-acting bronchodilators

Indacaterol is a new long-acting beta2 adrenergic agonist. Unlike other beta-adrenergic drugs, it produces bronchodilation for 24 hours so it only needs to be administered once a day.

a) Indacaterol (LABA) versus salmeterol/formoterol (LABA)

In the INLIGHT-2[116], INSIST[117], INVOLVE[118], INTEGRAL[119] and INPUT[120] studies, the effectiveness and safety of a daily dose of indacaterol is compared with the administration of two daily doses of other long-acting beta-adrenergic agonists. The clinical trials include patients over 40, smokers or ex-smokers, with moderate or severe COPD. Different doses of indacaterol are compared with salmeterol 50 ug, formoterol 12 ug and in all except for one, with placebo, too. Monitoring between the studies varied from 14 days to 52 weeks.

Bronchodilation

The results of the spirometries carried out at different times of the monitoring show a statistically significant result in favour of indacaterol. The FEV1 was between 60 and 110 ml higher in those patients who received indacaterol compared with those who received salmeterol or formoterol[116-120]. Low quality

Dyspnoea

On the contrary, the results provided by the assessment of dyspnoea via the TDI (Transition Dyspnoea Index) are not so clear. No differences were found when comparing indacaterol and formoterol[118]. With respect to salmeterol[50], in one of the studies, patients who received indacaterol showed around 40% more probabilities of obtaining a clinically important improvement117. In another of the studies, indacaterol was superior to salmeterol after 12 weeks' treatment, but the differences were not maintained at the end of the study (52 weeks)[116]. Low quality

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Quality of life

The quality of life was similar in both groups[116-120]. Low quality

Risk of suffering at least one exacerbation

There were no differences, either, in the risk of suffering exacerbation after 52 weeks and the annual exacerbation rate was similar in both groups[116-120]. Low quality

Use of rescue medication

In some studies, a reduction in the daily use of salbutamol was verified as well as more days without needing rescue medication among patients treated with indacaterol, although the differences were slight and probably not very clinically relevant[116-120]. Low quality

Adverse events

The incidence of adverse events was also comparable between the two groups and no important differences were registered, either, when compared with placebo. The percentage of patients who suffered at least one adverse effect was slightly higher, although not significant, among those that received indacaterol[116-120]. Low quality

A total of four deaths associated with indacaterol and four with the other beta-adrenergic agonists were registered in the studies. The death of one patient under treatment with indacaterol, who died due to cardiac arrest, was considered to be associated with the treatment[116-120].

b) Indacaterol versus tiotropium

Three studies (INTIME[121], INTENSITY[122] and INHANCE[123]) compare the effectiveness of indacaterol compared with tiotropium 18 ug in patients with moderate-severe COPD. The three studies are RCTs, one of them crossed[121], in which different doses of indacaterol (150-300 ug) are assessed, compared with tiotropium and in two of them compared with placebo, too[121,123]. The monitoring of the studies varied between 14 days and 26 weeks.

Bronchodilation

The results of the spirometries performed 24 hours after dose throughout the monitoring, indicate that the administration of one daily dose of indacaterol, of 150 or 300 ug, is at least as equally effective as a daily dose of tiotropium 18 ug. The difference in the FEV1 values between the groups that received indacaterol and tiotropium varied between 0 and 50 ml in favour of indacaterol[121-123]. The differences were not statistically significant, with the exception of one of the studies in which FEV1 values of between 40 ml and 50 ml higher were registered in patients who received indacaterol. However, at the start of the study, the average FEV1 of patients who received indacaterol was between 7 and 80 ml higher than the values of those who received tiotropium, so the superiority of indacaterol cannot be deduced from these results[123]. Low quality

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Dyspnoea

Dyspnoea was assessed in two of the studies, through the TDI. The probability of attaining a significant clinical improvement was higher in the group that received indacaterol 300 compared with tiotropium[122]. However, for indacaterol 150, only one of the studies that compared indacaterol and tiotropium, found significant differences[122,123]. — Very low quality

Exacerbation: risk of suffering at least one exacerbation.

The incidence of exacerbation after six months was slightly lower in groups of patients that received indacaterol, although these differences were not significant[123]. — Very low quality

Quality of life

The general state of health was measured in the studies using the SGRQ scale (St George's Respiratory Questionnaire), whose scores vary in a range from 0 (best possible score) to 100 points (worse possible score)). The scores on the scale dropped considerably with the use of indacaterol 150 and also with indacaterol 300 compared with tiotropium, although in the latter case, the differences were not significant at the end of the monitoring. The probability of obtaining a clinically significant improvement (a reduction in score > 4 points) was around 40-50% higher with indacaterol 150[122,123]. — Very low quality

Use of rescue medication

Likewise, the required use of rescue medication dropped considerably in the group that received indacaterol 150 and 300 compared with tiotropium; patients receiving treatment with indacaterol were able to reduce their daily inhalations by an average of 0.5 to 0.6 with respect to tiotropium, although the results were only statistically significant with indacaterol 300[122,123]. — Very low quality

Adverse events

The incidence of adverse events was similar for both drugs. The majority of these were slight and moderate, coughing being among the most frequent. Severe adverse events were also similar; the proportion observed was 7.7% for indacaterol 300, 8.4% for indacaterol 150 and 8.2% for tiotropium during a 26-week monitoring period. Only 6 deaths were registered in all the studies, none of them related to medication[121-123]. — Very low quality

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6.1.2 Economic assessments

Different treatments for COPD are compared in a cost-effectiveness study, in the Spanish health system with a five-year time horizon. According to this study, tiotropium would be more cost-effective than salmeterol or ipratropium both from the National Health System perspective and from a social perspective. Tiotropium is cost-effective in all scenarios proposed for the 20,000 Euro threshold per QALY: However, although tiotropium appears to be the better alternative, there is considerable uncertainty regarding this result, as in the probabilistic sensitivity analysis, for the willingness to pay 20,000 Euro per QALY, the probability of it being the best option is 50% (thus there is another 50% of possibilities of it not being the best option)[124]. A possible limitation of this assessment lies in that the model includes differences in the progression of COPD associated with treatment, determined by FEV1 and exacerbation or flare-ups, meaning that it may not be altogether appropriate[5,108]. On the other hand, the costs included in the assessment may not reflect the current costs of the treatments, as the prices considered in the study were from the year 2005, although after verifying today's prices, there is a considerable likelihood of them being comparable. Finally, it must be added that research studies published after this study[113] state that they would probably favour the superiority of tiotropium over salmeterol, if they were to be incorporated into the model.

Other economic studies in the context of other countries also conclude that tiotropium is the most cost-effective alternative compared with other bronchodilators. However, the results of these studies are not completely applicable to our country given the differences both in the cost of the drugs and in the costs of the treatment of the exacerbation[125-128].

More recently, a study has been published that analyses the cost-utility in Germany of different bronchodilators, including indacaterol, tiotropium and salmeterol. According to this study, indacaterol 150 ug is the prevalent alternative vis-à-vis other treatments[129]. However, the effectiveness studies that the model is based upon are small in size and with low methodological quality, and the clinical superiority of indacaterol compared with tiotropium is not clear in these studies. On the other hand, the price of indacaterol in our country is also lower than that of tiotropium.

6.1.3 Patients' values and preferences

A study was published in 2007 about the persistence in treatment with bronchodilators prescribed for the first time to patients with COPD in the Netherlands. In order to evaluate which treatments were still maintained at the end of one year, an extensive database was reviewed, which includes both the drugs dispensed in chemist's shops in the community and the hospital discharge records. It was observed that 37% of the patients who had started treatment with tiotropium, maintained this treatment after one year, compared with 13% to whom long-acting beta adrenergic agonists (salmeterol/formoterol) had been prescribed. The authors launch the hypothesis that the low adherence of patients to the treatment prescribed may be the main reason for interruption of the treatment and therefore for the differences observed[130]. However, adherence to treatment is a complex factor that does not just reflect the patients' preferences for a certain drug. Although it has been expressed that a reduction of the daily number of doses is associated with an increase in adherence to the treatment in chronic diseases, other socio-demographic and psychological factors or the patient's actual state of health, also have an influence on adherence to the treatment[131].

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An open and crossed RCT has been published recently, which compares the preferences of 82 patients regarding the use of a daily dose of two inhalers: indacaterol Breezhaler and tiotropium HandiHaler. After seven days' training in the use of these inhalers, the scores about the correct use of the inhalers reached 93.5% for BreezHaler and 94.4% for HandiHaler. 61% of the patients preferred BreezHaler as an inhaler for daily use compared with 31% who preferred the HandiHaler. Some of the reasons why patients preferred BreezHaler were that it was easier to open the cap and the nozzle, to close the nozzle after inserting the capsule and to hold the inhaler[132]. This RCT includes data about the use of inhalers, not about the effectiveness of the drugs.

6.1.4 Use of long-acting bronchodilators according to phenotype

The studies included in this review do not incorporate an effectiveness analysis according to the phenotypes considered in this guideline. One of the studies that compares the risk of exacerbation in patients treated with tiotropium or salmeterol only includes patients that have suffered at least one exacerbation treated with systemic glucocorticoids or antibiotics, or has required hospital admission113. Although the definition of exacerbator phenotype does not exactly coincide with this inclusion criterion, it is reasonable to think that a considerable proportion of patients included could be classified within this phenotype.

On the other hand, all the studies exclude asthmatic patients, one of the major criteria for diagnosing mixed phenotype, so some patients with this phenotype would not be contemplated in the studies.

Summary of evidence

Moderate overall quality of evidence	The bronchodilator effect of tiotropium is somewhat greater than that of formoterol/salmeterol, although clinically the differences are not very important[112].
	Tiotropium, in those patients who have suffered at least one prior exacerbation that has required hospital admission and/or treatment with systemic glucocorticoids and/or antibiotics during the previous year, significantly reduces the risk of hospital admissions related to COPD, exacerbation that require treatment with systemic glucocorticoids and/or antibiotics, and increases the time that elapses until the first exacerbation, compared with salmeterol[112,113].
	Dyspnoea, the general state of health and the use of rescue medication is similar among patients treated with tiotropium and salmetero[1114,115].
	The risk of having a dry mouth is greater in treatments with tiotropium than with salmeterol[112].
	The probability of abandoning the treatment because of the adverse effects is greater in patients treated with salmeterol compared with those treated with tiotropium[113,114].

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Low overall quality of evidence	The bronchodilator effect of indacaterol seems to be greater than other long-acting beta adrenergic agonists[116-120].
	There is not sufficient evidence to determine the superiority of indacaterol compared with other long-acting beta adrenergic agonists with respect to the improvement of dyspnoea, quality of life and reduction of the use of rescue medication[116-120].
Very low overall quality of evidence	The bronchodilator effectiveness of indacaterol is at least the same as the effectiveness of tiotropium[121-123].
	Indacaterol may improve the scores obtained using the TDI when compared with tiotropium and increase the probability of obtaining a significant clinical improvement with respect to dyspnoea, although there is not sufficient evidence to confirm these results[122,123].
	The risk of suffering at least one exacerbation or flare-up is similar with indacaterol and tiotropium[122,123].
	Indacaterol could improve the general state of health of patients with COPD, measured via the SGRQ scale, to a greater extent than tiotropium, increasing the probability of obtaining a significant clinical improvement, although there is little evidence[122,123].
	Treatments with indacaterol reduce the need to use rescue medication to a greater extent than treatment with tiotropium. However the differences only reach statistical significance with indacaterol 300[122,123].
	The incidence of adverse effects between treatments with indacaterol and tiotropium are similar[121-123].

Recommendations

Good clinical practice	In patients with stable phase COPD who require sustained action bronchodilators in monotherapy, it is suggested to base the final choice of bronchodilator on criteria such as the preferences of the individual patients, the individual response to the drug and/or economic aspects.
Weak	In patients with stable phase COPD and who have suffered at least one previous exacerbation that has required hospital admission and/or treatment with systemic glucocorticoids and/or antibiotics during the previous year and that require a sustained action bronchodilator in monotherapy, the use of tiotropium rather than salmeterol is suggested.
Research recommendation	It is recommended the realization of randomised controlled trials to assess the effectiveness and safety of indacaterol rather than tiotropium in patients with stable phase COPD that require sustained action bronchodilators in monotherapy, due to the identified evidence is insufficient to recommend one rather than the other.

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6.2 Combined therapy (IC/LABA) opposed to dual bronchodilator therapy (LABA+LAMA)

The current guidelines about the management of COPD recommend the prescription of combinations of inhaled treatments when bronchodilator monotherapy is insufficient to control the symptoms of the disease. Possible treatment combinations include combined therapy, which entails the combination of long-acting bronchodilators together with inhaled corticoids (IC/LAMA or IC/LABA) or dual bronchodilator therapy, in other words, a combination of two types of long-acting bronchodilators (LAMA/LABA). The majority of the guidelines focus on recommending the combination of long-acting beta adrenergic agonists and inhaled corticoids; however, they do not carry out a direct comparison between this intervention and the combination of LAMA and inhaled corticoids or dual bronchodilator therapy (LAMA/LABA)[5,108,109].

6.2.1 Quality of evidence

We have identified only one RCT that compares the administration of two long-acting bronchodilators and the administration of one long-acting beta adrenergic agonist together with inhaled corticoids. In this RCT, 605 patients diagnosed with moderate/severe COPD were randomised to receive a combination of two bronchodilators (tiotropium and formoterol) or a combination of bronchodilator plus corticoids (salmeterol/fluticasone) for six weeks[133].

Bronchodilation

The results of the spirometries at the end of the treatment show that the FEV1 measured several times over a 12-hour period was generally higher in the group that received tiotropium plus formoterol. The average difference of the AUC of the FEV1 over the 12 hours was 78 ml (95% CI: 34 at 122 ml) and of the peak of the FEV1 was 103 ml (95% CI: 55 at 150 ml) in favour in both cases of dual bronchodilator therapy[133].	Low quality

Use of rescue medication

The use of rescue medication was similar in both groups[133].	Low quality

Adverse events

The appearance of adverse events was similar in both groups. 28.5% of those that received dual bronchodilator therapy and 27.8% of those that received combined therapy suffered at least one adverse effect. Six patients from each group suffered a severe adverse effect and one patient from each one of the groups died[133]	Low quality

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This study presents important limitations. In the first place, the duration of the study is insufficient to evaluate both the effectiveness and the safety of each one of the two treatment combinations. On the other hand, patients with moderate COPD are included in this study, so the sample cannot be representative of the population to whom the treatments assessed would be applied. The selection criteria of the study contemplate inclusion of those patients with FEV1 after bronchodilation <80% of the forecast, FEV1/CVF< 70% during the first visit and pre-dose FEV1 ≤ 65% of the forecast during the second visit. Finally, the lack of clinical results and the report only of spirometry results, prevents making an adequate assessment, based on this study, of which of the two options is the most adequate for patients with COPD not controlled by monotherapy.

Exacerbation

2 meta-analyses published after this study[134,135], which compare, among other things, via a technique known as meta-analysis network, the effectiveness of the combined therapy compared with the dual bronchodilator therapy when reducing the frequency of exacerbation in patients with COPD. Multiple comparisons of possible treatments are offered in the first of the meta-analyses, in patients with COPD, including the comparison between IC+LABA and LAMA+LABA[135.] The second of the meta-analyses, although aimed at assessing the effectiveness of Roflumilast, also contemplates the comparison between IC+LABA and LAMA+LABA[134] The meta-analysis network technique purports to determine the effectiveness of one drug compared with another, although there are no studies that establish direct comparisons between the two drugs in question[136].

Low quality

In the meta-analysis network of Mills 2011, based on indirect comparisons, no significant differences are shown between IC+LABA and LAMA+LABA regarding the frequency of annual exacerbation when administered to patients with moderate, severe or very severe COPD: RR of LABA + IC versus LAMA+LABA =0.88; 95% CI: 0.61 to 1.24[135].

Along the same line, the meta-analysis of Riemsma 2011, based once again on indirect comparisons, does not find significant differences either between both interventions with respect to the frequency of annual exacerbation, in those patients with COPD and FEV1 post-bronchodilation ≤ 65% of the normal value: Rate ratio of LAMA+LABA versus IC+LABA=1.22; Credibility Interval (CrI) of 95%: 0.92 to 1.58[134].

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6.2.2 Economic assessments

We have not identified any economic assessments that compare the cost/effectiveness of the interventions studied, combined therapy compared with dual bronchodilator therapy. In the Riemsma study, a cost/effectiveness analysis is presented, focused on roflumilast. In this study, both the IC+LABA combination and the LAMA+LABA combination are included as alternatives in the treatment of patients with severe COPD who tolerate corticoids. Although these interventions are not compared with each other, the gross data suggest that both interventions are similar in terms of cost/effectiveness[134].

6.2.3 Patients' values and preferences

No studies were identified that consider the patient's values and preferences.

6.2.4 Use of IC/LABA or IC/LAMA opposed to LAMA+LABA according to phenotype

No study was identified that assesses the effects of administering combined therapy opposed to dual bronchodilator therapy in patients with COPD according to the phenotypes considered in this guideline.

Summary of evidence

Low overall quality of evidence	According to the results of one RCT, the spirometries at the end of the treatment show that the FEV1 measured several times over a 12-hour period is generally higher in the group that received tiotropium plus formoterol compared with salmeterol/fluticasone, with an average difference of the AUC of FEV1 over the 12-hour period of 78 ml (95% CI:34 to 122ml) and of the peak of FEV1 of 103ml (95% CI: 55 to 150 ml) after six weeks' treatment. This study presents important limitations (insufficient duration, sample may not be representative of the target population of each one of the treatments) to evaluate both the effectiveness and the safety of the interventions[133].
	Based on indirect comparisons, two meta-analysis networks did not detect differences regarding the frequency of annual exacerbation between the patients treated with LAMA+LABA and those who received IC+LABA[134,135].

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Recommendations

Research recommendation	It is recommended the realization of randomised controlled trials to assess the effectiveness and safety of combined therapy (IC/LAMA or CI/LABA) rather than dual bronchodilator therapy (LABA+LAMA) in patients with stable phase COPD, due to the identified evidence is insufficient to recommend one of the options rather than the other.

6.3 Use of roflumilast instead of inhaled corticoids as additional therapy to the maintenance treatment with bronchodilators in patients with COPD

Inhaled corticoids (IC) are used in patients with severe or very severe stable phase COPD (FEV1 post-bronchodilator < 50% of normal value), who suffer frequent exacerbation, combined with long acting beta-2 agonists or when combined with long acting anti-cholinergics and long acting beta-2 agonists[6]. However, long-term treatment with IC could be associated with a greater risk of adverse events, such as pneumonia, cataracts or open angle glaucoma[137,138].

Roflumilast (RF) is a new oral anti-inflammatory drug whose action mechanism is based on the selective inhibition of phosphodiesterase 4 (PDE4), an isoenzyme involved in the inflammatory processes of COPD. The European Medicines Agency authorised RF for the maintenance treatment of severe or very severe COPD (post-bronchodilator FEV1 < 50% of normal value) associated with chronic bronchitis in adult patients with a history of frequent exacerbation; not as exclusive treatment, but as additional treatment to the use of bronchodilators[111]. It is not indicated for other patients with COPD or for patients with asthma or with alpha-1 antitrypsin deficiency. It is not indicated, either, as rescue medication to relieve acute bronchospasm. Consequently, RF is also authorised in Spain under these indications. However, the National Institute for Health and Clinical Excellence (NICE) of the United Kingdom, published a report in January 2012 on the assessment of health technologies where it recommends the use of RF in the same indication as that mentioned by the European Agency, but only in a research context. In fact, the report concludes that high-quality evidence must be generated about the effects of adding RF to the LAMA+IC/LABA therapy (or to the LAMA+LABA therapy in those patients who do not tolerate IC). The report also suggests studying the effects of RF compared with theophylline in those patients in whom theophylline is indicated[139].

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6.3.1 Quality of evidence

No study has been identified that directly assesses the effectiveness or safety of RF compared with IC in patients with COPD, which does not necessarily mean there is a lack of effect. No studies in progress have been identified, either, that attempt to answer this question. Low quality

Two meta-analyses[134,135] have been identified that, using a technique known as meta-analysis network, assess the relative effectiveness of RF compared with IC to reduce the frequency of exacerbation or flare-ups in patients with COPD. The meta-analysis network purports to determine the effectiveness of one drug compared with another, although there are no studies that establish direct comparisons between the two drugs in question[136].

The Riemsma meta-analysis network forms part of the report on RF published by NICE139. Based on indirect comparisons, the Riemsma study suggests that administering RF in patients with severe or very severe COPD (post-bronchodilator FEV1 ≤ 50% of normal value) did not show any differences with respect to the IC regarding frequency of annual exacerbation: Rate ratio of IC versus RF=0.98; Credibility Interval (CrI) of 95%: 0.85 to 1.13; and rate ratio of LABA+RF versus IC+LABA=1.11; CrI 95% 0.95 to 1.28.

The meta-analysis network of Mills 2011, also based on indirect comparisons and published before the above one, did not show any differences either between RF and IC regarding the frequency of annual exacerbation in patients with moderate, severe or very severe COPD (it included patients with post-bronchodilator FEV1 < 90% of normal value): rate ratio of IC versus RF=0.94; CrI: 0.76 to 1.15; and rate ratio of IC+LABA versus LABA+RF=1.05; CrI: 0.75 to 1.43.

6.3.2 Economic assessments

Two cost-effectiveness analyses were identified for RF[134,140]. Riemsma 2011 presents a cost-effectiveness analysis of RF based on indirect comparisons (starting with the critical analysis of the cost-effectiveness study carried out by Merck 2011). In general terms, with respect to the RF versus IC comparison, the Riemsma 2011 and Merck 2011 studies suggest that the most effective COPD treatment options would include the use of IC and do not contemplate the use of RF without including the administration of IC.

6.3.3 Patients' values and preferences

No studies were identified that consider the patient's values and preferences.

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6.3.4 Balance between benefits, risks and disadvantages associated with the intervention

The consideration of the available evidence is insufficient to conclude that there is a clear benefit associated with the use of RF as an alternative to IC.

6.3.5 Use of RF compared with IC according to phenotype

No study was identified that assesses the effects of RF opposed to IC in patients with COPD according to the phenotypes considered in this guideline.

Summary of evidence

Low overall quality of evidence	No study has been identified that directly assesses the effectiveness or safety of RF compared to ICs, in patients with COPD, which does not necessarily imply the evidence of lack of effect. Therefore, it has not been possible to determine if the substitution of ICs for RF, as an additional therapy to the maintenance treatment with bronchodilators, is an effective and safety treatment option in patients with COPD. Based on indirect comparisons, two "meta-analysis networks"[134,135] did not detect any differences with respect to the frequency of annual exacerbation between patients treated with RF and those that received ICs. On the other hand, regarding the cost-effectiveness of RF compared with IC, two studies suggest that the most effective treatment options of COPD do not contemplate the use of RF without including the administrations of ICs[134,140].

Recommendations

Research recommendation	In patients with stable phase COPD in maintenance therapy with bronchodilators, the additional therapy with roflumilast, as an alternative to additional therapy with inhaled corticoids, must only be used in a research context.

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6.4 Mucolytics in the maintenance treatment of COPD

COPD may appear with excessive or thick mucus hypersecretion. Mucolytics are drugs that reduce the viscosity of the sputum, so they may facilitate expectoration. Some mucolytics, such as N-acetylcysteine (NAC) also have an antioxidant effect that could be useful in patients with COPD[108]. Due to these properties, maintenance therapy with NAC or carbocysteine could be beneficial in the stable phase of patients with COPD, mainly due to its potential capacity to reduce associated symptoms and prevent exacerbations.

Today there are considerable differences between countries regarding the prescription of mucolytics for the maintenance treatment of COPD. Thus, for example, in countries such as the United Kingdom, mucolytics are not used very often because it is considered that they are not effective[108].

6.4.1 N-acetylcysteine

Quality of evidence

Five systematic reviews were identified on the effects of mucolytics in patients with COPD[141-145]. After assessing their quality, we decided to update the Cochrane systematic review[142], which assessed the effects of oral mucolytics on adults with stable phase COPD or chronic bronchitis (it excluded studies with asthmatic patients, with cystic fibrosis or with less than two months' monitoring). This review identified a total of 28 RCTs of which 14 assessed the effects of NAC. We updated the search of this review to January 2012, thus permitting the identification of additional RCTs on the effectiveness of NAC on patients with COPD[a][147,148]. Finally, we combined the results of the RCTs via a meta-analysis when we considered this appropriate and possible.

A total of 16 controlled and randomised clinical trials (RCT)[147-162] were identified that assess the effects of NAC compared with placebo in patients with COPD or chronic bronchitis. All the RCTs are parallel designs except for one148, which presents a crossed design. All the RCTs identified included non-hospitalised patients diagnosed with chronic bronchitis (10 RCTs) or stable phase COPD (6 RCTs) in maintenance treatment with oral NAC (400 to 1200 mg per day). The duration of the treatment and monitoring of the patients were, in general, short, and varied from 3 weeks to 3 years (averaging 6 months). The duration of the treatment and of the monitoring was only over 1 year in two studies147,154 (specifically, 3 years).

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[a] Furthermore, the updating of the Cochrane review permitted the identification of another RCT146, presented in poster form at a congress, which assessed the effects of NAC compared with placebo in 42 patients with COPD in GOLD stage 3 or 4 with bronchial hypersecretion and hospitalised due to exacerbation of this COPD. It was decided not to consider this study, as it did not permit assessing the effects of NAC as maintenance treatment in stable phase COPD.

The quality of the evidence of the maintenance treatment with NAC is summed up below, compared with placebo in patients with stable phase COPD, in agreement with the critical or important variables selected.

Exacerbations: Number of exacerbations per patient

According to our meta-analysis (13 RCTs, 2796 participants in all, average monitoring of six months), patients treated with NAC presented an average of 0.05 exacerbations less per patient month, the differences being statistically significant (difference of means=-0.05; 95% CI -0.06 to -0.04) and its magnitude being clinically relevant. However, the studies presented a high bias risk and high statistical heterogeneity was detected in the results, which reduces confidence in them.

Very low quality

The BRONCHUS study[154] (523 randomised patients), included in our meta-analysis, did not detect statistically significant differences between individuals treated with NAC and those who received placebo, with respect to annual exacerbation rate. However, according to a subgroup analysis with the 155 patients who were not being treated with inhaled corticoids (IC), the exacerbation rate was lower in those treated with NAC (0.96 exacerbations/patient-year; standard deviation (SD)=1.35) than in those who received placebo (1.29 exacerbations/patient-year; SD=1.46). These differences were statistically significant (risk quotient 0.79; 95% CI: 0.631 to 0.989); P=0.040). Therefore, this subgroup analysis suggests that NAC could reduce the risk of exacerbations in patients who are not receiving IC.

However, the results of a recent clinical trial[147], identified in the update of the Cochrane review, and not included in our meta-analysis (due to the lack of essential information to meta-analyse the data), do not permit confirmation of this fact. This study presented three arms (NAC without IC; Fluticasone; and Placebo), and considered 192 participants in the NAC versus placebo comparison (46% of whom presented COPD with moderate obstruction and 18% COPD with severe obstruction, according to the GOLD classification). The clinical trial, with three years' monitoring and a high bias risk due to a high magnitude of losses, did not detect statistically significant differences with respect to the number of exacerbations/patient-year between patients treated with NAC without IC and those who received placebo (rate ratio (RR) NAC vs. Placebo=1.35; 95% CI not described; p=0.054).

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[a] Clinical trials that assess the effects of the NAC identified by the Cochrane review[142].

Exacerbations: Proportion of patients without any exacerbation during the study

According to our meta-analysis (13 RCTs, 2206 participants in all, average monitoring of six months), on patients treated with NAC, an increase of 42% in the proportion of patients without any exacerbation during the study was observed. These differences were statistically significant and clinically relevant (RR=1.42; 95% CI: 1.29 to 1.56) as, assuming that 36% of the patients without mucolytics did not present any exacerbation during the study period, an RR of 1.42 would mean that NAC would have to be administered to 7 patients so that one of them would be free from exacerbations during a six-month average period (95% CI of the NNT: 6 to 10 patients).	Very low quality

Frequency of hospital admissions

According to one RCT154 (523 participants, 3 years' monitoring), no statistically significant differences were detected (value p not described) with respect to frequency of hospital admissions (OR 0.79; 95% CI: 0.52 to 1.18). This RCT presented a high bias risk due to a high magnitude of losses. Furthermore, it is not clear if the assignment sequence was adequately concealed. Another RCT[150] also assessed the effects of NAC compared with placebo regarding the frequency of hospital admission. However, its results have not been considered as the data presented errors.	Very low quality

Quality of life

Two RCTs147,154 (715 participants in all; three years' monitoring) assess the effects of NAC compared with placebo on health-related quality of life (HRQOL). The HRQOL was measured with three questionnaires: 1) St. George's Respiratory Questionnaire (STRQ), designed to quantify the impact of the respiratory airway disease on the state of health and well-being perceived by respiratory patients (scale from 1 to 100, the lower the score the higher the quality of life. 2) Euroqol-5D (EQ-5D): Generic measurement instrument of the HRQOL (scale from 0 to 1, the higher the score, the higher the quality of life. 3) Chronic Respiratory Disease Questionnaire (CRQ): HRQOL of patient with COPD (modified Likert scale, values from 1 to 7, the higher the score, the better the HRQOL). However, none of the RCTs detected statistically significant differences as regards to changes in the HRQOL.	Low quality

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[a] 12 of the RCTs come from the Cochrane SR[142] and one from the update [147].

Respiratory symptoms

According to one RCT147 (192 participants, 3 years' monitoring), no statistically significant differences were detected between individuals treated with NAC and those who received placebo, with respect to the intensity of the respiratory symptoms (cough and production of phlegm) measured with the "Quality of life for respiratory illness" questionnaire (QoLRIQ). This study presented a high bias risk due to a high magnitude of losses. The researchers of the study mentioned that the differences in score of the symptoms were not statistically significant, although these differences are not quantified. — Very low quality

Tolerance to exercise

According to one RCT[148] (24 participants, 3 months' monitoring), the average duration of exercise was 22 seconds longer in patients treated with NAC than in those who received placebo, the differences being statistically significant ($p<0.001$), although clinically not relevant. It was considered that this study has a high bias risk as it does not present information to be able to evaluate any of the domains (except for one) proposed by the Cochrane Collaboration tool.. — Very low quality

Mortality due to any cause

Our meta-analysis (4 RCTs, 1,005 participants in all; monitoring range from 3 weeks to 3 years; average of 6 months)[147,154,157,161] assess the effects of NAC compared with placebo on mortality due to any cause, but it did not detect statistically significant differences (OR=0.75; 95% CI: 0.34 to 1.65). — Very low quality

Adverse events

Our meta-analysis (8 RCTs, 2,068 participants in all; monitoring range from 3 weeks to 1 year; average of 6 months) did not detect statistically significant differences with regards to the frequency of patients with at least one adverse effect (OR=0.80; 95% CI: 0.63 to 1.02). Furthermore, there was high statistical heterogeneity in these results, which decreases confidence in them. — Very low quality

Based on the update of the Cochrane review, another two RCTs were identified that evaluated the adverse effects associated with NAC, but their results were not included in the meta-analysis[147,148]. Schermer 2009 only presented information on the withdrawals of patients associated with adverse events (4 patients in the NAC group and another 4 in the control group), not specifying their nature. In Stav 2009, the presence of adverse effects was not quantified, only mentioning that mild epigastric pains were referred to by a reduced number of patients in the NAC group.

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Economic assessment

The Grandjean[141] study based its analysis on the direct costs of treatment with NAC and the treatment of an acute exacerbation and the indirect costs of sick leaves. This study concludes that maintenance treatment with oral NAC in autumn and winter is cost-effective compared with placebo, as it reduces the frequency of exacerbations (which entails a reduction of hospital admissions and consumption of resources) as well as time off work, which implies a decrease of indirect costs. However, it must be underscored that this study considered patients with chronic bronchitis (cough and production of regular sputum), a population that would not be a representative reflection of the group of patients with COPD. Furthermore, the Grandjean study suggested that a reduction of 0.6 exacerbations per patient over a six-month period would represent the cut-off point to consider the treatment as cost effective. According to our meta-analysis, there was a reduction of 0.05 exacerbations per patient and month associated with the use of NAC, which, assuming a constant exacerbation frequency per patient and month, would be the equivalent to a reduction of 0.3 exacerbations per patient over a six-month period. This would suggest that maintenance treatment with NAC in patients with chronic bronchitis does not reach the cut-off point indicated by Grandjean. Due to all these reasons, the results of this study do not clearly show that maintenance treatment with NAC is cost-effective in the group of patients with stable phase COPD.

The BRONCUS study[154] set out as a secondary objective the determination of the cost- benefit of NAC compared with placebo. In the article, which publishes the results referring to the main objectives of the study, and to another of the secondary objectives, quality of life, it mentions that the cost-benefit study would be published in another article. However, as at January 2012 we have no record of this article having been published.

Patients' values and preferences

No study has been identified that considers the values and preferences of patients and professionals on maintenance treatment with NAC compared with placebo. However, the fact that no statistically significant differences have been detected in the majority of critical variables for the patient, such as quality of life or frequency of hospital admissions, in the studies identified, this suggests that the patient's preferences may not necessarily support this treatment. On the other hand, it should be taken into account that maintenance treatment with NAC usually requires at least one daily dose, a fact that could go against patient's preferences.

Balance between benefits, risks and disadvantages associated with the intervention

Based on all these factors, it can be concluded that the available evidence (of a very low overall quality and the majority referring to the exacerbator phenotype with chronic bronchitis) points to the fact that maintenance treatment with NAC could prevent exacerbations in patients with stable phase COPD and do not present associated relevant risks. However, it is impossible to state that there is a clear net benefit associated with this treatment, as it has not been shown that NAC has any influence on other critical or relevant variables (frequency of hospital admissions, quality of life, respiratory symptoms, tolerance to exercise or mortality) or that it is cost effective in the group of patients with COPD. Therefore, it is impossible to state that there is a clear net therapeutic benefit associated with NAC as maintenance treatment in the stable phase of patients with COPD.

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Use of N-Acetylcysteine according to phenotype

No study has been identified that explicitly assesses the effects of NAC compared with placebo in patients with COPD according to the phenotypes considered in this guideline. However, the majority of patients considered, presented chronic bronchitis and more than one exacerbation each year, which suggests that the results could be extrapolated to the exacerbator phenotype with chronic bronchitis.

Summary of evidence

Very low overall quality of evidence	The evidence identified, of a very low overall quality, the majority of which refers to patients with exacerbator phenotype with chronic bronchitis, suggests that, when compared with placebo, patients treated with NAC present fewer exacerbations, although it has been impossible to demonstrate that NAC has any influence on the other critical or important result variables (frequency of hospital admissions, quality of life, respiratory symptoms, tolerance to exercise or mortality). No relevant risks associated with treatment with NAC were detected. The available evidence does not clearly show that maintenance treatment with NAC is cost-effective in the group of patients with stable phase COPD and it has not taken into account the values and preferences of patients and professionals.

Recommendation

Weak	The generalised use of N-Acetylcysteine as maintenance treatment* is not suggested in patients with stable phase COPD.

* According to the subgroup analysis of one of the RCTs identified (very low evidence quality), NAC could reduce the risk of exacerbations in patients who are not receiving IC. However, the results of another recent clinical trial have not permitted the confirmation of this fact. Therefore, the existing evidence is insufficient to be able to generate a recommendation on the effects of NAC in patients with COPD who are not being treated with IC.

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6.4.2 Carbocysteine

Quality of evidence

One systematic review[142] was identified on the effects of oral mucolytics in adults with stable phase COPD or chronic bronchitis (it excluded studies with asthmatic patients or cystic fibrosis and also those who had been monitored for less than two months). The review identified a total of 28 RCTs, three which assessed the effects of carbocysteine. Another clinical trial identified by this review163 assessed the effects of carbocysteine combined with sobrerol. We updated the review search up to January 2012, but we did not find any RCT or additional systematic review. Finally, we combined results of the RCTs identified by the relative meta-analysis when we considered this appropriate and possible.

Three parallel RCTs were identified on the effects of oral carbocysteine compared with placebo in patients with COPD[164,165] or chronic bronchitis[166]. All the RCTs included patients in maintenance treatment with oral carbocysteine (1500 to 2700 mg per day). The duration of the treatment and monitoring of the studies varied from six months[164,166] to one year[165]. The studies were performed in China (708 patients)165, Italy (441 patients)[164] and in the United Kingdom (109 patients)[166].

The quality of evidence of the maintenance treatment with carbocysteine is summed up below, compared with placebo in patients with stable phase COPD, in agreement with the critical or important variables selected.

Exacerbation: Number of exacerbations per patient and month

According to our meta-analysis (2 RCTs[b], 1,148 participants in all, average monitoring of 8 months), patients treated with carbocysteine presented an average of 0.03 exacerbations less per patient and month, the differences being statistically significant (difference of means=-0.03; 95% CI -0.02 to -0.04) and its magnitude being clinically relevant. The Zheng study did not detect any modification, due to the presence of concomitant treatment with IC, in the effect of carbocysteine, which could be due to the fact that the doses of IC used were very low.	High quality

Exacerbations: Proportion of patients without any exacerbation during the study

According to our meta-analysis (3 RCTs, 1,168 participants in all, average monitoring of 8 months), on patients treated with carbocysteine, an increase of 16% in the proportion of patients without any exacerbation during the study was observed. These differences were statistically significant (RR=1.16; 95% CI: 1.03 to 1.30). Assuming that 45% of the patients who receive placebo do not present any exacerbation during the study, an RR of 1.16 would mean that carbocysteine would have to be administered to 14 patients for an average of 8 months in order for one additional patient to be free from exacerbations during this period (95% CI of the NNT: 8 to 69 patients).	Low quality

[a] This study was not considered because it did not permit the determination of the effects of carbocysteine.

[b] Allegra 1996 and Zheng 2008: clinical trials that assess the effects of the carbocysteine identified by the Cochrane review[142]

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Frequency of hospital admissions

None of the studies identified considered this variable.

Quality of life

In the RCT performed in China[165] (707 participants; 1 year's monitoring) the effects of carbocysteine compared with placebo on the health-related quality of life (HRQOL) are assessed, measured with STRQ. This questionnaire is designed to quantify the impact of the respiratory airway disease on the state of health and well-being perceived by patients (scale from 1 to 100, the lower the score the higher the quality of life). According to this RCT, the STRQ score in patients treated with carbocysteine was, on average, 5.27 units less (95% CI: -8.54 to -2.00) than the average score presented by patients who received placebo, which is considered clinically relevant.	High quality

Respiratory symptoms

According to the Zheng study (707 participants; 1 year's monitoring), the STRQ score referring to the dimension on respiratory symptoms in patients treated with carbocysteine was, on average, 6.69 units less (95% CI: -10.17 to -3.21) than the average score of patients who received placebo, these differences being statistically significant and clinically relevant.	High quality

Tolerance to exercise

According to the Zheng study (707 participants; 1 year's monitoring), there were no statistically significant differences with regards to the STRQ score referring to the dimension on physical activity among patients treated with carbocysteine and those who received placebo (Mean difference= -2.10 units (95% CI: -5.60 to 1.40).	Moderate quality

Mortality due to any cause

Our meta-analysis (2 RCTs, 816 participants; 6 and 12 months' monitoring)[165,166] assessed the effects of carbocysteine compared with placebo on mortality due to any cause, but it did not detect statistically significant differences (OR=0.75; 95% CI: 0.06 to 16.71)[a].	Very low quality

Adverse events

Our meta-analysis (3 RCTs, 1.257 participants; monitoring range from 6 to 12 months) did not detect statistically significant differences with regards to the frequency of patients with at least one adverse effect (OR=0.87; 95% CI: 0.64 to 1.19). There is statistical heterogeneity in these results, which decreases confidence in them.	Very low quality

[a] The Zheng study (707 participants) did not provide data for the meta-analysis as, although this variable was assessed, it did not present any event (death) in any of the arms.

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Economic assessment

No economic assessment studies were identified for maintenance treatment with carbocysteine in patients with stable phase COPD.

Patients' values and preferences

No studies were identified that consider the patient's values and preferences.

Balance between benefits, risks and disadvantages associated with the intervention

Based on the factors presented above, it can be concluded that available evidence (with low overall quality) suggests that maintenance treatment with carbocysteine prevents exacerbations in patients with stable phase COPD and/or chronic bronchitis, and that it does not present any associated relevant risks. Furthermore, it could improve the quality of life and the respiratory symptoms. Although no influence on other critical or important variables (frequency of hospital admissions, tolerance to exercise or mortality) has been demonstrated and no studies that assess its cost effectiveness or the patients' and professionals' values and preferences have been identified, we could conclude that there is a clear benefit associated with the use of carbocysteine for maintenance treatment of patients with stable phase COPD and/or chronic bronchitis.

Use of Carbocysteine according to phenotype

No study has been identified that explicitly assesses the effects of carbocysteine compared with placebo in patients with COPD according to the phenotypes considered in this guideline. However, the majority of patients considered presented chronic bronchitis and more than one exacerbation each year, which suggests that the results could be extrapolated to the exacerbator phenotype with chronic bronchitis.

Summary of evidence

Low overall quality of evidence	The evidence identified, with low overall quality and the majority referring to patients with exacerbator phenotype with chronic bronchitis, suggests that, when compared with placebo, maintenance treatment with carbocysteine prevents exacerbations in patients with stable phase COPD and does not present associated relevant risks. Furthermore, it could improve the quality of life and respiratory symptoms. However, no influence on other critical or important variables (frequency of hospital admissions, tolerance to exercise or mortality) has been demonstrated and no studies that assess its cost effectiveness or the patients' and professionals' values and preferences have been identified. Furthermore, the duration of the studies was relatively short (6 months to 1 year).

Recommendation

Weak	The use of carbocysteine as maintenance treatment of COPD is suggested in patients with stable phase COPD and exacerbated phenotype with chronic bronchitis.

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7. Treatment of exacerbation in patients with COPD

Questions to be answered

- Must systemic corticoids be used in moderate exacerbations of COPD?
- Must systemic corticoids be used in mild exacerbations of COPD?
- Is pulmonary rehabilitation beneficial in the context of an exacerbation?

7.1 Definition and impact of the exacerbation

Exacerbation is defined as an acute episode of clinical instability that occurs during the natural course of the disease and is characterised by a sustained worsening of the respiratory symptoms that goes beyond its daily variations. The main symptoms referred to are worsening of dyspnoea, coughing, increase in volume and/or changes in the colour of the sputum.

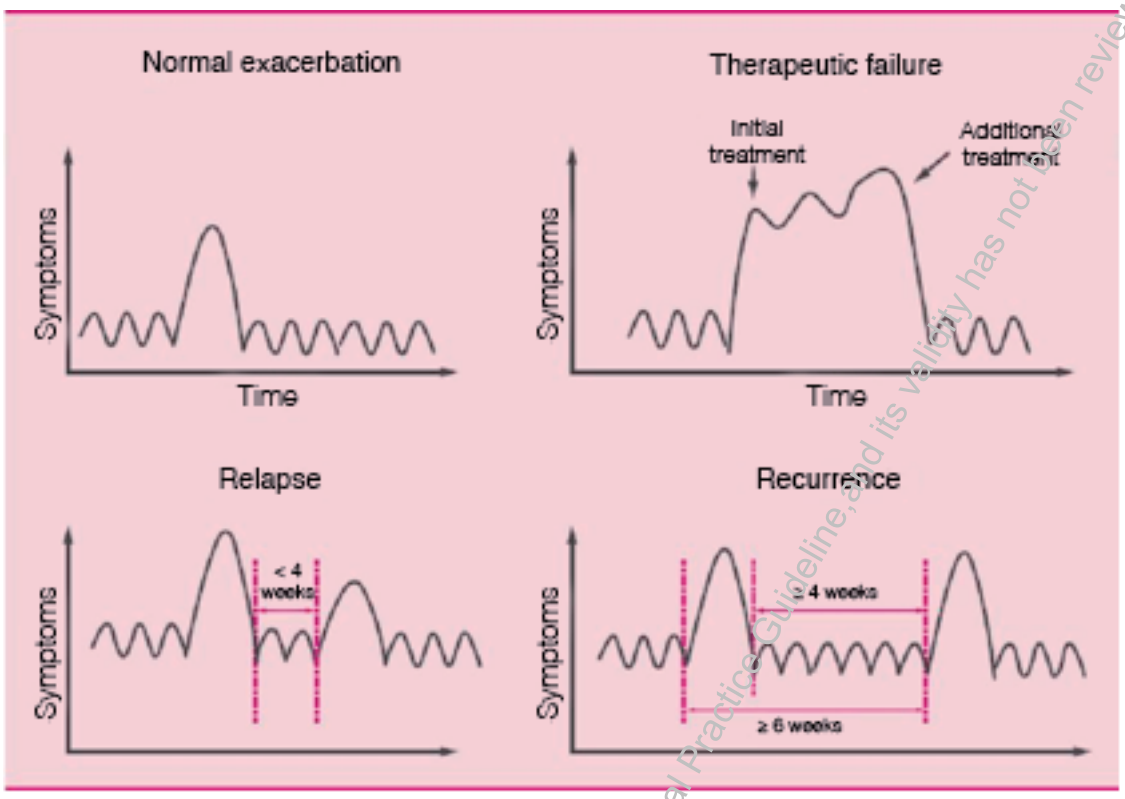
Normally, these symptomatic changes are accompanied by changes in medication, which is why, in many clinical trials and epidemiological studies the use of drugs (antibiotics and/or systemic corticoids) or the use of health resources (visits to A+E, hospital admissions, etc) are evaluated as indirect markers of exacerbations. However by using daily records of symptoms, it has been observed that more than half of the exacerbations are not reported to the doctor (non-documented exacerbations)[167,168].

On average, patients with COPD experience 1-4 exacerbations/year[169]). However, the distribution is very variable. Whilst some people do not suffer these episodes, others have them repeatedly (exacerbator phenotype)[35]. Many of these episodes are observed grouped together in bunches[170], which poses the doubt of whether they are really new exacerbations or if they are incomplete resolutions of the previous episode. To distinguish these situations, GesEPOC establishes the following definitions (figure 7.1):

- Therapeutic failure: This is defined as a worsening of symptoms that occurs during the actual exacerbation and that requires additional treatment[34].
    - o The average recovery after suffering an exacerbation is approximately 2 weeks. However, some patients do not fully recover until 4-6 weeks[171,172].
- Relapse: When a new worsening of symptoms occurs between the end of the treatment of the exacerbation and the following four weeks.
- Recurrence: This occurs when the symptoms re-appear within less than one year following the previous exacerbation, after a period of relatively good health. To this end, it is established that at least 4 weeks must have elapsed after completing the previous exacerbation treatment or else 6 weeks following the onset of symptoms[34].
    - o Recurrences will be considered as early ones if they appear between 4 and 8 weeks following the previous episode, and late ones if they appear after this period of time.

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Figure 7.1. Normal exacerbation, therapeutic failure, relapse and recurrence according to GesEPOC



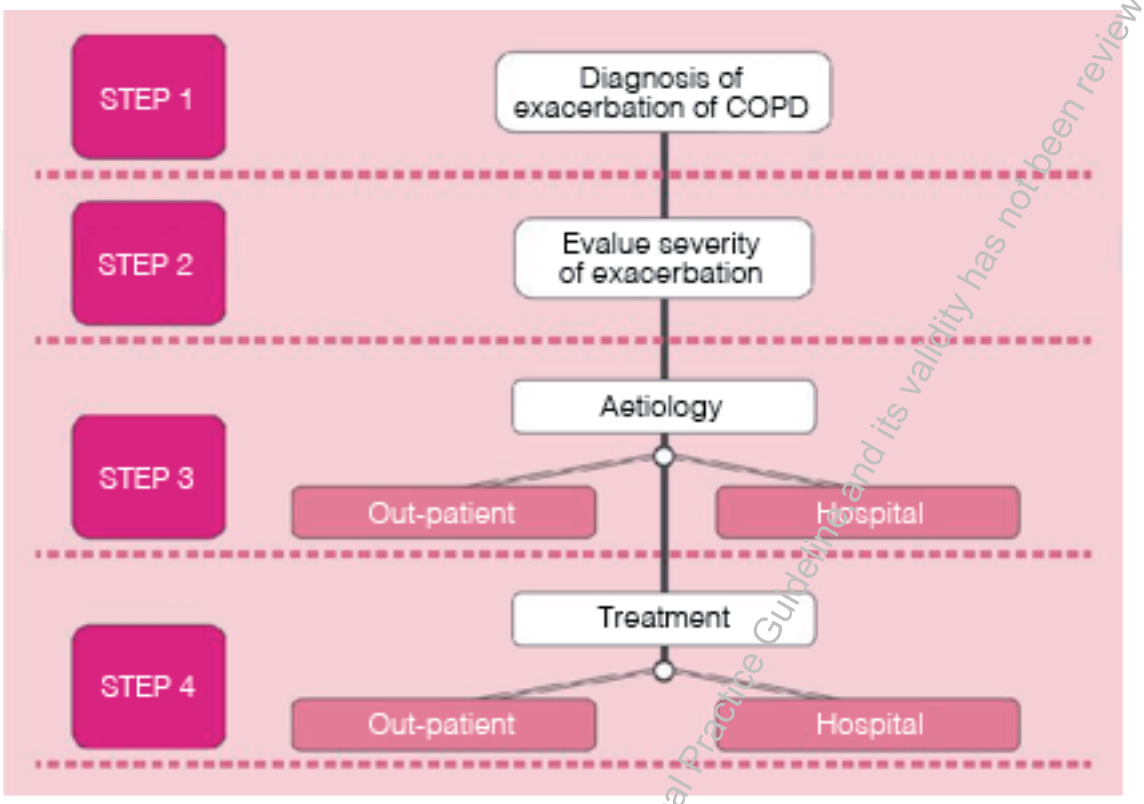
The intensity, duration and frequency of the exacerbations vary enormously from some patients to others and even in the same patient, so it is difficult to specify the consequences. However, different studies suggest that the exacerbations produce an impairment of health-related quality of life, they generate high costs, affect the multi-dimensional progression of the disease and increase the risk of death[25,103,168,169,173,174].

Figure 7.2 establishes which are the 3 diagnostic steps to be followed in order to adequately characterise an exacerbation. The first thing to do is to confirm that it is an exacerbation of the COPD, ruling out other processes with similar symptoms.

The second thing to do is to evaluate the severity of the exacerbation and finally try to establish its cause. For this final point, the diagnostic tests to be carried out may differ depending on whether the exacerbation takes place inside or outside the hospital.

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Figure 7.2. Diagnostic steps to be followed to characterise an exacerbation or flare-up



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7.2 Severity of the exacerbation

After establishing the diagnosis of exacerbation of the COPD, it is very important to describe the severity of the episode. Over the last few years, the main clinical practice guidelines (CPG) have used an exacerbation severity classification based on the consumption of drugs or on the use of resources (e.g. severe exacerbation if the patient had an exacerbation that required hospital admission, or moderate exacerbation if the patient received treatment with oral corticoids and/or antibiotics). However, this classification does not follow pathopsychological criteria, it is not linked to decision-making and it may be influenced by socio-economic criteria or criteria related to accessibility to the system. GesEPOC proposes a new classification that has been agreed upon by an extensive group of experts (table 7.2). The severe or very severe exacerbation criteria identify a risk of death, whilst the criteria that are used to identify moderate exacerbation are related to the risk of therapeutic failure.

Table 7.2. Criteria to establish the severity of exacerbation of COPD

Very severe exacerbation (or life threat)	At least one of the following criteria must be fulfilled: - Respiratory arrest - Reduction of consciousness level - Haemodynamic instability - Severe respiratory acidosis (pH<7.30)
Severe exacerbation	At least 1 of the following criteria must be fulfilled, and none of the life threatening criteria: - Dyspnoea 3-4 on the mMRC scale - New onset cyanosis - Use of accessory musculature - New onset peripheral oedemas - Sp02<90% or Pa02<60 mmHg - PaCO2> 45 mmHg (patient without previous hypercapnia) - Moderate respiratory acidosis (pH: 7.30 — 7.35) - Severe significant comorbidity - Complications (severe arrhythmias, heart failure, etc)
Moderate exacerbation	At least 1 of the following criteria must be fulfilled, and none of the previous ones: - Basal FEV1 < 50% - Non-severe heart comorbidity - History of 2 or more exacerbations during the last year
Mild exacerbation	No previous criterion must be fulfilled.

mMRC: Modified dyspnoea scale of the Medical Research Council; §Recent ischaemic cardiopathy, chronic renal insufficiency, moderate-severe hepatopathy, etc.

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7.3 Systemic corticoids in moderate or mild exacerbations of COPD

Exacerbations may require admission into hospital, where treatment with systemic corticoids (by oral or parenteral way) is frequent. According to a Cochrane systematic review[175], the use of systemic corticoids to treat exacerbations of COPD, such as prednisone, helps improve dyspnoea, improves the pulmonary function, it reduces the hospital stay and the need to look for additional medical care. However, the majority of the studies included in this review considered the treatment of exacerbations that were severe enough to require hospital admission. Therefore, the effectiveness and the benefit-risk balance of the treatment with systemic corticoids of mild or moderate exacerbations of COPD is still not well known.

7.3.1 Systemic corticoids in moderate exacerbation of COPD

Quality of evidence

Six systematic reviews on the effectiveness of systemic corticosteroids were identified for the treatment of acute exacerbations in patients with COPD[137,175- 179]. Following their evaluation, we decided to update the Cochrane systematic review[75], whose bibliographic search was closed in August 2008. This review included a total of 11 clinical trials, of which only two[180,181] considered the treatment of moderate exacerbations. We updated the search of this review to March 2012 but no additional clinical trial was identified. Finally, we combined results of the identified RCTs by a meta-analysis when this was considered appropriate and possible[180,181].

According to the criteria proposed in this guideline to establish the severity of the exacerbations of COPD (table 7.2), the exacerbations considered by these two studies could be defined as moderate. In the study by Aaron[180], patients were recruited from those coming to the A+E service due to an exacerbation of COPD without requiring admission (Average FEV1 of patients at start of the study: 50.29±12.6 % of the forecast). In Thompson's study181, patients were recruited within the Primary Care context (average FEV1 of patients at start of study: 43.±19.7 % of the forecast).

The two randomised clinical trials identified are parallel designs and assess the effects of oral prednisone compared with placebo: in Aaron's study, 40 mg of prednisone/day was administered for 10 days, and in Thompson's study, 60 mg/day the first three days, 40 mg/day for the following 3 days, and 20 mg/ during the last 3 days (9 days' treatment in all). Both studies admitted concomitant medication to the oral corticoids or to the placebo, for example β2 agonists, ipratropium bromide or corticoids, all of them inhaled, or antibiotics. Patients were monitored for 30 days in Aaron's study and 14 days in Thompson's study.

The quality of evidence of the treatment with systemic corticoids of moderate exacerbations in patients with COPD is summed up below in agreement with the critical variables selected.

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Therapeutic failure

According to our meta-analysis (2 RCTs, 167 participants in all, monitoring of 30 and 15 days), the administration of oral prednisone reduced the risk of suffering therapeutic failure in 49% (RR=0.51; 95% CI: 0.32 to 0.80). However, high statistical heterogeneity was detected in these results, which decreases confidence in them. "Therapeutic failure" was defined as "non-scheduled visit to a doctor's surgery or to emergency services due to deterioration of symptoms within the 30 days following the randomisation"180 or as "the lack of improvement of dyspnoea that requires additional oral prednisone or hospital admission due to worsening of the pulmonary function within the first 14 days following the onset of the study"[181]. Moderate quality

Recurrence

None of the identified studies evaluated recurrence, understood as the re-appearance of symptoms within less than one year following the previous exacerbation, after a period of relatively good health.

Need for hospital admission

Our meta-analysis (2 RCTs, 170 participants in total, monitoring of 30 and 15 days), did not detect any statistically significant differences with respect to the incidence of hospital admissions (RR=0.47; 95% CI: 0.21 to 1.03). No statistically significant heterogeneity was detected. Moderate quality

Mortality attributable to exacerbation of COPD

Our meta-analysis (2 RCTs, 174 participants in total, monitoring of 30 and 15 days), did not detect any statistically significant differences with respect to the mortality attributable to the exacerbation of COPD (RR=1.00; 95% CI: 0.06 to 15.73). It was not possible to evaluate statistical heterogeneity. Low quality

Respiratory symptoms (dyspnoea)

According to Aaron's study (147 participants, 10 days' monitoring), the improvement in the score of the Transitional dyspnoea index* on the 10th day of treatment with respect to the score on the first day was higher in patients treated with oral corticoids, the differences being statistically significant and clinically relevant (DM=1.88; 95% CI: 0.23 to 3.53). In Thompson's study (27 patients, 10 days' monitoring) dyspnoea** was measured over the 10 days of treatment but statistically significant differences were not found regarding changes in dyspnoea. Moderate quality

* Range of values from -9 to 9; a positive score indicates improvement and a change of a unit is considered clinically significant.

** Dyspnoea measured via a visual analogical scale where the patient scored the change in dyspnoea from 0 to 100 (higher score, less dyspnoea).

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Quality of life

Aaron's study (147 participants in total, 10 days' monitoring), did not detect any statistically significant differences with respect to the changes in score of a specific quality of life questionnaire for chronic respiratory disease* (DM=0.38; 95% CI: -0.09 to 0.85). Moderate quality

* Chronic Respiratory Questionnaire (CRQ): Validated questionnaire, range 1 to 7, the higher the score the better the quality of life. Changes of at least 0.5 units are considered clinically relevant.

Adverse events

According to Aaron's study (140 participants in 10 days monitoring), patients treated with oral prednisone were more likely to present an increase in appetite (RR=2.13; 95% CI: 1.27 to 3.57), increase in weight (RR=9.00; 95% CI: 1.17 to 69.16), and insomnia (RR=2.31; 95% CI: 1.36 to 3.94). These differences were statistically significant. However, no statistically significant differences were detected with respect to the risk of hypo-leukaemia, depression, anxiety or dyspepsia. Thompson's study did not present information about adverse events associated with the administration of corticoids. Moderate quality

In all, the adverse effects detected, associated with the use of corticoids are not severe and are not very likely to persist when the treatment ends.

Economic assessment

No economic assessment has been identified of treatment with systemic corticoids of moderate exacerbations of patients with COPD.

Patients' values and preferences

No study has been identified that considers the patients' values and preferences with respect to treatment of moderate exacerbation of COPD with systemic corticoids. However, even after having taken into account the adverse effects associated with corticoids, the fact that these can be administered orally outside the hospital, suggests that as a treatment it could be well accepted by patients and professionals.

Balance between benefits, risks and disadvantages associated with the intervention

The evidence assessed, of moderate overall quality and based only on two clinical trials, suggests that the oral administration of prednisone during exacerbations of moderate intensity of patients with COPD may reduce the risk of therapeutic failure and improves dyspnoea. No influence on other critical or important variables (recurrence, frequency of hospital admissions, quality of life or mortality attributable to the exacerbation) has been proven, or that it is cost-effective in this type of patient. Prednisone was associated with the appearance of adverse effects (increase in appetite, increase in weight and insomnia), none of which were serious. However, even after having taken into account the adverse effects associated with corticoids, the fact that these can be orally administered outside the hospital suggests that, as a treatment, it could be well accepted by patients and professionals.

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Considering all of these factors, there may be a clear benefit associated with the oral administration of corticoids during moderate exacerbations of non-hospitalised patients with COPD. However, before administering this treatment, the benefit-risk balance must be considered for each patient, in agreement with their susceptibility to the adverse effects associated with corticoids.

Summary of evidence

Moderate overall quality of evidence	The evidence assessed, of moderate overall quality, was based only on two clinical trials: in one of them, 40 mg of prednisone/day was administered orally for 10 days, and in the other, 60 mg/day the first three days, 40 mg/day for the following 3 days, and 20 mg/ during the last 3 days. This evidence suggests that the oral administration of prednisone during exacerbations of moderate intensity of patients with COPD reduces the risk of therapeutic failure and improves dyspnoea. However, no influence on other critical or important variables (recurrence, frequency of hospital admissions, quality of life or mortality attributable to the exacerbation) has been proven, or that it is cost-effective in this type of patient. On the other hand, prednisone was associated with the appearance of adverse effects (increase in appetite, increase in weight and insomnia), none of which were serious. No economic assessment of treatment with systemic corticoids of moderate exacerbation of patients with COPD has been identified, or any study that considers the patients' and professionals' values and preferences; however, the fact that corticoids can be orally administered outside the hospital suggests that, as a treatment, it could be well-accepted by patients and professionals.

Recommendation

Weak	The oral administration of prednisone for 9 or 10 days is suggested in non-hospitalised patients with COPD to treat moderate exacerbations.

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7.3.2 Systemic corticoids in mild exacerbations of COPD

Quality of evidence

No clinical trial has been identified that assesses the effectiveness and safety of systemic corticoids for the treatment of mild exacerbations of patients with COPD.

Economic assessment

No economic assessment has been identified of treatment with systemic corticoids of mild exacerbations of COPD.

Patients' values and preferences

No study has been identified that consider the patients' and professionals' values and preferences. However, the fact that these can be orally administered outside the hospital suggests that, as a treatment, it could be well-accepted by patients and professionals.

Balance between benefits, risks and disadvantages associated with the intervention

The consideration of the available evidence is insufficient to conclude that there is or is not a clear benefit associated with the use of systemic corticoids during mild exacerbations of COPD.

Summary of evidence

No study has been identified that assesses the effects of systemic corticoids in the treatment of mild exacerbations of patients with COPD. No economic assessment on the topic or study has been identified, either, that considers the patients' and professionals' values and preferences.

Recommendations

Research recommendation	The use of systemic corticoids is suggested in non-hospitalised patients with COPD to treat mild exacerbations only in a research context.

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7.4 Pulmonary rehabilitation in the context of an exacerbation

Pulmonary rehabilitation is important for the comprehensive treatment of patients with COPD; its use is aimed at improving their exercise capacity, their physical condition and their quality of life by reducing dyspnoea and fatigue[5,182-184].

Pulmonary rehabilitation is generally comprised of least physical training and psychoeducation. It can also be accompanied by other interventions such as strategies for smoking cessation, training respiratory muscles, training to help eliminate bronchial secretions, managing medication, nutritional advice, motivation strategies and psychological support[5,182,184,185]. Emphasis is usually placed, in a pulmonary rehabilitation programme, on the importance of it being[184]:

- Multidisciplinary: It must be a comprehensive programme, adapted to the needs of each patient.
- Individual: The needs of each individual must be assessed together to establish personalised objectives
- Attention to physical and social function: Attention must be paid to emotional and social problems, as well as to the physical impairment.

The quality of evidence with respect to pulmonary rehabilitation within the context of an exacerbation of patients with COPD is summarized below, in agreement with the critical or important variables selected.

Hospital admissions

The Puhan Cochrane review[185] includes five RCTs with a total of 250 patients, comparing the effect of the RR with the group of normal care, where the RR must at least include training in physical exercise and it must be offered immediately to patients after finishing the treatment of the exacerbation or until three weeks after this.

Moderate quality

They found that a significant reduction in the probabilities of readmission occurred in the pulmonary rehabilitation group (OR = 0.22; IC 95%: 0.08 to 0.58; I2=51%). In order to reduce the heterogeneity index of the studies, the analysis was repeated using the pre-protocol data, finding that the results did not change significantly (OR 0.19; 95% CI 0.09 to 0.39; I2=0%).

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Quality of life

As to the quality of life, in the Cochrane review[185], as in the variable of the number of hospital admissions, five RCTs were included, where this variable was measured by specific respiratory disease questionnaires, more specifically CRQ and SGRQ. The total number of patients from the studies included was 259 for the CRQ and 128 for the SGRQ. When the pulmonary rehabilitation was compared with the control group, the scores in the CRQ group were better in the pulmonary rehabilitation group than in the control group (DM 0.93; 95% CI -0.13 to 1.99), as in the group of patients measured with SGRQ (DM -9.88; 95% CI -14.40 to -5.37).

Moderate quality

In the Seymour et al. RCT186, 60 patients were assessed, who were divided into two groups, pulmonary rehabilitation (N=30), compared with normal care (N=30). They measured the quality of life using the SGRQ questionnaire and found that after three months' treatment, the group that had received pulmonary rehabilitation presented a significant improvement in the quality of life in the global subscale (p=0.02), in activity (p=0.03) and in emotional function (p=0.05).

Murphy et al.[187], with one RCT assess quality of life with the SGRQ and the EuroQol-5D (EQ-5D), in a group of patients who received pulmonary rehabilitation (N=13) compared with another group of patients on the waiting list, who received normal care (N=13). The results that obtained after six weeks' treatment, both with the EQ-5D and with the SGRQ, are that with respect to their basal state, the pulmonary rehabilitation group obtain a significant improvement in the total scale of both questionnaires (p<0.05) with compared with the control group that does not obtain any significant improvement.

In another RCT, Man et al.[188] measured quality of life with SGRQ, CRQ and SF-36, a generic quality of life instrument, on a total of 42 patients, 21 in the pulmonary rehabilitation group and 21 in control (normal care). With respect to the scores obtained with the SGRQ, they found that after three months' treatment, the pulmonary rehabilitation group presented higher scores on the impact subscale (p=0.001) and on the total subscale (p=0.002). In the CRQ scores, the pulmonary rehabilitation group presented better scores on the disease control subscale (p<0,001) and on the emotional function subscale (p=0.008). Finally, with respect to SF-36, the pulmonary rehabilitation group presented higher scores both on the physical scale (p=0.057) and on the mental scale (p=0.02).

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In the Ghanem et al. RCT189 they compare a group of patients who have received pulmonary rehabilitation (N=25) with a group of patients who received normal care (N=14); quality of life was measured by the CRQ and SF-36, at the start of the study and after two months' treatment with pulmonary rehabilitation or with normal care. They found that, after two months' treatment, there was a significant improvement in the total quality of life score in the pulmonary rehabilitation group of both questionnaires, with respect to the basal state ($p<0.001$); this was not the case in the normal care group. In some of the subscales, they also found differences in the pulmonary rehabilitation group with respect to the basal state, both in total physical functioning ($p<0.001$), and in vitality ($p<0.05$) and in role functioning ($p<0.001$).

When they compare one group with the other after two months' treatment, they find that the pulmonary rehabilitation group has better results than the normal care group, both in physical functioning and in total mental functioning ($p<0.05$).

Dyspnoea

In the Cochrane review[185], dyspnoea was measured by the CRQ, and as in all the other domains, the pulmonary rehabilitation group presents better results than in the normal are group (DM 0.97; 95% CI 0.35 to 1.58). Moderate quality

Along the same line, when Seymour et al.[186] measure dyspnoea with the SGRQ, they find that the PR group, compared with the normal care group, has a better score on this subscale ($p=0.03$).

The same occurs in the study by Man et al.[188] where the score in dyspnoea is also better in the pulmonary rehabilitation group than in the normal care group (5.5; 95% CI 2.0 to 9.0; $p=0.003$).

In the study by Ghanem et al.[189] no intra-group comparison is made for this variable, but when they compare the pulmonary rehabilitation group with the normal care group two months after starting treatment, they find that the former has better results than the latter ($p<0.01$).

Fatigue

As in dyspnoea, in the Cochrane review[185], fatigue was measured by the CRQ, and the pulmonary rehabilitation group also obtained better results than the normal care group (DM 0.81; 95% CI 0.16 to 1.45). Moderate quality

Likewise, Man et al.[188] found that score in fatigue was better in the pulmonary rehabilitation group than in the normal care group (5.3; 1.9 to 8.8; $p=0.004$).

As in dyspnoea, in the study by Ghanem et al.[189] no intra-group comparison is made for this variable, but when they compare both groups after two months' treatment, they find that the pulmonary rehabilitation group has better results than the normal care group ($p<0.01$).

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Tolerance to exercise

With respect to tolerance to exercise, the studies presented by the Cochrane[185] review measure this variable using the 6-minute walk test and the shuttle walk test. With respect to the former, the distance covered by the pulmonary rehabilitation group is significantly greater (≥ 35m) than in the normal care group (DM 77.70; 95% CI 12.21 to 143.20). In the Shuttle walk test, it is also the pulmonary rehabilitation group that obtains better results than the control group (DM 64.35; 95% CI 41.28 to 87.43). Moderate quality

In the Seymour et study al.[186], they found that the normal care group did not improve in the Shuttle walk test, compared with the pulmonary rehabilitation, which did significantly improve (p=0.02).

Murphy et al.[187] assess tolerance to exercise in the group of patients who received pulmonary rehabilitation compared with a group of patients on the waiting list who received normal care. The results they obtained are that with respect to the basal data, the pulmonary rehabilitation group obtained a significant improvement (p<0.001) in the Shuttle walk test and in the 3-minute walk test compared with the control group, which did not obtain any significant improvement.

On their part, Man et al.[188] found that the difference in metres covered between the RR group and the normal care group was 60 m in favour of the first group (p=0.0002).

In the study by Clini et al.[190], a comparison is made in hospitalised patients (N=1826) who are divided into 5 groups depending on the degree of severity of dyspnoea (1-5) in agreement with the Medical Research Council (MRC). They find that in the 6-minute walk test, all the groups, except for the group with mildest dyspnoea, present a significant improvement (+54m) after having followed a RR programme (p<0.001).

In the study by Ghanem et al.[189], they also find that the pulmonary rehabilitation group presents a significant improvement (+58m) in the 6-minute walk test compared with the normal care group (p<0.001).

Incidence of exacerbations

Murphy et al.[187] find that after three months' monitoring, three patients from the control group (N=13) presented exacerbations again compared with none from the pulmonary rehabilitation group (N=13), although this difference is not significant (p=0.06); and after six months, five patients from the control group and two from the pulmonary rehabilitation group (N=13 in each group) presented exacerbations, but without significant difference (p=0.1). Moderate quality

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Summary of evidence

Moderate overall quality of evidence	Pulmonary rehabilitation in patients with COPD after they finish the treatment of the exacerbation or until three weeks after the treatment, including at least training in physical exercise, may reduce the number of re-admissions in patients with COPD who have suffered exacerbations[185,186,188] compared with patients who have followed the normal treatment.
	Pulmonary rehabilitation improves the quality of life (measured by the *Chronic Respiratory Questionnaire* (CRQ) and the *St George's Respiratory Questionnaire* (SGRQ)) of patients with COPD who have suffered exacerbations, compared with the initial quality of life[188], as well as compared with the group of patients who have followed normal treatment[185-189].
	Dyspnoea and fatigue in patients with COPD who have suffered exacerbations improve in the pulmonary rehabilitation group compared with the normal care group[185,186,188], as well as when compared with the initial dyspnoea[187].
	In patients with COPD who have suffered exacerbations, tolerance to exercise, measured mainly with the 6-minute walk test and the *Shuttle walk test*, increases after having followed a pulmonary rehabilitation programme compared with patients who have followed the normal care[185,186,188-190].

Recommendations

Strong	In patients with COPD who have suffered an exacerbation, it is recommended start pulmonary rehabilitation immediately after finishing the treatment of exacerbation or during the following three weeks.

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8. Treatment of tobacco dependence in smoking patients, diagnosed with CPOD

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Tobacco dependence presents certain characteristics, which may lead it to be considered as a chronic disease. The majority of smokers present this behaviour over several years and there are very few that manage to permanently stop smoking at the first attempt[191].

In the case of COPD, where it is one of the most important risk factors, the elimination of this habit is considered to be the most efficient measure both for prevention and for the reduction of mortality caused by this disease[5,192]. In Spain, the prevalence of COPD in adults is 9.1%. This prevalence is 15% in smokers, 12.8% in ex-smokers and 4.1% in non-smokers[15].

In this regard, the Global Strategy for the Diagnosis, Management and Prevention of Chronic Obstructive Pulmonary Disease (GOLD), recommends quitting smoking as the most efficient and cost-effective measure in the treatment of people with COPD, to stop the progression of the disease[3]. There are many studies that support this measure as essential in the treatment of patients with COPD; in a systematic review, Godtfredsen et al.[193] show that smoking cessation delays the loss of pulmonary function and improves survival in patients with COPD, even in those who present severe COPD. Hylkema et al.[194] also show the improvement in the response to treatment with inhaled corticoids, the reduction of the risk of developing cancer and cardiovascular diseases, and the improvement of these patients' health.

As mentioned above, there are very few smokers who manage to stop smoking permanently at the first attempt[191], but furthermore, if the percentage of relapses in the general smoking population is 70-80% during the first year, in the group of smokers with COPD, this percentage increases[195]. Jiménez et al.[196] analyse the reasons why the relapse percentage in this group of patients is greater than in the general population. According to these authors, the reasons that could explain the smoking cessation success difficulties of patients with COPD are the following:

- Pathopsychological disorders in patients with airflow obstruction would favour a greater amount of inhalation and deposit of toxic substances.
- Greater physical nicotine dependence among smokers with COPD. According to the IBERPOC[15] study, 30 % of smokers with COPD scored 7 or more points in the Fagerström test. It is a known fact that patients with greater dependence are more likely to undergo relapses.
- Presence of psychiatric comorbidity in smokers with COPD.
- Different degrees of motivation among the different types of smokers with COPD.

These difficulties will have to be taken into account when patients with COPD are offered different aid strategies to stop smoking. It has been demonstrated that both individual counselling interventions and interventions given in group format are effective measures to stop smoking, as well as pharmacological treatment; furthermore health practitioners can play a comprehensive role in the multi-dimensional approach to smoking cessation[191,197-199].

The strategies that can be followed to help patients stop smoking are:

- Medical/psychological counselling, which can vary from a short intervention in the surgery to psychosocial type interventions in groups or individually.
- Pharmacological treatment, which includes nicotine replacement therapy (NRT) in any of its formats, chewing gum, patches, inhalers, etc; antidepressants such as Bupropion and Nortriptyline; and nicotine receptor partial agonists, such as Varenicline.

8.1 Medical/psychological counselling

The importance of medical counselling is highlighted in the review of the GOLD regulation, as well as its effectiveness in helping patients stop smoking, and it is recommended that this type of strategy should be offered to all smokers who come to the surgery[5]. Furthermore they propose a 5-step programme to help patients stop smoking (see table 8.1)[5].

Table 8.1 Brief strategies to help patients willing to stop smoking

Ask	Systematically identify all smokers during every medical visit. Implement a tobacco use log system for each patient.
Advise	In a clear, strong and personalised manner, urge all smokers to stop smoking.
Assess	Determine motivation to stop smoking. Ask all smokers if they are willing to stop at that time.
Assist	Help patients stop smoking. Provide counselling and support. Help patients find social support during and after treatment. Recommend the use of authorised drugs, except in special circumstances, and provide supplementary materials.
Arrange	Schedule a follow-up programme for patients either in person or via telephone.

Translated and modified from GOLD 2011[5]

More than 5 years have passed since the publication of this Clinical Practice Guideline, and its validity has not been reviewed

Abstinence

In all the studies found, which compare use of medical/psychological counselling and normal treatment to stop smoking, which mainly consists in pointing out to patients the importance of quitting, medical/psychological counselling is found to obtain better rates of abstinence in the medium/long term (6 months-33% vs. 21%, 9 months-36.5% vs. 12.7%, 12 months-52% vs. 7%, 36 months- 38% vs. 10%) than normal treatment[198,200-207].

Moderate quality

Furthermore, when the minimum contact interventions are compared with structured programmes to stop smoking both in a group and individually, it is observed that in the minimum contact programmes, a positive attitude towards stopping smoking represents an independent significant predictive factor of smoking cessation (OR:11.8; 95% CI 1.7 to 81.5; p=0.013). With respect to structured programmes, no independent predictive factor is found, thus suggesting that these programmes may be an alternative when the patient has not clearly decided to stop smoking[200,204].

The use of Bupropion or of NRT apart from medical/psychological counselling, as opposed to normal care, in the short term (12 weeks), does not present significant differences; however, those differences are significant after one year when the abstinence rates are better in the group of Bupropion or NRT + medical/psychological counselling, than in the normal care group[192,195,208,209]. This is also shown in a systematic review of clinical trials on smoking cessation in smoking patients with COPD, who had shown biochemically validated 12 month abstinence rates. The different interventions of this review were grouped into four categories: normal care, minimum counselling (less than 90 minutes), intensive counselling (more than 90 minutes) and intensive counselling plus pharmacological treatment (NRT, Bupropion or Nortriptyline). The abstinence figures after the one-year monitoring for each of the categories were: 1.4%, 2.6%, 6% and 12.3%, respectively. Compared with normal treatment, the cost per quality-adjusted life-year gained for minimum counselling was €16,900, for intensive counselling €8,200 and for intensive counselling plus pharmacological treatment €2,400[210].

Furthermore, in patients who present low motivation to stop smoking, the use of Bupropion or NRT + medical/psychological counselling also improves the long-term tobacco habit abandonment rates when compared with the exclusive use of medical/psychological counselling[199,208].

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8.2 Pharmacological treatment

Nicotine Replacement Therapy (NRT)

It is known that smokers with COPD suffer a much higher degree of physical dependence on nicotine than smokers without COPD.

Abstinence

NRT, both in the form of patches and chewing gum, is effective to help smokers with COPD stop smoking[5,191,199]. Moderate quality

In a study on smoking patients with medical comorbidities and with high motivation to stop smoking in whom the administration of reduced monthly doses of nicotine is compared with the daily adaptation of nicotine, depending on the concentrations of cotinine in saliva, they found that there were no differences in the abstinence rates in the medium/long term[211].

One meta-analysis network[212] suggests that the use of NRT together with medical counselling achieves the highest rates of prolonged abstinence, compared with normal treatment (OR 5.08, p<0.0001), compared with medical counselling alone (2.80, p = 0.001) and compared with medical counselling combined with an antidepressant (1.53, p = 0.28). In another study that compares the normal use of NRT with the use of NRT combined with the administration of Bupropion in order to increase the effectiveness of the NRT, they find that the administration of this drug together with NRT does not improve the long-term abstinence rates[213].

Bupropion

Abstinence

With respect to the effectiveness of Bupropion, it has been demonstrated that it has higher rates of prolonged abstinence compared with placebo (OR:13.1;[95% CI, 1.2-25]). When compared with other types of antidepressants such as nortriptyline, both present similar results, although nortriptyline compared with placebo did not present statistically significant differences (OR:10.2;[95% CI, -1.7-22.2])[5,191,214-217]. Moderate quality

Varenicline

Varenicline is a nicotine receptor partial agonist, which has proved to be effective in the main studies published[5,191,218-221].

Abstinence

In studies that compared the use of varenicline with placebo, they find that the abstinence rates after one year's monitoring are higher in varenicline (OR:8.40;95% CI 4.99 to 14.14; p<0.0001). Moderate quality

When compared with Bupropion, the abstinence rates after one year are also better for varenicline (OR:1.93; 95% CI 1.40 to 2.68; p<0.001). When compared with the use of nicotine patches, it also presents better results after 12 months (OR:1.70; 95% CI 1.26 to 2.28)[218-221].

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Adverse events

The Spanish Agency of Medicines and Health Products warned, through an information memo about the review of the drug safety data in Europe[222], that the appearance of depressive symptoms has been notified in patients who were trying to stop smoking with varenicline, and that these symptoms may include suicidal thinking or suicide attempts, having to suspend the treatment immediately in this case. Furthermore, it recommends special precaution in patients with underlying psychiatric disturbances.

Low quality

8.3 Patients' values and preferences

As mentioned above, patients with COPD encounter greater difficulties when starting smoking cessation treatment than other types of patients; therefore, studies have been performed that explore the values and preferences of these patients with COPD, as well as the attitudes of the health staff with respect to smoking cessation in this type of patient

With respect to the patient's preferences and values, studies[223–225] have been found that explore the reasons why patients with COPD continue to smoke although they are receiving some type of support to quit, and the feelings generated in these patients by the fact that they are not able to quit. They find the reasons why patients find it difficult to stop smoking are: Considering the cigarette "as a friend", believing that it is too late to quit and not finding the necessary motivation to do so[224,225]. Furthermore the most common feeling that this type of patient has when they are not able to stop smoking is blame, because they are aware of the problem that continuing to smoke represents for them and of the deterioration of their quality of life, but they are not able to quit[223].

When the attitudes of health professionals regarding smoking patients diagnosed with COPD are analysed, these are found to believe that these types of patient feel guilty for their condition and for not being able to stop smoking; they also refer to the fact that smoking patients with COPD feel more guilty than other types of smoking patients, such as those with chest angina[226].

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Summary of evidence

Moderate overall quality of evidence	Medical/psychological counselling has proven to be effective to help patients with COPD stop smoking [5,198,200-207]
	In minimum contact programmes, a positive attitude towards stopping smoking represents an independent predictive factor of smoking cessation (OR:11.8; 95% CI 1.7 to 81.5; p=0.013). In structured programmes, no independent predictive factor is found, thus suggesting that these programmes can be an alternative in patients who have not clearly decided to stop smoking[200,204].
	The different interventions of a review grouped into four categories (normal care, minimum counselling (less than 90 minutes), intensive counselling (more than 90 minutes) and intensive counselling plus pharmacological treatment (NRT, Bupropion or Nortriptyline) show abstinence figures after one year's monitoring of 1.4%, 2.6%, 6% and 12.3%, respectively. Compared with normal treatment, the cost per quality-adjusted life-year gained for minimum counselling was €16,900, for intensive counselling €8,200 and for intensive counselling plus pharmacological treatment €2,400[210].
	In patients who have low motivation to stop smoking, the use of Bupropion or NRT + medical/psychological counselling improves the long-term tobacco habit abandonment rates when compared with the exclusive use of medical/psychological counselling[199,208].
	NRT, both in the form of patches and chewing gum, is effective to help patients with COPD stop smoking[5,191,199].
	The daily adaptation of the nicotine dose depending on cotinine in saliva compared with the administration of monthly reduced doses of nicotine, does not improve medium/long-term abstinence[211].
	One meta-analysis network suggests that the use of NRT together with medical counselling achieves the highest rates of prolonged abstinence, compared with normal treatment, with medical counselling alone and combined with an antidepressant. Another study that compares the normal use of NRT compared with the use of NRT together with Bupropion finds that the latter does not improve long-term abstinence[212,213].
	Bupropion, compared with placebo, increases prolonged abstinence rates. When compared with other types of antidepressants such as Nortriptyline, both present similar results, although Nortriptyline compared with placebo did not present statistically significant differences[5,191,214-217].
	Varenicline presents higher rates of abstinence compared with the use of placebo, NRT (patches) or Bupropion[218-221]. The appearance of depressive symptoms has been notified, which may include suicidal thinking or suicide attempt[222].

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	Smoking patients with COPD point out that it is difficult for them to stop smoking because they consider the cigarette "as a friend", believe that it is too late to stop and do not find the necessary motivation to do so. The most common feeling they have when they are not able to stop smoking is blame. Health professionals believe that they feel guilty about their condition and about not being able to stop smoking, and they refer to the fact that they feel more guilty than other types of smoking patients (chest angina)[223-226].

Recommendations

Strong	The offer of smoking cessation medical/psychological counselling is recommended in smoking patients with COPD.
Weak	The use of medical/psychological counselling, accompanied by pharmacological therapy, is suggested in smoking patients with COPD, who have little motivation to stop smoking.

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9. Treatment of anxiety and depression in patients with COPD

Depression is a frequent problem among patients with COPD, with important consequences on their state of health. According to a recent meta-analysis, the prevalence of depression symptoms in patients with COPD is calculated at around 25%227, although it is also true that considerable variability is observed between the different studies[228]. In these patients, untreated depression has been associated with a reduction in adherence to medical treatment[229], early abandonment of pulmonary rehabilitation programmes[230], increase in hospital stay[99,231] and a decrease in quality of life[231,232].

Anxiety is also very frequent. Generalised anxiety disorders may appear in 10-33% of patients with COPD, whilst the prevalence of disorders and panic attacks is situated between 8 and 67%[228].

Current CPGs on the management of COPD place emphasis on the need for routine checks to detect anxiety and/or depression at an early stage in patients diagnosed with COPD. With respect to treatments, faced with the lack of conclusive evidence, some of the guidelines recommend that these disorders should be treated normally, as there is no evidence that anxiety and depression must be treated in a different way in patients with COPD[5]; in some cases it specifies that treatment must depend on the patients' illness and age, avoiding anxiolytics that may produce sedation in patients with severe COPD[233]. Other guidelines highlight the importance of offering psychological and psychosocial interventions before pharmacological treatment is considered[108,234].

9.1 Pharmacological treatment

In patients with COPD, the ideal antidepressant (AD) would be an antidepressant with a low adverse effect risk profile, short-medium life and without active metabolites, which does not present important interactions and that can be administered once or twice a day[235,236].

Evidence about the effectiveness of pharmacological treatment in patients with COPD and depression is scarce, due to the limited number of studies, methodological deficiencies and the small sample size of these studies. Furthermore, considerable heterogeneity is observed between studies, both related to the drugs used and the type of patients included, as well as the scales used to measure the results.

Three RCTs have been identified that assess the administration of Selective Serotonin Reuptake Inhibitors (SSRI) and two that assess the administration of tricyclic antidepressants (TA) as treatment of depression in patients with COPD. The duration of the studies varies between 6 and 12 weeks.

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Patients with COPD and depression

Depressive symptoms

Depression symptoms improved in two of the studies in which paroxetine was administered, although the differences compared with placebo did not reach statistical significance[237,238]. In another of the studies with SSRI, no significant differences were found between citalopram and placebo for the global population of the study. However, citalopram was more effective than placebo in those patients who presented mild or moderate depression symptoms at the start of the study, but not in those with severe symptoms[239]. Very low quality

On the other hand, the two studies with TA show contradictory results; whilst one of the RCTs did not find significant differences between doxepin and placebo[240], in the other study, those patients who were administered nortriptyline improved the scores of the scales with which the depression was assessed by 60% (from 29.6 points to 12.6), whilst those who received placebo only improved by 17% (29.5 to 22.8). The differences were significant[241].

Dyspnoea, fatigue, quality of life or tolerance to exercise

No differences were found for these variables when comparing the ADs with placebo[237-241]. Very low quality

Adverse events

Adverse events were not described accurately in all the studies. In one of the studies, treatment had to be changed in four of the 14 patients who received SSRI[237]; another of the studies informed that the adverse effects were similar between placebo and the drug, and one patient of the 12 who received paroxetine had to abandon the pharmacological treatment due to adverse effects[238] Very low quality

With respect to the TAs, in one of the studies, 3 patients out of the 12 who received doxepin abandoned it due to adverse effects[240].

Patients with COPD and anxiety

Anxiety symptoms

With respect to anxiety, a recent SR sets out the results of four RCTs which assess the effectiveness of the pharmacological treatment of anxiety disorders in patients with COPD; of these four, the two studies that compared SSRI with placebo showed a reduction in anxiety symptoms in the short term (monitoring of up to 6 months) associated with the use of SSRI). In one of the studies, the differences, although clinically relevant, were not significant. In the other study, the raw data suggest a favourable result with the use of SSRI, although the small sample size of the studies prevents reaching strong conclusions. On the other hand, the RCTs that assessed tricyclic antidepressants or azapirones did not find significant differences when compared with placebo[242]. Very low quality

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Quality of life, dyspnoea, tolerance to exercise or length of hospital stay and re-admissions

For the rest of the variables studied, such as quality of life, dyspnoea, tolerance to exercise or length of hospital stay and re-admissions, either no evidence was found or the evidence found was limited, and no clear benefit associated with pharmacological treatment was observed[242].

Very low quality

Adverse events

Insofar as adverse effects are concerned, the two studies that assessed SSRI inform about the appearance of adverse effects, although they are not described in a sufficiently clear manner. In one of the studies, six of the eight patients treated with SSRI suffered mild or moderate adverse effects. Two patients suffered important adverse effects, and in one of the cases this required eliminating the patient from the study. In the other study, four of the 14 patients who were administered SSRI had to change the drug due to important adverse effects[242].

Very low quality

9.2 Psychological interventions

The application of psychological interventions to improve depression and/or anxiety symptoms in patients with COPD have also been assessed in studies with small sample size. One recent SR includes nine studies in which the effectiveness of different techniques (cognitive behavioural therapy-CBT, educational interventions based on CBT, psychotherapy and progressive muscular relaxation) is studied in a population made up mainly by patients with moderate-severe COPD and anxiety or/or depression considered to be mild or moderate[243].

Depression and anxiety symptoms

The results of this SR show a small although significant effect of psychological interventions when reducing anxiety, but only when compared with the basal situation of the patients, not when compared with the control group.

Very low quality

The studies in which the effectiveness of these techniques to reduce depressive symptoms was assessed found contradictory results, like those studies that assessed patients' quality of life.

Four of the seven studies that assessed depression found significantly favourable results associated to the psychological interventions, although only when compared with the basal state, not finding any differences in the comparison with the control groups.

On the other hand, the results of a later RCT seem to indicate that CBT offers a slight improvement both of anxiety symptoms and of depression when compared with normal care in patients with COPD.

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Quality of life

In the case of quality of life, no significant differences were found either between the groups, although in some of the studies an improvement was observed with respect to the situation at the start of the study[243]. The results of a later RCT did not find differences with respect to quality of life between CBT and normal care of patients with COPD[244]. In this sense, in another RCT that assessed the effectiveness of an intervention carried out by nurses and based on the principles of CBT and self-care, it was observed that those patients that received the intervention obtained better scores on the scales that evaluated anxiety, depression and quality of life, than those who received normal care at the end of the nine months' monitoring. However, since the baseline scores were slightly different among both groups, although not in a significant way, these results must be taken with caution.[245].

Very low quality

9.3 Pulmonary rehabilitation

Another SR compared the effectiveness of outpatient pulmonary rehabilitation with normal care and with exclusively educational programmes. Pulmonary rehabilitation programmes included those that lasted for four weeks or more and that offered at least two weekly sessions of supervised training. Multidisciplinary programmes were also included, which apart from the exercises, included other activities. On the other hand, it is important to highlight that in the studies included in the review, the psychological state of the patients was not taken into account when they were included in the study. In other words, the target population of this review was comprised of patients diagnosed with COPD, with clinical and subclinical symptoms of anxiety and depression, and even without either of the two conditions[246].

Depression systems

One SR included six RCTs, lasting from between 5 and 12 weeks, although in one of the studies the monitoring lasted for up to one year, in patients with moderate or severe COPD. In the six studies, an assessment was made of the effectiveness of rehabilitation in the treatment of depression. A moderate beneficial effect was observed in the reduction of the depression symptoms and a significant effect in favour of multidisciplinary rehabilitation programmes when compared with normal care. These programmes also appear to offer better results than purely educational programmes, although, in this case, statistical significance was not reached. The comparison between rehabilitation programmes with exercises and normal care was not significant, either. At the end of one year, the differences compared with normal care were not significant. The proportion of depressed patients at the end of the year was similar between the group that received rehabilitation and the control group[246].

Very low quality

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Anxiety

The effectiveness of pulmonary rehabilitation in the management of anxiety was also assessed in the six studies. A small, but significant, beneficial effect associated with the treatment was observed. The subgroup analysis showed that multi-disciplinary rehabilitation was better than both normal care and purely educational programmes, although statistical significance was only reached for the first of the comparisons. No significant differences were found when comparing rehabilitation with exercises and normal care. According to one of the studies, the effect of rehabilitation and anxiety decreased with time, and no significant differences were found between pulmonary rehabilitation and normal care at the end of one year[246].

Very low quality

Quality of life

Results regarding the effects of pulmonary rehabilitation on quality of life are contradictory. When compared with normal care, multi-disciplinary rehabilitation appears to improve the quality of life, although the results are not significant in all studies, and once again, the effect seems to decrease with time. When compared with educational programmes, the results also seem to favour pulmonary rehabilitation. However the differences are not significant and in one of the studies a greater benefit associated with educational programmes even seemed to be observed[246].

Very low quality

In one RCT after the review, with a small sample size, it was observed that in those patients who attended a multidisciplinary rehabilitation programme for two months, there was a significant improvement of their scores of depression, dyspnoea and quality of life with respect to their basal situation. An improvement in the anxiety symptoms was also observed, without reaching statistical significance. No significant changes were observed in the control group with respect to their basal situation[247].

9.4 Patients' values and preferences

There is not much evidence about what type of treatment (pharmacological versus psychological interventions) is most preferred by patients with COPD and anxiety and/or depression symptoms. In one study on older patients with moderate or severe COPD and diagnosed with depression, only 28% accepted to follow pharmacological treatment. The remaining 72% rejected it for different reasons, though in quite a few cases this was due to the patients' mistaken beliefs. On the other hand, only 50% of those who accepted to receive pharmacological treatment completed the study. The majority of the patients abandoned the study due to adverse effects[248].

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9.5 Economic evaluation

No economic assessments were identified about the interventions set out in this section.

Summary of evidence

Very low overall quality of evidence	SSRI seem to improve the anxiety and depression symptoms to a certain extent, although the small sample size of the studies and their low quality prevent reaching solid conclusions regarding their effectiveness in the treatment of anxiety and depression in patients with COPD[237-239,242]
	With respect to ATs, the evidence is contradictory, not having found differences between doxepin and placebo in the treatment of depression. However, in another RCT, nortriptyline proved to be more effective than placebo in reducing depression symptoms in patients diagnosed with COPD. On the other hand, no differences have been observed between ATs and placebo with respect to the treatment of anxiety[240-242]
	The adverse effects of antidepressant drugs cause a considerable percentage of abandonment of the treatment[237,238,240,242]
Very low overall quality of evidence	Psychological interventions improve depression and anxiety symptoms in patients with COPD when compared with their initial situation, although it has not been possible to demonstrate that there are differences with normal care. Interventions based on cognitive-behavioural therapy show slight differences in favour of psychological interventions when compared with control groups[243-245]
Very low overall quality of evidence	Multidisciplinary pulmonary rehabilitation programmes moderately improve depression and anxiety symptoms, and quality of life compared with normal care although the effect of pulmonary rehabilitation on these symptoms decreases with time, not finding significant differences after one year[246,247]

Recommendations

Good clinical practice	In patients with COPD, anxiety and depression must be treated in the traditional manner, although the age of the patients, adverse effects of the drugs and pharmacological interactions must be taken into account, especially in polymedicated patients.
Weak	In patients with COPD with symptoms of anxiety and/or depression and who are poor predisposed to follow pharmacological treatments, it is suggested to offer psychological treatment based on cognitive-behavioural therapy principles.
Weak	In patients with COPD and subsidiary anxiety and/or depression symptoms of pulmonary rehabilitation, a multi-disciplinary pulmonary rehabilitation programme is suggested.

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10. Perspective of patients with COPD

The value of an institution (or of a product created by an institution) increases insofar as it adapts to the "refined" preferences of the citizens249. The patients' viewpoint has been incorporated into the framework of this guideline, through the direct participation of patients' representatives (Spanish Patient Forum) in the development group. Furthermore, the work has been carried out directly with the patients themselves (survey and discussion group) and literature has been reviewed with respect to the competences and skills for health of patients with COPD.

10.1 Survey and discussion group with patients with COPD and their caregivers

Within the framework of the development of the guideline, information about the needs and preferences of patients with COPD and their caregivers has been studied, through two actions: a survey carried out with 104 patients from 9 hospitals diagnosed with COPD and an organised debate session in which 12 patients with COPD and caregivers have participated. The methodology is described in further detail in the methodological section available on the website of GuiaSalud as well as on the website of the UETS.

The most relevant results of the survey are given below:

- 11% of the patients declare information was non-existent at the time of diagnosis.
- 29% suggest that coordination among doctors should be improved.
- 30% have contact with more than 4 professionals.
- The caregiver is usually the wife
- Small role of the pneumologist in the case of exacerbation.
- 27% of the patients would be willing to take decisions by themselves during the course of the exacerbation (after receiving medical advice).
- Hospital admission is one of the situations that patients fear the most.

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The key points of the organised debate of the group of patients are summarize in the table below:

Information	– Especially at the onset of the illness. – Explain the causal relationship with the consumption of tobacco – Need to receive written, simple and practical information. – Information throughout the evolution of the illness, especially in advanced stages.
Education for health (self-care)	– Importance of therapeutic education programmes. – Good evaluation of group activities. – Involve patients in their own care (action plans). – Importance of physical exercise and of rehabilitation.
Tobacco withdrawal	– Withdrawal units are not the only solution. – Patients require personalised treatments.
Healthcare quality	– Simplify administrative procedures. – Guarantee continuity of care and coordination of the different healthcare levels. – Highly positive evaluation of the professional responsible for the "case management". – Speed up referrals when necessary. – Promote proximity care whenever possible
Exacerbations	– Exacerbation is one of the problems that concerns patients the most. – The existence of a professional reference could play a very important role – in the management of exacerbations. – Mechanisms to anticipate exacerbations and act at an early stage.
Personal and social support	– The importance of guaranteeing support to the caregiver is recognised (including access to economic resources). – Access by health professionals to information on personal and social support – in order to be able to disseminate it. – Psychological support must be considered both for the patient and for the caregiver: – Little practical presence of patients' organisations (there should be an increase in the role of these organisations).

10.2 Competences and skills for health of patients with COPD

The capacity of patients and their caregivers to understand the clinical manifestations of their disease and act in the best way possible is very important. Deficiencies in this field may have a negative impact for the patient on the health results250.

The Anglo-Saxon concept of Health literacy, which in our medium could be translated by **"competences and skills for health"** (Spanish acronym, CHS) refers to the patient's capacity to obtain, process and understand the basic health information that will enable him or her to take decisions[251]. CHS require knowledge about health problems, the skills to use appropriately health-care devices, intellectual competences and initiative[251,252]. Sometimes it is difficult to identify patients with deficits in CHS[253], especially in those cases where the oral expression level seems sufficient but they have problems in understanding written information[254]. The majority of patients find it hard to accept that they do not know how to read. Moreover, deficits can be detected in CHS despite having higher studies.

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10.2.1 Identification of competences and skills for health

CHS are what enable patients to appropriately "surf" through the health system in order to solve their health needs. Different elements appear in patients with COPD that contribute to deficits in CHS (persistence of the smoking habit, low social-economic or depression, for example) and that lead to therapeutic non-compliance in more than 50% of the cases[255]. There are few instruments that evaluate the degree of CHS[256] and attention must be paid to some clues that may help identify patients with a deficit in CHS[257]:

- Difficulties to find their way in hospital.
- Reading difficulties:
    - The instructions are usually read by the companion.
    - Excuses in order not to read ("they have forgotten their glasses")
- Difficulties to fill in forms or arrange visits.
- Oral comprehension difficulties:
    - Difficulties to understand normal languages in a society.
    - Hearing problems.
- Following instructions:
    - Limited adherence to treatments.
    - Difficulties to follow instructions on personal or eating habits.
    - Difficulties to get ready for a test or procedure.
    - Forgetting visits.
- Postponing decisions (especially when they have to read).
- Mimetic behaviours.

10.2.2 Self-care programmes for patients.

The promotion of self-care must not be a synonym of education[257,258]. The promotion of self-care must bear in mind two key aspects: education for health (in the sense of providing the patient with intelligible information to improve CHS) and collaboration with the patient in decision-making. Bodenheimer et al[257,259] suggest that the proposal of objectives and motivational interviews are tools that help promote self-care.

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10.2.3 Active role of health professionals during the consultation

The consultation is an ideal moment to promote CHS but professionals' communication skills must be improved[260] in order to give patients time to explain their situation[261] and facilitate shared decision making[262].

The use of some tools can be helpful during the consultation.

- Graphic materials.
- Audiovisual support.
- Avoid technical language (but using correct and rigorous language).
- Personalised written information for the patient, with key messages.
- Written information for the other health professionals who attend to the patient.
- Contacts (telephone, text messages, e-mail,…) between visits.

10.2.4 The training programme at home

Bourbeau et al[263] show the benefits of a global training programme to promote self-care of patients with COPD, which was carried out at the patient's home, by means of a weekly visit by a health professional over a two-month period. Each visit had some well-structured educational as well as knowledge and skill obtaining objectives.

10.2.5 Group visits

There is little experience about the role of group visits in patients with COPD. DeVries et al[264] propose some group visits (6 highly motivated patients with COPD) held on a monthly basis for three months and, later on, every three months for three years. The visits last for 90 minutes and during the last 15 minutes the action plans of each patient are discussed together. Despite the potential benefits of group visits, more studies are required to verify the feasibility of this strategy and the reproducibility of the models[265].

10.2.6 Action plan

One of the key elements is to provide patients with tools so that they can cope with the exacerbations as early on as possible. These include identification and treatment. The action plan identifies symptoms and clinical manifestations that suggest that the actual patient should carry out therapeutic changes. The action plan refers to changes in the use of oxygen, the start of antibiotics, an increase in bronchodilator dose or the use of cortisone. Alarm signals as well as the actions and contacts to be made are established in the action plan. Adherence to the action plans reduces recovery time in an exacerbation[266].

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10.2.7 Active role of patients: Medical visit kit

The *University of patients* has designed a "medical visit kit"[257] which is a tool that provides very simple reminders and tips to help patients organise better their visit to the doctor. It is available at: http://www.universidadpacientes.org/kitdevisitamedica/

10.2.8 Use of support technologies

The use of information and communication technologies (ICTs) may play an important role in the improvement of CHS. The objective of ICTs is not to replace face-to-face contacts, but to complement them in such a way that, although the number of (traditional) visits is reduced, the total number of contacts (traditional visits + technological interactions) increases.

Lorig et al[267] show the benefits of self-care programmes based on the Internet and Martí et al[268] set out the results of a call centre for chronic patients, focused on improving self-care. Mobile phones are useful to give support to patients included in a pulmonary rehabilitation programme[269]. In short, services for patients that offer ICTs can be grouped into[270]: direct access to professionals, monitoring (vital signs and symptoms), virtual visit or access to educational material.

10.2.9 Social networks

New technologies permit the creation of extensive social networks that can offer patients multiple tools to communicate with each other[271]. The capacity of the actual patient to generate useful information for other patients is an element that must not be underestimated[272].

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11. Dissemination and implementation

- What is the strategy for disseminating and implementing the guideline?
- What indicators are used to monitor the recommendations?

11.1 Dissemination and implementation strategy

CPGs are useful to improve the quality of healthcare and results in patients. The great challenge today is to achieve the adherence of professionals to the recommendations of these guidelines. An implementation strategy, aimed at overcoming the existing barriers in the medium where it is going to be applied is therefore essential.

The plan to implement the Clinical Practical Guideline for the Treatment of Patients with COPD includes the following interventions:

- Presentation of the guide by the health authorities to the media.
- Presentation of the guideline to the directorates and sub-directorates for Primary Care and Specialised Care of the different Regional Health Services.
- Institutional presentation of the guideline in collaboration with the Ministry of Health, Social Services and Equality, to the different scientific and professional societies involved, as well as to groups and associations of patients interested.
- The information aimed at patients with COPD will be highlighted at all the presentations, in order to favour its distribution among all the health professionals and also among patients with this health problem.
- Effective distribution aimed at professional groups involved (specialists in pulmonology, internal medicine, family medicine, nursing staff, emergency care, physical medicine and rehabilitation, preventive medicine and public health, psychology and physiotherapy), and at patients and associations of patients interested in order to facilitate dissemination.
- Interactive presentation of the guideline at health centres and hospitals by the local opinion leaders.
- Dissemination of the guideline on electronic format on the web pages of the Ministry of Health, Social Services and Equality, of GuiaSalud, of the UETS and of the scientific societies and associations of patients involved in the project.
- Publication of the guideline in scientific magazines.
- Establishment of good care criteria for patients with COPD in programme contracts and clinical management contracts, as established in the guideline.

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Assessment of the effectiveness of the implementation, establishing clinical decision support systems, integrating the guideline and the indicators selected in the information systems of the health centres.

11.2 Indicator proposals

A series of indicators have been designed for this CPG, which it must be possible to measure through the information systems in primary and specialised care, in order to assess both the health care to the patient with COPD and the possible impact of the implementation of the guideline.

It has not been the authors' intention to design an exhaustive and detailed assessment that involves the use of all the indicators proposed. The aim is to provide interested professionals and stakeholders with a tool that may be useful to specifically design the assessment of care of patients with COPD.

Two types of indicators are proposed:

- **Control indicators:** with this list of indicators the aim is to carry out a follow-up of the distribution of the patients with COPD according to the use of the treatments proposed in the guideline.
- **Compliance indicators:** these are based on the recommendations proposed in this guideline and therefore on the available scientific evidence and on the consensus of professionals. To define the compliance standards proposed, the reality of the context of care to patients with COPD in Spain has been taken into account.

11.2.1 Maintenance treatment of stable phase COPD

Follow-up indicators

Assessment criterion	Follow-ip indicators
Sustained action bronchodilator in monotherapy at the onset of treatment of stable phase COPD	Percentage of patients with COPD who, the previous year, have required hospital admission, treatment with systemic glucocorticoids or antibiotic treatment for at least one exacerbation and who, requiring a sustained action bronchodilator in monotherapy, receive tiotropium.
	Percentage of patients with COPD who, the previous year, have required hospital admission, treatment with systemic glucocorticoids or antibiotic treatment for at least one exacerbation and who, requiring a sustained action bronchodilator in monotherapy, receive salmetrol.
	Percentage of patients with COPD who, the previous year, have required hospital admission, treatment with systemic glucocorticoids or antibiotic treatment for at least one exacerbation and who, requiring a sustained action bronchodilator in monotherapy, receive indacaterol.
Combined therapy (IC+long-acting beta adrenergic agonists) opposed to dual bronchodilator therapy (LABA+LAMA)	Percentage of patients with stable phase COPD in treatment with combined therapy (IC/LAMA or IC/LABA)
	Percentage of patients with stable phase COPD in treatment with dual bronchodilator therapy (LAMA/LABA)

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Roflumilast as an alternative to the use of inhaled corticoids as additional therapy to the maintenance treatment with bronchodilator in patients with COPD	Percentage of patients with COPD who, although not in a research context, receive roflumilast instead of inhaled corticoids as additional therapy to sustained treatment with bronchodilators.
N-acetylcysteine as maintenance treatment of patients with stable phase COPD.	Percentage of patients with stable phase COPD who receive N-Acetylcysteine as maintenance treatment
Carbocysteine as maintenance treatment in patients with stable phase COPD and exacerbator phenotype with chronic bronchitis	Percentage of patients with stable phase COPD and exacerbator phenotype with chronic bronchitis who receive carbocysteine as maintenance treatment.

11.2.2 Treatment of exacerbations of COPD

Follow-up indicators

Assessment criterion	Follow-up indicators
Systemic corticoids in moderate exacerbations of COPD	Percentage of moderate exacerbations in non-hospitalised patients with COPD, who receive oral prednisone.
Systemic corticoids in mild exacerbations of COPD	Percentage of mild exacerbations in patients with COPD who receive oral prednisone in a research context.

Compliance indicators

Good care criterion	Compliance indicators	Standard
Pulmonary rehabilitation in the context of an exacerbation of COPD	Percentage of exacerbation of patients with COPD who receive pulmonary rehabilitation within three weeks after the end of the treatment of the exacerbation.	90%

11.2.3 Treatment of tobacco dependence in patients with COPD

Follow-up indicators

Assessment criterion	Follow-up indicators
Medical/psychological counselling	Percentage of smoking patients with COPD who have received medical/psychological anti-tobacco counselling.
Pharmacological treatment	Percentage of smoking patients with COPD who have little motivation to stop smoking, who receive structured medical/psychological counselling accompanied by pharmacological therapy.

Compliance indicators

Good care criterion	Compliance indicators	Standard
Medical/psychological counselling	Percentage of smoking patients with COPD who are offered medical/psychological anti-tobacco counselling.	100%

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11.2.4 Treatment of anxiety and depression in patients with COPD

Follow-up indicators

Assessment criterion	Follow-up indicators
Psychological treatment	Percentage of patients with COPD and with anxiety, depression or both, who receive psychological treatment.
Pharmacological treatment	Percentage of patients with COPD and with anxiety, depression or both, who receive pharmacological treatment.
Pharmacological and psychological treatment	Percentage of patients with COPD and with anxiety, depression or both, who receive psychological and pharmacological treatment.
Pulmonary rehabilitation	Percentage of patients with COPD and with anxiety, depression or both, who receive pulmonary rehabilitation

Compliance indicators

Good care criterion	Compliance indicators:	Standard
Psychological treatment	Percentage of patients with COPD and with anxiety, depression or both, in psychological treatment, whose therapy is based on cognitive-behavioural therapy principles.	75%
Pulmonary rehabilitation	Percentage of patients with COPD and with anxiety, depression or both, in treatment with pulmonary rehabilitation whose therapy is framed within a multidisciplinary programme.	75%

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12. Future research lines

12.1 Combined therapy (IC/LABA) compared with dual bronchodilator therapy (LABA+LAMA) for the treatment of stable phase COPD

In patients with stable phase COPD, current evidence does not permit giving priority to treatment with combined therapy (IC/LAMA or IC/LABA) or dual bronchodilator therapy (LAMA/LABA). Randomised controlled clinical trials are recommended, with adequate allocation sequence concealment to assess the effectiveness and safety of IC/LAMA or IC/LABA compared with dual bronchodilator therapy via direct comparisons. These clinical trials should consider clinically relevant result variables, such as the frequency of exacerbations (both those that require hospital admission and those who do not), mortality, presence of respiratory symptoms, tolerance to exercise and quality of life. On the other hand, the sample size should be sufficient and they should last long enough to be able to assess the effectiveness and safety of both treatments.

Studying the patients' and professionals values' and preferences on risks and benefits of the treatment of COPD with both combinations is recommended.

Assessing the costs associated with pharmacological maintenance treatment of COPD with IC/LAMA or IC/LABA vs. dual bronchodilator therapy is recommended.

12.2 Use of roflumilast instead of inhaled corticoids as additional therapy to the maintenance treatment with bronchodilators in patients with CPOD

Additional therapy with roflumilast instead of inhaled corticoids, should only be used in a research context in patients with COPD in maintenance treatment with bronchodilators.

Randomised controlled clinical trials are recommended, with adequate allocation sequence concealment to assess the effectiveness and safety of roflumilast (replacing inhaled corticoids) compared with inhaled corticoids via direct comparisons. These clinical trials should consider clinically relevant result variables, such as the frequency of exacerbations (both those that require hospital admission and those that do not), mortality, the use of rescue medication, the presence of respiratory symptoms, tolerance to exercise and quality of life. On the other hand, the sample size should be sufficient and it should last long enough to be able to assess the safety are both treatments.

It is recommended studying the patients' and professionals' values and preferences about the risks and benefits of the treatment of COPD with roflumilast when compared with inhaled corticoids.

It is recommended assessing the costs associated with the pharmacological maintenance treatment of COPD with roflumilast in comparison with inhaled corticoids.

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12.3 N-Acetylcysteine in the maintenance treatment of COPD

The generalised use of N-Acetylcysteine as maintenance treatment of patients with stable phase COPD is not recommended.

Due to the lack of high quality evidence, specific research is recommended to be able to reduce existing uncertainty and clarify the balance between benefits and risks and disadvantages associated with maintenance treatment with NAC during the stable phase of patients with COPD.

To determine the effects of NAC, it is recommended to perform randomised controlled trials with an adequate allocation sequence concealment, lasting for sufficient time (at least one year), with blinding of patients and professionals, with minimal losses of patients and an adequate analysis strategy ("intention-to-treat"). These clinical trials should have sufficient sample size to assess the effects on low frequency events (for example, adverse events associated with NAC). Furthermore, it would be advisable to consider in these research studies the influence that certain factors may have, such as for instance, the severity of COPD, the patients' patients, the basal risk of suffering exacerbations or the presence of concomitant treatment (for example, inhaled corticoids).

The execution of studies is recommended to determine the effects of NAC on patients with COPD who are not receiving inhaled corticoids.

The execution of studies is recommended to determine the cost-effectiveness of NAC as well as patients' and professionals' values and preferences.

12.4 Systemic corticoids in moderate exacerbations of COPD

Oral prednisone may be used for 9 or 10 days to treat moderate exacerbations of - patients with COPD.

Clinical trials should be carried out that permit reducing the existing uncertainty and clarifying the balance between benefits and risks and disadvantages associated with the treatment of moderate exacerbations of non-hospitalised patients with COPD with systemic corticoids. Thus, randomised clinical trials are recommended, with an adequate allocation sequence concealment, lasting for sufficient time (at least one year to be able to assess therapeutic failure, relapse and recurrence), with blinding of patients and professionals, with minimal losses of patients and an adequate analysis strategy ("intention-to-treat"). These clinical trials should have sufficient sample size to assess the safety of the corticoids. Furthermore, it would be advisable to consider the influence that certain factors may have, such as for instance, the severity of COPD, patients' phenotype, the basal risk of suffering exacerbations, or the presence of concomitant treatment (for example, inhaled corticoids). The use of these drugs in patients with moderate exacerbations, who satisfactorily respond to the initial treatment, should also be assessed as well as the benefit-risk balance in patients with a high risk of developing adverse reactions to corticoids, for example, diabetics. The execution of studies is recommended to determine the cost-effectiveness of systemic corticoids as well as patients' and professionals' values and preferences. The studies should establish a minimum dose and duration of treatment with corticoids with the best risk-benefit balance.

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12.5 Systemic corticoids in mild exacerbations of COPD

The use of systemic corticoids is recommended to treat mild exacerbations of patients with COPD only in a research context.

Clinical trials should be carried out that permit reducing the existing uncertainty regarding treatment with systemic corticoids of mild exacerbations of patients with COPD. Thus, randomised clinical trials are recommended, with an adequate allocation sequence concealment, lasting for sufficient time (at least one year to be able to assess therapeutic failure, relapse and recurrence), with blinding of patients and professionals, with minimal losses of patients and an adequate analysis strategy ("intention-to-treat"). These clinical trials should have sufficient sample size to assess the safety of the corticoids. Furthermore, it would be advisable to consider the influence that certain factors may have, such as for instance, the severity of COPD, patients' phenotype, the basal risk of suffering exacerbations, or the presence of concomitant treatment (for example, inhaled corticoids). The use of these drugs in patients with mild exacerbations, who do not satisfactorily respond to the initial treatment, should also be assessed as well as the risk-benefit balance in patients with a high risk of developing adverse reactions to corticoids, for example, diabetics. The execution of studies is recommended to determine the cost-effectiveness of systemic corticoids as well as patients' and professionals' values and preferences. The studies should establish a minimum dose and duration of treatment with corticoids with the best risk-benefit balance.

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Appendixes

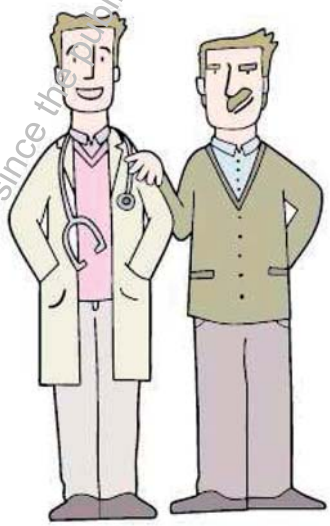
Appendix 1. Information for patients

Learning to understand and live with COPD

Information for the patient

What is COPD?

Questions and answers for patients about chronic obstructive pulmonary disease



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This information for people with COPD forms part of the Clinical Practice Guideline for the Treatment of Patients with Chronic Obstructive Pulmonary Disease (COPD). It is an initiative of the Spanish Society of Pneumologist and Thoracic Surgery (SEPAR) and it has been developed within the framework of the Quality Plan for the National Health System of the Ministry of Health, Social Services and Equality. 2011. Clinical Practice Guideline in the Spanish National Health System (SNS) UETS No. 20...

This information is also available in electronic format on the websites of GuiaSalud (www.guiasalud.es) of the Lain Entralgo Agency (www.madrid.org/lainentralgo) and of GesEPOC (www.gesepoc.com) On these websites, you can also consult the full version and the summarized version of the Clinical Practice Guideline for the Treatment of Patients with COPD.

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Table of Contents

Presentation

1. How do we breathe?

What is COPD?

What types of COPD exist?

What are the symptoms?

What are the causes of COPD?

How is COPD diagnosed?

2. Living with COPD

How to live with COPD and how to manage the disease?

- Exercises to keep active
- Pulmonary rehabilitation
- Breathing control
- Nutrition: eating and diet
- Sleep comfort
- Anxiety
- Depression
- Sex and relations
- Leisure and travelling
- Activities of daily living
- Work and environmental setting

Stopping smoking

Information for the caregiver

3. Treatment and control of COPD

What are the treatment options?

What are the complications of COPD?

What must I take into account when I visit my health centre or if I go to hospital?

4. Resources and additional information

Where can I learn more about COPD?

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Presentation

This document is aimed at people who have chronic obstructive pulmonary disease or COPD, their family members and the people who care for them when this becomes necessary.

The information provided in this document will help you have a better knowledge of this disease, so you will be able to take better care of yourself and thus improve your quality of life. You may have to read it several times or use the different sections, depending on when you need the information. The document integrates and includes information on COPD, its diagnosis and treatment, advice on how you can manage the disease in your daily lives and other useful resources such as contacts of associations of patients or online resources. This information does not replace the opinion of your physician or of other professionals such as nurses and physiotherapists, of your health team. The information provided will be in addition to that offered by the team that looks after you and will be a guide to be able to "know more".

This document has been prepared by the Health Technology Assessment Unit (UETS), of the Lain Entralgo Agency. It is based on and forms part of the GesEPOC project of the Clinical Practice Guideline for the Treatment of Patients with Chronic Obstructive Pulmonary Disease (COPD), of the National Health System, The recommendations you will find here have been developed based on existing scientific literature, on the agreement of the development group of this guideline and on the documents drawn up for patients by the Spanish Pneumologist and Thoracic Surgery Society (SEPAR). Other information documents on COPD, drawn up by scientific societies and official organisations in Spain, in the US, United Kingdom and other countries have also been taken into account. Furthermore, the information derived from studying the needs and preferences of patients with COPD, of their caregivers and health -practitioners; prepared by the Fundació Josep Laporte within the framework of the Aula Respira project of the University of Patients, with the collaboration of the Spanish Patient Forum, has been used.

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1. The disease and its diagnosis

Chronic obstructive pulmonary disease or COPD includes a series of chronic respiratory illnesses. In the information that we are now developing, an explanation is given on how our respiratory system works, what the disease consists of and how it is diagnosed.

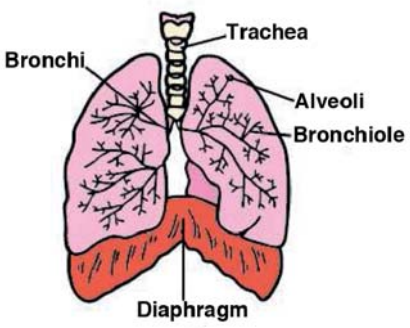
How do we breathe?

In order to understand why COPD develops, it is important to know how the breathing process works and the role played by our lungs.

The ***respiratory system*** is comprised of respiratory tracts, in other words, nostrils, pharynx, larynx, trachea, bronchi and bronchioles.

The ***trachea*** is a pipe measuring 12 cm long approximately. It is situated in front of the oesophagus. The bronchi are the two tubes into which the trachea is divided. They penetrate the ***lung*** where they form many different ramifications until they form the ***bronchioles.*** These end in tiny air spaces or ***alveoli*** surrounded by ***capillaries***.

The lungs are two pink-coloured spongy organs and they are located on both sides of the heart, protected by the ribs. Each lung is divided into lobules. The right lung has three lobules and the left lung only has two so that the heart can fit in. They are coated with a layer of protective tissue (the pleura) which protects them rubbing against the ribs.



The function of the lung is to help you breathe and to this end two activities must be taken into account. The human body is made up of millions of cells, which, in order to work correctly, require oxygen. When we take in air, or breathe in, the lungs transfer oxygen to the blood stream for it to be sent to the whole body. But, the bloodstream also contains carbon dioxide which is a waste product of the organism and which must be eliminated on a regular basis. When we breathe out or exhale the lungs eliminate this waste.

For our organism to work correctly the oxygen must penetrate the blood and the carbon dioxide must abandon the blood at a regular pace. This exchange takes place in the alveoli. When the alveoli are full with the inhaled air, the oxygen is disseminated towards the blood of the capillaries, which is pumped by the heart to all the tissues of the body. Carbon dioxide is disseminated from the blood to the lungs from where it is exhaled.

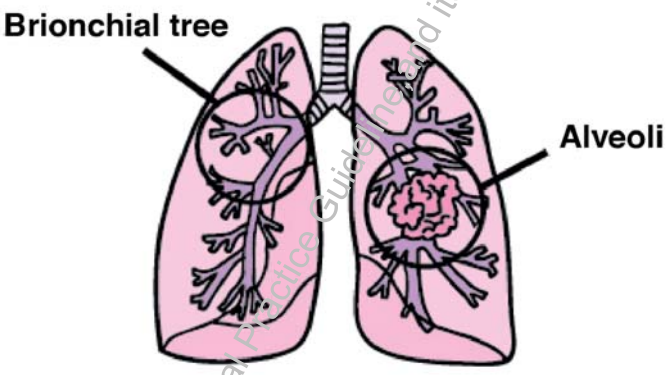
It seems complicated but breathing takes place without us having to think consciously about it. Alveoli are elastic. When we breathe, each one of them fills up with air like a small balloon. When we exhale, they deflate and the air comes out.

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What is COPD?

Chronic obstructive pulmonary disease (COPD) is a chronic respiratory disease that can be prevented and treated. As its name suggests, it affects the respiratory system, in which an obstruction to the airflow takes place, making it difficult to empty the air out of the lungs. This harm leads to the bronchioles and the alveoli losing elasticity, destroying the fine walls of the alveoli. The bronchi get thicker and the lungs manufacture more mucus than normal, which leads to the obstruction of the respiratory tracts.

When the damage is serious, it becomes more and more difficult to breathe and therefore complicated to take sufficient oxygen to the blood and eliminate the excess of carbon dioxide effectively. With time, the damage and the inflammation become chronic.



In Spain, studies show that more than 10% of adults between the ages of 40 and 80 suffer from this disease (15% in men and 6% women); although the figures vary depending on the different geographical areas. It is estimated that more than 2 million Spanish people in this age range suffer from COPD; and that there may be more than one and a half million who have still not been diagnosed and therefore do not receive any treatment for their COPD. The number of people with COPD increases due to population ageing and above all, to the increase in number of smoking female population.

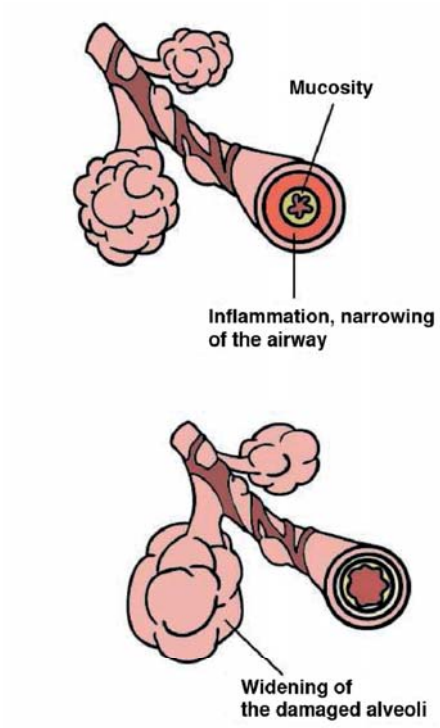
Chronic obstructive pulmonary disease (COPD) is a chronic disease of the lungs; therefore, it is not cured but it can be prevented and treated. Taking control of the disease and improving its prognosis is in your hands.

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What types of COPD exist?

COPD is a term that includes chronic bronchitis, emphysema and a combination of both conditions. Each one of these conditions, which contains the same disease, has different forms of beginning and evolving, which we sum up below.

In ***chronic bronchitis***, an obstruction of the respiratory tracts takes place because the bronchi are inflamed and produce large amounts of mucus. The inflammation and the mucus make it difficult to breathe because the inside of the bronchi gets narrow or closes, which in turn makes it difficult to expel excess mucus. The bronchi also easily become infected.



Emphysema, on the other hand, entails damage to the walls of the alveoli of the lung. There are more than 300 million alveoli in the lungs. These are like small elastic balloons. In emphysema, the walls of some of the alveoli have been damaged, which makes them lose their elasticity and more air gets trapped inside them. As it is difficult to expel all the air from the lungs,-because they are not efficiently emptied, these contain more air than normal. This retention of air causes the lungs to swell up obstructing the respiratory tracts. The combination of constantly having additional air in the lungs and the extra effort required to breathe, is what makes people have problems breathing and thus the symptoms of the disease appear.

What are the symptoms?

The first symptoms begin with ***coughing*** and ***expectoration*** followed by ***difficulty to breathe*** or ***dyspnoea*** and with ***fatigue*** or ***breathlessness*** when walking or when physical activity is increased, such as, for example, going up stairs or walking up a slope. Bit by bit the person, without realising that he has the first symptoms of the disease, stops doing those tasks that require greater efforts and that caused him the breathlessness, and with time tasks such as getting dressed or having a bath represent an effort. As the amount of oxygen in the blood decreases and the carbon dioxide also increases because it has not been eliminated, other symptoms are suffered such as a feeling of exhaustion, lack of concentration and even pressure in the chest. If the heart and circulation continue to be affected, swelling or oedema in ankles and legs may occur.

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People with COPD have a greater risk of suffering a heart disease, because COPD and heart diseases often go hand in hand. In the long-term, tobacco addiction is one of the greatest risks to suffer both diseases. Controlling these factors and others that may be suffered will improve this situation.

People who suffer from COPD may initially think they have just got a slight cough, normal in smokers, or that everything is due to age or to not being in good physical conditions, but COPD symptoms are usually present constantly from the start and they slowly but progressively get worse over the years.

If you are one of the many people who suspects or suffers any one of these signs or symptoms of COPD, you should go to your health centre for the disease to be correctly diagnosed and prevent greater harm to the respiratory tracts.

COPD is a ***preventable and treatable disease***. Although it does not have a definite cure, the symptoms, however, can be controlled to improve the quality of life. Damaged lungs and respiratory tracts cannot be repaired, but all the symptoms of COPD can be reduced if the right measures are taken and you actively collaborate. By doing this you will increase your years of life and the quality of these years. This depends on you and on the degree of control you take over your disease.

You must learn not to avoid an activity just because it causes a sensation of breathlessness or dyspnoea. This may mean that the COPD is taking control and that you are reducing your control over your breathing problem.

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What are the causes of COPD?

There are several factors that intervene in the appearance of COPD. The main factor is smoking or breathing in tobacco smoke for a long period of time. In fact, in the majority of people who have COPD, smoking is the main cause. However, the reason why some non-smoking people develop COPD and some smokers will never have the disease is not completely known.

Tobacco produces harm because, when you smoke, the irritation of the respiratory tracts is maintained for a long time. The respiratory tracts of the lungs do not work as they should. It is more difficult to move the air from the lungs. The mucus glands produce excess mucus which accumulates in the lungs and becomes more and more difficult to eliminate. Therefore, coughing increases and, once again, the production of mucus increases, too. The excess mucus that accumulates in the lungs favours the growth of bacteria, -as in a stagnated pond- and frequent infections take place. Interrupting or stopping smoking may curb this vicious circle from the very start.

There are other factors that increase the risk of developing the disease. Inhaling certain substances that irritate the lungs, such as smoke, some types of dust and vapours from chemicals at the workplace; air pollution in outdoor or indoor spaces, as well as the fuels used for cooking and heating badly ventilated homes, are some examples. In some cases, hereditary or genetic questions also have an influence, such as deficiency in a protein that protects the lungs. The influence of age must also be taken into account. As COPD develops slowly with time, the majority of people are over the age of 40 when the symptoms appear.

The majority of the causes that produce COPD can be prevented.

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How is COPD diagnosed?

It is often difficult to diagnose COPD in its initial stages. Faced with the presence of the symptoms that we have described above, the disease must be suspected. To diagnose it, the doctor will take into account your clinical history and medical tests such as a spirometry. chest X-ray and other laboratory tests. If necessary. other tools can be used at your health centre to evaluate and establish the diagnosis of the disease.

Clinical history: You will be asked about your symptoms, such as coughing, spittle, difficulty to breathe or dyspnoea; when they appeared for the first time or how long you have had them; if they appear with exercise; if you have had asthma, if you are a smoker or ex-smoker. Also about aspects of your family history or if you are exposed to risk factors related to the disease such as pollution or chemicals.

Physical exploration: This is the physical examination. The doctor will examine you and listen to your chest, your breathing, your heart and will explore other parts of your body to exclude the possibility of other conditions giving rise to the symptoms. All of this helps diagnose the disease and know if your symptoms can be caused by something else other than COPD.

Spirometry: This is a test that measures the pulmonary function. It is one of the most important tests to determine if a person has COPD. The spirometry can detect COPD even in people who still have no symptoms, so it is performed on patients in whom COPD or other respiratory diseases are suspected.

During the spirometry, first of all you have to breathe in deeply and then breathe out, as strongly and as quickly as possible, inside the tube connected to machine called spirometer. The spirometer measures the velocity and amount of air that enters and can be expelled from the lungs. This test is used to confirm the diagnosis and know the severity of the disease. Once COPD has been diagnosed, this test is repeated to monitor the state of the disease over time and response to treatment.



Laboratory tests: Blood analyses are carried out, measuring the number of red and white blood cells, the level of urea, sodium, potassium and other important values to know your state of health.

Chest X-ray: This provides us with an image of the lungs. It is useful to diagnose the disease and rule out other diseases such as pneumonia or pleural effusions, which may cause the symptoms.



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More complicated radiological tests are sometimes requested:

Computed tomography or CT scan: The computed tomography is a radiological test that permits capturing many detailed cross-sections of the lungs to evaluate the structure of the respiratory tracts and the pulmonary tissues. This is usually recommended if there are doubts about the diagnosis or in some people with COPD who have been selected for surgery.

Other pulmonary function tests can also be requested in some cases:

Body plethysmography: This is a test that measures the lung volume. It measures the amount of air that remains in the lung after forced expiration, or in other words, if air is trapped in the lung. Therefore, it permits knowing the value of the total lung capacity. It is generally done sitting down in a hermetically sealed booth.

Oximetry: This measures the amount of oxygen (or saturation of oxygen) in the blood. To do so, a device called pulsiometer is used, which is fastened to the finger or to the ear lobe. It is not a painful test and it does not entail any risk as it measures the oxygen with light rays.

Arterial blood gas: This permits obtaining data directly from the arterial blood about the level of oxygen and of carbon dioxide. It is performed by obtaining a blood sample either from the artery in the wrist, the femoral artery in the groin or the brachial artery in the arm.

Sample of sputum and secretion culture: When bacterial infection is suspected, the analysis of a sample of sputum and its culture may be requested. This test consists in collecting the mucosity or mucus that the patient expels with the cough, to analyse its content. This makes it easier to select the antibiotic that is going to be used against the infection.

Sleep study by polysomnography: This is a technique that records throughout the entire night different aspects related to the patient's sleep and breathing. It is used for people with COPD when sleep apnoea is also suspected. The doctor will place electrodes on the chin, the scalp and on the outer edge of the eyelids, whilst the person sleeps. Monitors are placed on the chest to record heart rate and breathing. The number of times the person stops breathing (apnoea) will be measured.

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2. Living with COPD

It is important for people with COPD to remain in the best possible health conditions. With the information we provide below you will be able to see how many things you can do to improve your quality of life.

How to live with COPD and how to manage the disease?

COPD is a progressive disease, in other words it worsens with time if the causes are not prevented and it is not treated correctly. Although it is not a curable disease, stopping smoking, following the pharmacological and non-pharmacological treatment as well as other advisable measures are efficient to manage, control and slowing its progression. It is possible to live well with COPD. When the person suffering from COPD takes control over the disease, it is possible to improve symptoms and quality of life. Everything depends on you taking control.

Remain active

With COPD, it is possible that you have fear of that exercise causes more difficulty for you to breathe and breathlessness or that this cause you some harm. This is not true! Doing regular exercise can help you improve your breathing because making your lungs work through physical activity improves symptoms such as dyspnoea and fatigue. The activity will also strengthen your arms, legs, trunk, heart and, in general, your physical condition. This, in turn, will mean that the activities of daily living will cause less tiredness and that you will have greater vitality, and thus the inactivity cycle is inverted, that is, “the less you do the less you want to do or can do”.

What exercises must I do?

The type of exercise depends on your personal situation and on your symptoms. The first thing you must do before starting any activity or exercise programme is to consult your health professional and prepare an individual plan with him. The aim is to carry out some type of activity for at least 20 or 30 minutes almost every day, periodically changing the exercises to avoid routine boredom. Try to do the exercises in company but without effort and at your pace. Propose feeling satisfied and if you should have problems when you carry out the activity, consult your doctor or nurse or physiotherapist.



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You can carry out activities such as walking, swimming, cycling or exercising on a static bicycle at home, dancing and other mild activities. Everything will depend on your preferences. You must start with simple activities, such as walking. Then, you can increase your activity level and consider carrying out exercises to strengthen your legs, such as static bicycle or going upstairs. These exercises will also help you increase your muscle tone and flexibility. Then, to strengthen the upper part of your body you can carry out light exercises with weights, to improve the strength of your respiratory muscles, the muscles of your arms and shoulders.

COPD makes it difficult for the heart and lungs to take oxygen to all the parts of the body. Exercise improves the use of oxygen, it strengthens muscles, decreases fatigue and helps control dyspnoea. Do things bit by bit, take your time and control your breathing. When you do exercises you may have a feeling of breathlessness, but that "breathless" feeling with exercise is normal. With practice and time this feeling will decrease and you will tolerate exercise better. In any case, tell the professional who looks after you about the exercises you are carrying out and your progress. Below we give you an example of a simple exercise to carry out at home. Ask your doctor or physiotherapist about other exercises that you can also do at home.

Example of exercise to go upstairs
• Stand on the first step and breathe in through your nose.
• Go up the steps that you can (1, 2 or 3), blowing.
• Stop and take in air through your nose again.
• Carry on going up and blowing (1, 2 or 3).



To help you remain active, there are associations of patients that periodically organise activities, which will also enable you to get to know other people with COPD. At the end of the document, check the section on additional information and resources.

Respiratory rehabilitation

If you have been diagnosed with COPD, your doctor must offer to include you in a pulmonary or respiratory rehabilitation programme. Respiratory rehabilitation is generally comprised of physical training and psycho-education, but it is usually accompanied by other interventions, such as strategies to stop smoking, training respiratory muscles, training to clear up the respiratory tracts, managing medication, nutritional advice, motivation strategies and psychological support. This therapy will improve your exercise capacity and your quality of life, helping you manage and know how to live with your disease.

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There are different rehabilitation programmes that vary depending on their duration, the type of exercises used and the work that you must also do at home. The programmes usually last for several weeks, once or twice a week. Depending on the severity of COPD, you will require one or several components of the programme. The team attending to you will inform you of what is the best treatment. Each programme is organised and coordinated by a health professional, who is usually a nurse or physiotherapist. With the respiratory rehabilitation programmes people with COPD can experience great benefits such as less need for medication, reduction in hospital stays and visits to the doctor, less dependence on others, controlling anxiety and stress. If you commit to the programme, the benefit you will obtain, apart from being greater, will last longer.



For people with COPD, pulmonary rehabilitation is a very important as part of the holistic treatment of your COPD. If you engage in the respiratory rehabilitation programme, your exercise capacity, your physical condition and quality of life will improve.

Breathing control

Breathing control forms part of a normal respiratory rehabilitation programmes. It is very useful to learn to control your breathing. Control permits combining relaxed and gentle breathing, using the lower part of your chest or diaphragmatic breathing, relaxing the upper part of your chest and shoulders. With practice, you can use breathing control to get your breath back after physical activity or during an episode of breathlessness. You can use it, for example, to help you, if you are going out for a walk and have to stop and rest because you notice breathlessness. It also helps you to maintain a more normal breathing pattern and makes air enter the lower part of your lungs.

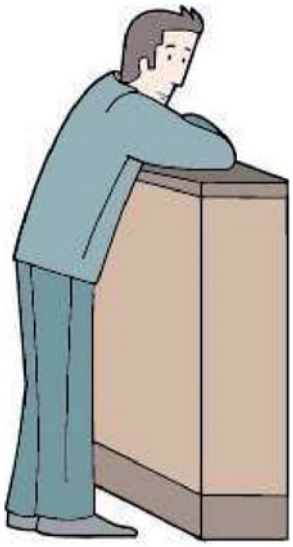
Learning to control your breathing is done by combining two techniques. The first consists in breathing by pursing your lips. To do this:

1. Relax your neck and your shoulder muscles
2. Breathe in slowly through your nose and count to 2 in your head
3. Purse your lips, closing them but not tight
4. Let the air out slowly counting to 4 or more

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The second technique is called diaphragmatic breathing, and to do this:

1. You must get into a comfortable position and relax your neck and shoulders
2. Place one hand on your chest and the other on your abdomen
3. Take air in through your nose counting in your head to 2. You must feel your abdomen relax and your chest still.
4. Breathe out using your abdomen counting to 4.
   You must feel your abdomen contract and your chest still



You must practice these techniques until you get used to them. To do them, you can use different positions such as sitting down, lying down, standing up or resting on ledges or on furniture or with your back to the wall. Try to find the position that it suits you best.

These techniques not only help you relax but also introduce more air into your lungs and empty them more effectively. With diaphragmatic breathing, we especially manage to fill the lower part of the lungs with air. If you carry out these exercises on a routine basis you will manage to interiorise them until you finally get your breathing to be more normal and effective.



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Nutrition: eating and diet



It is important to have a balanced and healthy diet, which will help you to keep healthy. Maintaining an adequate weight is very important to control COPD. If you are overweight or too thin, or if you suffer malnutrition, are all harmful for the evolution of the disease An adequate and healthy diet will help you achieve your optimal weight.

For a healthy diet you are recommended to
• Eat light and not very copious meals, several times a day (4-6 times a day) with food that is easy to chew and eating slowly. As your stomach is directly under your lungs, eating a copious meal may push against the diaphragm and make breathing more difficult.
• Drink a lot of liquids to keep your respiratory tracts clean and to keep mucus thinner. The best drink is water and approximately one and a half litres a day should be drunk.
• Prevent constipation. Your diet must be rich in fruits and vegetables, increasing the intake of wholemeal cereals.
• Steam, boil or grill food instead of frying it.
• Eat slowly. Take your time in order to enjoy your meals.
You must avoid
• Eating food that takes a long time and is difficult to chew, as well as food that produces wind and/or heavy digestives (cabbage, cauliflower, onion, sparkling drinks,…). These foods may make your stomach swell and press against your diaphragm.
• An excessive intake of carbohydrates (bread, potatoes, pasta, rice,…),
• Eating very cold or very hot food, or food that, based on your experience, causes irritation to the throat, because these may cause coughing and/or breathlessness.
• Talking too much while you are eating.

If you are **overweight**, losing those extra kilos will help you a great deal in breathing better because obesity can increase dyspnoea. It is like a vicious circle. If you are obese, the thoracic wall and abdominal wall are heavier due to the accumulated fat and this means that you have to work a good deal more to breathe well, to inflate your lungs and expand your chest. It is advisable for you to seek help from a health professional to have a healthy diet and manage to lose weight. You must not be in a hurry or try to find “miracle diets” which may be harmful, as the best way to lose weight is to do so slowly.

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Apart from the diet, there are exercises that can help you, such as a short walk every day, or make an effort to go from one place to another by foot, using the car or bus as little as possible. You can check the above sections on exercise and physical activity to know what exercises you must carry out.

If you have malnutrition or are too thin, the problem will probably get worse if you have COPD. If the effort to eat, even though the quantities are small, causes you to choke, you will stop eating and as a result you will not nourish yourself correctly or cover your energy needs. Furthermore, it is easy to lose more muscle mass when you lose weight. For example, you should eat small amounts whenever possible. It is good to keep high calorie snacks at home to eat from time to time such as nuts, crisps, cheese, biscuits, yoghurt, ice cream, sweets or chocolate; or also drink high calorie drinks such as milk, chocolate, energy drinks and diet supplements from the chemists. Drinking liquids with a small straw requires less effort than drinking from a glass or cup. It is recommendable to seek advice from your doctor about patterns and possible nutritional supplements.

Sleep comfort

Many people with COPD find it difficult to breathe at night. This may frighten them and produce anxiety making it even more difficult to breathe. Knowing that this can occur may help you calm down when it happens. To cope with it use the following advice:

- If you wake up breathless, sit down and lean forwards for example on the edge of the bed, resting your arms on the bedside table.
- Keep a fan near your bed and switch it on if you feel breathless.
- Keep your medication near your bed in case you need it.
- Try to control your breathing. Do not force it.
- Relax your shoulders. Tensing your muscles will only make you use up more energy.
- Perhaps you will sleep better if you are higher up in bed.

Lie on your side and place pillows as shown in the picture.



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COPD, combined with factors such as obesity, smoking or consumption of alcohol, among other things, may contribute to some people having a sleep disorder called sleep apnoea-hypopnoea syndrome (SAHS). In SAHS, whilst the person affected sleeps, an obstruction of the upper airway occurs and therefore the air flow towards the lungs, which produces symptoms such as excessive somnolence during the day (the person involuntarily falls asleep during the day and when carrying out normal activities), the feeling of not having rested during the night, snoring, morning headaches, irritability, attention and memory problems. Consult your pneumologist if you have these symptoms.

Anxiety

Lack of air or dyspnoea, typical of COPD, is not always associated with making an effort. If you find it difficult to control your breathing this can cause you anxiety. Your breathing becomes quicker and other systems may appear at the same time such as palpitations, oppression, nausea, sweating, dizziness, and even fainting. These symptoms also contribute to making your breathing worse and for your anxiety to increase, which may sometimes cause a crisis of angst or a panic attack. Thoughts such as the following may occur to you: What will happen to me if I have symptoms of anxiety in public? What will happen if I cannot control myself or if people do not know how to help me?

Thus, anxiety causes a considerable worsening of your disease. Taking control of the dyspnoea and learning to wrestle with anxiety and panic attacks will help you continue with your daily activities and know you have more energy to do things and cope with these situations. The following advice may help you to achieve that.

Advice to manage your anxiety

- Rationally plan your daily tasks, prioritise your needs, think about one day at a time.
- Try to leave a space every day to include tasks that you find pleasant such as reading, listening to music, doing a bit of exercise or walking.
- Learn to handle your feelings. Positive thoughts also have a positive effect on your state of mind.
- Practising breathing control exercises and some relaxation techniques will help you cope with stressful situations that might arise.
- Learning to relax when you start to feel stress will mean that you are less likely to feel anxiety.

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Below, we suggest a simple exercise.

Relaxation exercise
• Close your eyes. • Concentrate on your breathing. Breathe in deeply through your nose and slowly breathe out through pursed lips. • Learn to recognise the tension in your body. First clench your fist strongly. Then slowly open your fingers and feel the tension leave. Your heart will feel lighter and more relaxed. • You can do the same to relieve tension in your entire body just by contracting and relaxing a group of muscles every time. • Every time you breathe out think about relaxing. Imagine that clouds are passing over your head and that you mentally write one of your concerns on each of them so that the wind blows them away.

How to combat a crisis of anxiety?
• It is important for you to remember that what you are feeling is only an exaggeration of the normal reaction to a crisis of anxiety. • You are not facing an important risk, nor is it as serious as you may believe. Nothing worse is going to happen. • Do not let the panic increase with other daunting thoughts. Interrupt what you are thinking and you will see that, in this way, the fear begins to disappear on its own. • Tried to calm down and relax progressively. • Practice slow and relaxed breathing. Imagine that it is a balloon that you are slowly blowing up and then it deflates. • When you start to feel better and ready to carry on, begin in a calm and relaxed manner. There is no need to hurry or make an effort. • Try to amuse yourself now that the nervousness has decreased.

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Depression

It is very common for people with COPD to feel depressed. Your disease can reduce your capability to work or it may make you give up activities that you used to enjoy, making you lose your self-esteem. If you add physical limitations to this you may also get the feeling of being isolated or locked in. Depression can affect both your state of mind and the way you cope with your daily life. You may feel as if you do not want to get up in the morning or do not want to go out of the house or see relations or friends. You may start to notice symptoms such as sadness or attacks of crying, loss of self-esteem and of interest in life, mood changes, tiredness, loss of energy, concentration difficulties, changes in appetite, lack of motivation, feelings of impotence and despair, and sleeping problems. Some of these symptoms are similar to those caused by COPD. Therefore, if you think that you may be depressed, comment on it with your family and talk to a health professional about your mood as soon as possible. Mild depression may improve with good advice on how to cope with your problems. Bear in mind that for people with COPD to continue to have good health, this depends to a great extent on trying to be active. If depression is treated, you will quickly feel its benefits and your quality of life will increase substantially. Below, we give some recommendations that may be useful to you.



Advice to manage your depression
• Plan on a daily basis. It may be really difficult to start and do something. However, the more active you are the more likely you are to feel better.
• Make a list with the activities you propose carrying out every day; do not be too demanding of yourself.
• Plan some physical activity every day.
• Also plan to carry out a gratifying activity at least once a day.
• If you fail to carry out any point of your plan continue with the next activity.
• See how your mood varies depending on the progress you make and share them with others.
• Enjoy little things.
• Maintain a routine in your sleep times and carry out something relaxing before you go to bed.
• Abuse of alcohol, tobacco and other drugs may make your depression get worse and generate other problems.

If indicated by your doctor, in some cases the use of antidepressants may be useful. Depression can be treated successfully.



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You can also go to an association of patients, where they can also give you advice. For many people, attending mutual aid groups with other family members or people who have the same problem helps them overcome depression.

Sex and relations

Although problems of lack of energy and oxygen, coughing and dyspnoea may affect your interest in sex, COPD does not decrease sexual ability. Sometimes you may feel that it is better to avoid sexual relations because they may be too "dangerous" for your health; but sex, just like other physical activities, is not dangerous for your lungs. You must know, however, that slight increases in heart rate and breathing are normal during this activity, but they are not dangerous. And, it is also important that, together with social relations, you should maintain this type of activity to help you fight against the solitude and isolation that you may feel on suffering from COPD. Talk to your partner about how you feel and about any concerns you may have. Thus, it will be easier to cope with the situation before it becomes a problem. Do not hesitate to visit your doctor and ask during one of your visits about the limitations and problems that the disease causes you in your relations or any questions you may have in this regard.

Some advice to help you and that you must bear in mind about your relations:

• Do not start to have sex immediately after a heavy meal or after consuming alcohol or when you are stressed.

• Make sure the temperature in the room is adequate.

• Begin with a prior period of rest, carrying out breathing, relaxation and bronchial hygiene exercises.

• You may use your rescue medication if you need it before and after having sex.

• Control your breathing in the same way as you would with any other activity, and stop and rest if necessary.

• Choose a comfortable position that does not make breathing difficult or represents too much effort, avoiding pressure on your chest (for example, on your side, or in positions where your partner assumes a more active role).

However, remember that relations with your partner are not exclusively based on sexual relations, but that other aspects such as communication, intimacy, kindness, support and feeling loved by your partner is essential.

You must bear in mind that some medications, such as those used for high blood pressure, antidepressants and oxygen therapy equipment may have a negative effect on your sexual desire. Talk to your doctor to see if your medicine has a side effect. Consult the possibility of using Viagra or similar medication that are not generally contraindicated in people with COPD. Bear in mind that if you control your disease and plan suitably you will have more confidence in maintaining your sexual activity in agreement with your partner.

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Leisure and travel

You must not relinquish enjoying leisure and travel during your holidays. Foster relations and maintain an interest in carrying out leisure-social activities, take an interest in other people with your disease or other similar diseases, share entertainment with other people such as going to relaxation classes, listening to music or going on outings or travelling.



You can travel to go on holiday even though you have COPD, taking some precautions into account. It is advisable to prepare in advance. Consult your needs with your doctor and with the travel agency. For example, your doctor will help you get oxygen or other medications necessary during your trip and will inform you if you must adapt the dose of your treatment. Plan your holiday place. If you want to travel to places with extreme temperatures, choose milder times of the year. You must take into account the altitude of the place where you are going. It is advisable, in general, not to go to places that are more than 1500 m above sea level to prevent a lack of air and oxygen due to the altitude.

You must reach the airport or train or bus station early and not carry heavy luggage. You may request a wheelchair to facilitate your transport in advance.

If you are travelling by car, you must place the oxygen equipment in an upright position so that it does not fall over. If you are going to travel by ship, train or bus, take the same precautions as in the case of the car. In these cases, it is advisable for you to get in touch with the transport company some weeks before starting your journey to get information about the regulations to be complied with, respect to the use of oxygen equipment.



If you are going to fly and require oxygen during the flight, you must notify the airline company. There are many airline companies that, by notifying this sufficiently in advance, provide aid to people with breathing problems such as COPD. Put your medication in your cabin luggage to make sure you have got it in case there are delays or you lose your luggage. Take a medical report that includes your needs and treatment.

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Organise your time. Carry out daily tasks that require the greatest effort at times of the day when you have more energy. At a constant pace even though this is slow, you will consume less energy. Be flexible and rest from time to time. By planning your tasks in advance you will avoid having to hurry.

Organise the way you do things better. Use a trolley to carry your shopping or to pick up and move household things. Buy small amounts and more often so that you do not go home with too much of a load. Maintain a good posture, trying not to bend over. When you use your hands to carry out a task, such as preparing a meal or reading the newspaper, rest your arms on a surface.



Organise your space. Put the utensils you use the most in drawers or on shelves that are at a comfortable height and keep them in the place where you normally use them, to prevent unnecessary searches and carrying. Avoid lifting objects and doing things that require you to raise your arms.

Getting dressed. You must wear clothes according to each time of the year not exaggerating the number of garments, which must be loose and easy to put on. Do not use belts, corsets or any other garments that may compress your chest or abdomen. It is recommendable to use braces and shoes without laces.

Having a bath or shower. You must pay attention to your personal hygiene even though this activity may cause breathlessness or fatigue. To make things easier you can put a stool in the bath and sit down to wash yourself. Do it slowly. A relation may help you wash the more difficult parts. Use small towels to dry yourself.



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Your work and environmental setting

Irritating substances. Some things in the air that you breathe, in your surroundings, may cause irritation to the lungs. It is almost impossible to completely avoid all irritating substances, but it is possible to protect yourself from contaminated environments with tobacco smoke, sprays, paints and solvents, dust, gases and traffic pollution, pet hairs, insecticides, lacquers, air fresheners and strong perfumes. Try to keep your home a "smokeless area", both for you and for your family members or friends.

Temperature. Cold and changes in temperature can be a real problem for some people with COPD. Try to keep all the rooms of your house at the same temperature, especially your bedroom. Going from a warm room to another colder room may cause dyspnoea. If you go out on a cold day, wear a scarf to help warm the air you breathe.

Dry environment. Some people with COPD are affected by environmental dryness. Some heating systems can dry up in the air. Keep the atmosphere humid by placing containers with water near radiators or using a humidifier.

Damp environment. Too much humidity in the house may also cause an important problem for people with COPD. Mould, dust, mites and bacteria depend on humidity to develop and they may cause you respiratory irritation. This can be avoided by good ventilation or by having a dehumidifier. If it is not solved, the origin of the humidity must be identified and corrected. To do this you can consult a plumber who will give you guidance about the humidity problem and how to solve it.

Work and COPD. There are certain jobs or hobbies that, due to exposure to gases, dust and toxic fumes, are a risk factor and therefore favour COPD. Jobs in mines, quarries and foundries are some of the ones that represent the greatest risks. If you think that your problem may be related to your work, you must ask your doctor for him to refer you to a specialist for consultation.

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Stopping smoking

Stopping smoking forms part of the treatment of COPD. Stopping smoking is the only efficient measure to curb the progression of COPD, regardless of how long ago the disease was diagnosed and of its severity. It is the best measure that you can take to improve your life with COPD; although it may be one of the most difficult things you have tried to do and it may be difficult for you to achieve the first time round. Stopping smoking may slow down the progression of the loss of pulmonary function. The benefit is stopping smoking is greater the sooner you stop. People with COPD who carry on smoking, even with the best treatments, contract more infections and their symptoms progress and get worse.

Smoking, and probably exposure to tobacco smoke in childhood, compromises the growth of the lungs, causing a reduction in the maximum pulmonary capacity in young adults. Furthermore, passive smoking is a risk factor and may be the cause of some of the cases of COPD that are seen in non-smokers.

You may lack the necessary motivation to stop smoking or you may think that it is already too late for you; and that you also feel to blame for it. You can always count on help from your health team. A personalised programme can be prepared that will include medical and psychological advice and even, if necessary, pharmacological treatment. With help, managing to stop smoking will be a success and they can also give you encouragement and support to prevent a relapse.

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Information for caregivers or for people who live with the patient

Living with COPD can include difficult moments. And your family must sometimes make an effort to cope with significant changes that may be necessary in daily or leisure activities.

People with COPD must try to maintain a good family climate. You can help them do this by sharing their fears and feelings. They must assume responsibility for their disease and not demand or make their caregivers, or the people live with them take responsibility for their state.

The following advice may be useful for caregivers or people who live with patients with COPD, to manage the disease and help them:

Try not to be overprotective. You cannot give them their health back, but, if you protect them too much, they may feel as if they were invalids.

Try to be positive. There will be bad days; but do not get discouraged. Remember that negative thoughts

Try not to be overprotective. You cannot give them their health back, but, if you protect them too much, they may feel as if they were invalids.

Try to be positive. There will be bad days; but do not get discouraged. Remember that negative thoughts are only that, thoughts, not facts.

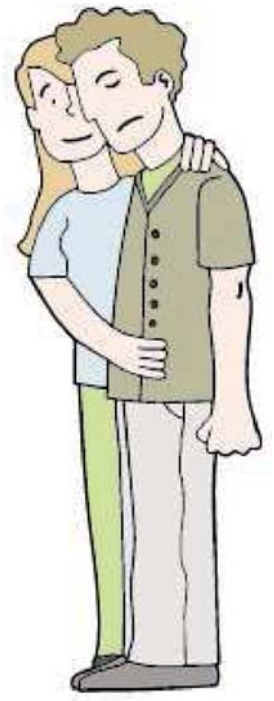
Search for information about COPD.

If you consider that you need counselling or information about other types you can be given, look for advice from a social worker at your health centre.

You can find help and advice from people who have had similar experiences at associations of patients. pacientes.

If it is your partner, bear in mind that: that

You must try to keep the disease from taking over your lives. Your partner is not a victim and neither are you. You are not responsible for the COPD of your partner. Be honest with your partner and with yourself.



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Make a list of activities that you can enjoy together.

Take time for yourself, finding things that stop you thinking about your partner's disease.

Find a moment to take a rest or break, too, carrying out some recreational activity outside the home. To do this, ask for help from your relations or friends or from some association of patients. In this way you will not feel so oppressed by leaving your partner alone.

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3. Treatment and control of COPD

Although the treatment of COPD may not eliminate the symptoms altogether, you can control them and slow down the progression of the disease. The majority of patients require continuous treatment to keep their symptoms under control. The term "chronic" in COPD means that it persists in time. Breathlessness or fatigue may not disappear altogether; however, people who suffer from COPD can learn to control their disease and carry on living a full life with adequate treatment.

Stopping smoking is the only efficient measure to slow the progression of COPD. Below we present other options for treating the disease.

What are the treatment options?

o Pharmacological treatment

Pharmacological treatment may improve the symptoms of COPD, increase exercise capacity, reduce the number and severity of exacerbations, and improve patients' quality of life. However, nowadays there is no treatment that is able to completely cure the disease. It is important for you to understand what your medication does for you and that it must be taken regularly and constantly for it to improve your breathing and other symptoms.

Below we briefly explain the medical treatments that are commonly used to treat COPD.

• Bronchodilators: They are used to prevent and revert the hardening of the muscles that surround the respiratory tracts or bronchospasm. They increase the diameter of the bronchi when these have become narrower, thus reducing the obstruction and improving the passage of air to the respiratory tracts. They reduce the feeling of breathing difficulty. There are two types: Short-acting, that last between 4 and 6 hours and long-acting that last for 12 hours

• Muscarinic receptor antagonists: Although they, like the bronchodilators, act upon the respiratory tracts, their pharmacological action mechanism is different and they take a bit longer to take effect. They are normally inhaled.

• Anti-inflammatory drugs: They are used to reduce the inflammation of the respiratory tracts. They must be taken as prescribed by your doctor, preferably in the morning and reducing the dose as indicated.



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This is the main action mechanism of corticoids. Corticoids can be combined with a bronchodilator. If the hardening and inflammation of the respiratory tracts are controlled, they will improve problems such as wheezing and breathlessness.

Apart from you knowing which drugs are used in the disease, it is important for you to know how you must take them, either by inhalers, sprays, dry powder, pressurised cartridges, nebulisers or inhalation chambers. You must know how the medicines are prepared and administered with these devices. Read the instructions carefully to know how they work before using them and consult your doctor or health professional if in doubt. Inhalers and other similar mechanisms enable the medication to act directly on the lungs. Thus, smaller amounts of medication can be administered with a similar effect and less adverse reactions.



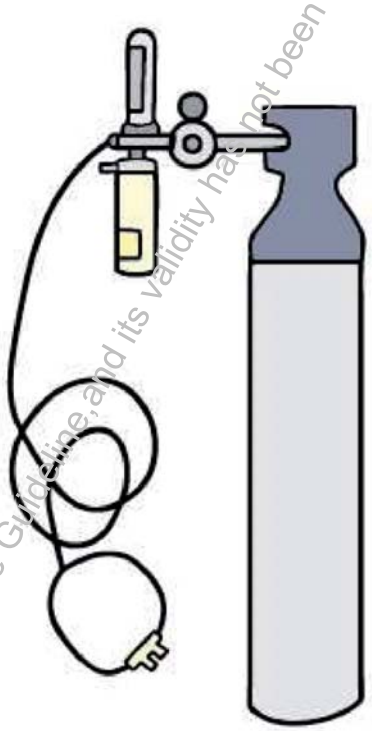
• Antibiotics: They are used to treat the infection and for acute exacerbations or in the case of worsening of the attacks when there is infection. It is essential for you to take your medication at the time and dose prescribed during the time indicated, for it to have full effect and avoid bacterial resistances.

o Non-pharmacological treatment

• Respiratory rehabilitation: Pulmonary rehabilitation programmes offer supervised exercises and education for people with respiratory problems. It is a therapy that produces improvements in aspects such as dyspnoea, exercise capacity and quality of life. It is carried out individually to optimise the physical capacity and autonomy of people with COPD. Several professionals such as physiotherapists or nurses intervene. With the respiratory rehabilitation programmes, people with COPD may reduce the need for medication, hospital admissions and visits to the doctors.

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o Other treatments



• Oxygen: COPD can also cause the level of oxygen in the blood to be low, and if this occurs, supplementary oxygen is prescribed. Breathing air with a greater concentration of oxygen may help reduce some of the symptoms caused by the lack of oxygen. Oxygen improves exercise capacity, sleep and the cognitive capacity of people with COPD.

If you have been prescribed oxygen at home you must use it for at least 16 hours a day (at times such as after meals, after making an effort, when you are at home and also during the night). If used for less than 16 hours, they will not produce any therapeutic benefit. When you have more dyspnoea, use it throughout the entire day. Oxygen has been indicated because you have "low oxygen in blood", and not because you have “breathlessness or fatigue”. Oxygen does not get rid of fatigue or breathlessness but it is an important part of your treatment.

Oxygen can be supplied in different ways, with oxygen cylinders, with concentrator and with liquid oxygen. Both the system that you have to use and way you use it, as well as the quantity of oxygen, will depend on your needs. The indication will be given by the team that is looking after you and it can never be changed because this may “cause harm to your organism” if it does not receive the adequate amount of oxygen.

• Surgery: In some cases of COPD, surgical procedures, such as surgery to reduce pulmonary volume or lung transplants, may be necessary.

• Vaccination: In COPD, the flu virus may cause worsening of the disease. Every year, unless otherwise indicated, you must be given the flu vaccination. In the majority of cases, the vaccination prevents you from suffering flu or, at least, makes it less serious. Visit your health centre at the start of autumn to get information about the starting date of the vaccination campaign. In any case, avoid contact with people with colds or with flu. Try to wash your hands frequently to avoid the propagation of these germs.



The pneumococcal vaccine is indicated in certain people with COPD and reduces the risk of developing pneumonia. Ask your doctor who tell you about the need or not to receive this vaccine. The anti-pneumococcal vaccine is generally administered for the first time in people over the age of 65 and afterwards every five years. Your health team will inform you when you must have it.

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What are the complications of COPD?

Respiratory infection

People with COPD are more inclined to contract respiratory infections. Frequent respiratory infections, if not controlled, may cause permanent harm to the lungs and may even have very serious consequences for the patient. Timely treatment may slow the worsening and the need to be admitted into hospital. To do this, watch must be kept over the symptoms and signs that may make you consider if there is an infection: general discomfort, fever, increase in dyspnoea, nasal congestion, increase of coughing, changes in sputum (if this has increased, if there is a changing colour or consistency). Visit your doctor if you have these symptoms.



However, to reduce the risk of suffering respiratory infections and preventing their complications, you must follow these recommendations:

How to decrease the risk of an infection?

- Make sure you are up to date with your flu and pneumonia vaccines
- Comply with the treatment times and patterns that are prescribed, for example, antibiotics.
- To minimise risk, when you notice any respiratory infection symptom, avoid contact with anybody who is sick and try to spend the least possible time in closed and small spaces where there are a lot of people.

Exacerbation or decompensation

Even when treatment is continuous, there may be moments when the symptoms of your COPD suddenly get worse. This is called an acute *exacerbation*, or *decompensation*, and it may cause pulmonary insufficiency if you do not receive the right treatment. Exacerbations may be caused by a respiratory infection due to virus and/or bacteria, due to a sudden change in temperature, high air pollution levels or due to stopping treatment, among other factors.

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You can identify these situations by being familiar with the alarm signals. Recognising the first symptoms may help you prevent a serious attack and even hospital admission.

Alarm signals of exacerbation

- Greater difficulty in breathing both when carrying out an activity or resting
- Wheezing in the chest
- Changes in colour and quantity of mucus
- More mucus and greater difficulty in expelling mucosity from the lungs
- More serious or more frequent coughing (worsening of cough)
- Cold or flu symptoms, such as nasal secretion, sore throat, muscle pains, shivering, fever or feeling of passing fever
- Appearance of swollen legs (oedemas in feet)
- Appearance of pain (above all in the side)

What do I have to do in the case of decompensation?

In case of decompensation try to follow this advice:

If your doctor has given you an action plan for these cases, start it up. If he has not given you one, ask him about it.

Take the medication you have been told for this situation without exceeding the limits proposed.

Keep calm at home, sit down and rest, leaning forward a little bit. You can also stand up, leaning forward, resting on a shelf or leaning over it a little bit. These postures will help you breathe better.

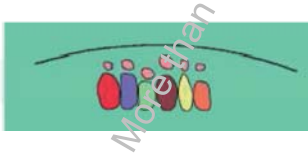
If you use oxygen at home, use it as indicated a day, without increasing it.

Use expectorants for more mucosity to appear.

Drink more water.

If you have oedemas, take less liquids, raise your feet and check the colour of your legs.

Try to expectorate the mucosity.



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Check your temperature with a thermometer.

Do breathing control exercises and respiratory physiotherapy.

Move slowly, in this way "you will save" energy.

Avoid sudden changes in temperature and polluted atmospheres.

Eat light meals, not too much food and often (4-6 times a day).

You must follow the prescription instructions for your medication and finish the antibiotic treatment, even when you start to feel better. Talk to your doctor about your treatment with oxygen, because your needs for this type of therapy may have changed during this time.

Call your doctor immediately if your symptoms do not improve or:• Greater difficulty in breathing both when carrying out an activity or resting

• If you have greater difficulty in breathing and this is not solved with the above measures.

• Your cough gets worse.

• The secretions increase or change consistency (more mucus than normal or thicker mucus and/or impossibility of expectorating them).

• The mucosity changes from a transparent or white colour to green or yellow.

• You bring up blood when you cough or the mucus contains blood

• You have a fever or shivering.

• The swelling of your ankles or legs increases or appears suddenly.

• You have a pain in your chest or side.

• You are irritable.

• You are disorientated.

• You are sleepier than normal

You have headacheAfter recovering from an acute exacerbation, it may be recommendable to carry out pulmonary rehabilitation exercises to recover the physical level that you may have lost after a stay in hospital or in bed. This will help improve your pulmonary function, decrease breathlessness and strengthen your muscles.

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Palliative care

COPD is a chronic disease. Age, the repetition of infections or the fact that you continue to smoke may accelerate or worsen the disease. With time, if the symptoms of COPD become difficult to control, due to the severity of your situation, as occurs in other chronic diseases, the doctor may mention the need to receive specific care for patients in an more advanced phase of their disease or palliative care services. Emphasis will be placed on seeking support to control your symptoms and providing all the help you may need. An assessment of palliative care entails a complete assessment of your symptoms and how they are affecting your daily life, the treatment you are receiving at that time and if you require another treatment that may be useful.

If you require additional information or help, consult your health team or a patient's association.

What must I take into account when I visit my Health Centre or if I go to hospital?

During your visit to the Health Centre or hospital, for the diagnosis, treatment, assessment and control process of your disease, you are going to deal with different professionals. To facilitate the relationship and communication with them, the following suggestions may be useful:

√ Before your appointment prepare what you want to say. You are the person that knows your symptoms the best and your Information may be valuable to the professional attending to you. What you tell your doctor about your problems, activities, family and life style will help him/her determine the best plan to be followed.

√ Preparing a list with the answer to questions mentioned below may be helpful: What symptoms have you got or experience? When have the symptoms started and what makes them get worse or improve? Has anybody in your family got COPD? Have you received any treatment for COPD before this? If so, what was it? Are you receiving treatment for any other disease? Or, what medication do you normally take?

√ Remember that you must always take the treatment that you are receiving with you.

√ Warn about any allergy to medications that you may have.

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√ You must inform about any substance, medication, herbal products or alternative medicine that you are taking for your health problems.

√ Do not be afraid of asking questions if everything is not clear.

√ Ask them to give you the information in simple and understandable language. Clarify the problems that have arisen.

√ You may want to be accompanied to your medical appointment by a family relative or friend. Normally two pairs of ears are better than one when you are learning about a problem with complicated medical terms such as COPD. Take notes if this helps or ask for information in writing.

Bear in mind that you are the most important part of this process, so you should express your needs and preferences both during the diagnosis and with the different treatment options.

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4. Resources and additional information

Where can I learn more about COPD?

Apart from the Health Centre or hospital where you normally are attended, there are other organisations, such as associations of patients and relatives where you can get in touch with other patients and families, and who can offer you advice and help. There are also websites on the Internet where you can find additional information about COPD.

Patient's associations

• APEAS. Patien's association with COPD and Sleep Apnoea

Telephone: 695 468 799 (Madrid)

E-mail: infoapeas@gmail.com

Website: http://www.apeas.es

• ASOCPEPOC – Spanish Association of Relatives and Patients with COPD

Telephone: 671 632 556 (Badalona-Barcelona)

E-mail: epoc@epoc.org.es

Website: http://asocepoc.blogspot.com

• ASSOCIATION OF PEOPLE WITH CHRONIC DISEASES OF RESPIRATORY TRACTS "A TOT PULMÓ"

Telephone: 696 80 65 60

E-mail:atotpulmo@hotmail.com

Website:

• FENAER – National Federation of Associations of Respiratory Patients

Telephone: 630 451 215 (Madrid)

E-mail: Contact: fenaer@gmail.com

Website: http://www.fenaer.es/

• APIR. Association of People with Respiratory Failure

Telephone: 96 3312253//656594695 (Valencia).

E-mail: apir@telefonica.net

• ASPATER

Telephone: 954 171217 / 902 363402 (Seville)

E-mail: aspater@aspater.com

• LOVE AIR

Telephone: 644 458 550 (Cadiz)



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• Alfa 1 Association of Spain (ALFA 1)

Telephone: 981 555 920 (Santiago de Compostela)

Website: http://www.alfa1.org.es

E-mail: secretaria@alfa1.org.es

• AMALEPOC. Malaga Association of COPD

Telephone: 657 57 52 24 (Malaga)

E-mail: epocmalaga@gmail.com

• Spanish Patient Forum

Telephone: 93 433 50 32

Website: www.webpacientes.org/fep

E-mail: foropacientes@foropacientes.es

• University of Patients. Aula RESPIRA

Telephone: 93 433 50 32

Website: http://www.universidadpacientes.org/respira/

E-mail: universitat.pacients@uab.es

Online resources

Other information sources that can be used to increase your knowledge of COPD are:

• Spanish Society of Pneumology and Thoracic Surgery (SEPAR)

http://www.separ.es/pacientes

• European Lung Foundation ELF

http://www.ersnet.org/lrPresentations/copd/files/patients_sp/index.html

• American Academy of Family Physicians.

http://familydoctor.org/familydoctor/es.html

• National Institute of Cardio-Respiratory Health

http://www.nhlbi.nih.gov/health-spanish/health-topics/temas/copd/

• Spanish Society of Cardio-Respiratory Rehabilitation (SORECAR)

http://www.sorecar.org/index.php?idtema=1

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Learning to understand and live with COPD

Information for the patient

The information contained in this document aims to provide advice as well as practical and simple patterns for people who have chronic obstructive pulmonary disease or COPD, their family members and the people who look after them when this becomes necessary. All of this will provide a better knowledge of the disease and will contribute to better care and an increase in your quality of life.

It includes information on COPD, its diagnosis and treatment, advice on how you can manage the disease in your daily lives and other useful resources such as contacts of associations of patients or online resources, which may also help you manage COPD.

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Appendix 2. Acronyms

ATS	American Thoracic Society
CHS	Competences and skills in health (Health literacy)
IC	Inhaled corticoids
CNPT	National Committee for the Prevention of Nicotine dependence
SGRQ	St. George's Respiratory Questionnaire.
CRQ	Chronic Respiratory Disease Questionnaire
HRQOL	Health-related quality of life
MD	Mean difference
RCT	Randomised clinical trial
COPD	Chronic obstructive pulmonary disease
EMEA	European Medicines Agency
ERS	European Respiratory Society
EQ-5D	Euroqol-5D
PDE4	Phosphodiestarase 4
FEVI	Forced expiratory volume in 1 second
FEP	Spanish Patient Forum
FVC	Forced vital capacity
GesEPOC	Spanish Guideline of COPD
GOLD	Global Initiative for Chronic Obstructive Lung Disease
CPG	Clinical Practice Guideline
GRADE	Grading of Recommendations Assessment, Development and Evaluation Working Group
GRAP	Primary Care Respiratory Society
IBERPOC	Epidemiological Study of COPD in Spain
LABA	Long-acting beta-adrenergic antagonists
LAMA	Long-acting muscarinic antagonists
MRC	Medical Research Council
MSSSI	(Spanish) Ministry of Health, Social Services and Equality
NHMRC	National Health and Medical Research Council
NICE	National Institute for Health and Clinical Excellence
NAC	N-acetylcysteine

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NNT	Necessary number of patients to treat to prevent an event
OR	Odds ratio
WHO	World Health Organisation
QoLRIQ	Quality of life for respiratory illness
RF	Roflumilast
RR	Relative risk
RT	Rate ratio
SABA	Short-acting 2-agonist
SAMA	Short-acting muscarinic antagonist
SEMERGEN	Spanish Society of Primary Health Care Physicians
SEMES	Spanish Society of Emergency Medicine
SEMG	Spanish Society of General and Family Medicine
SEMI	Spanish Society of Internal Medicine
SEPAR	Spanish Society of Pneumology and Thoracic Surgery
SERMEF	Spanish Society of Rehabilitation and Physical Medicine
SIGN	Scottish intercollegiate guidelines network
SNS	Spanish National Health System
SORECAR	Spanish Society of Cardio-Respiratory Rehabilitation
semFYC	Spanish Society of Family and Community Medicine
AHRACT	High resolution axial computed tomography
CAT	Computed axial tomography
TDI	Transition Dyspnoea Index
NRT	Nicotine replacement therapy
UETS	Health Technologies Assessment Unit

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Appendix 3. Declaration of interest

Juan José Soler-Cataluña has received support from the pharmaceutical industry to attend the Annual Congresses of SEPAR, ERS and ATS, in consultancy work, as a speaker at different conferences and for a research project. Ramón Coll Artés has received fees from the pharmaceutical industry as a speaker. José Tomás Gómez Sáenz has received support from the pharmaceutical industry to attend Annual Congresses, for different training activity programme workshops and to finance a research project on the prevalence of COPD. Juan Enrique Cimas Hernando has received support from the pharmaceutical industry to attend Annual Congresses and as a speaker at conferences and courses. Fernando Gómez Ruiz has received support from the pharmaceutical industry to attend different regional, national and international Annual Congresses and fees as a speaker at workshops, courses and round tables. Luis Puente Maestu has received support from the pharmaceutical industry to attend the Annual Congresses of SEPAR and ERS, as a speaker at different courses, to participate in clinical trials and as research project coordinator. Jesús López Alcalde has received fees from the pharmaceutical industry as a speaker at a training workshop. Juan Antonio Trigueros Carrero has received fees from the pharmaceutical industry as a speaker at different conferences. Carlos Mª de San Román y de Terán has received support from the pharmaceutical industry to attend different Symposiums, as a speaker at different courses/conferences, to finance a research project on stable angina and for advisory work. Luis Pérez de Llano has received support from the pharmaceutical industry to attend the Annual Congresses of SEPAR and ERS and as a speaker at courses/conferences. Carles Llor Vila has received support from the pharmaceutical industry to attend Annual Congresses, as a speaker at courses/conferences and to finance a research project. José Miguel Franco Sorolla has received fees from the pharmaceutical industry as a speaker at courses/conferences. Julio Ancochea Bermúdez has received support from the pharmaceutical industry to attend meetings and congresses, as a speaker and chairperson at conferences, in consultancy work for a pharmaceutical company and to finance a research project. MªAntònia Llauger Rosselló has received fees from the pharmaceutical industry for workshops, courses and work meetings. Myriam Calle Rubio has received support from the pharmaceutical industry to attend Annual Congresses of SEPAR, as a speaker at conferences, for training activity programme workshops and to finance a research project. Pedro José Almagro Mena has received support from the pharmaceutical industry to attend Annual Congresses, for different training activity programme workshops, in consultancy work for a pharmaceutical company and to finance a research project. Ramón Agüero Balbín has received support from the pharmaceutical industry to attend Annual Congresses of the SEPAR and as a speaker at meetings. Adolfo Baloira Villar has received support from the pharmaceutical industry as a speaker at conferences and courses and in consultancy work for a pharmaceutical company. Agustín Julián Jiménez has received support from the pharmaceutical industry to attend several Annual Congresses of SEMES, SEIMC and EUSEM, as a speaker at workshops and courses and to publish different books/handbooks. Francisco de Borja García-Cosío Piqueras has received support from the pharmaceutical industry to attend Annual Congresses, as a speaker at different conferences, for training activity programme workshops, in consultancy work on experts panels and to finance a research project. Daniel López Fernández has received support from the pharmaceutical industry to attend Annual Congresses of SEPAR, as a speaker at conferences and to publish books/handbooks. Alfredo de Diego Damia has received support from the pharmaceutical industry to attend Annual Congresses and meetings of SEPAR and to publish books/monographs. Jose Luis López-Campos Bodineau has received support from the pharmaceutical industry to attend Annual Congresses, as a speaker at conferences, in consultancy work and to finance a research project.

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*The model of form used to facilitate the collection of the declaration of interests is include in the methodological material, available both on the web page of GuiaSalud and on the web page of the UETS, and where the information is presented in a detailed manner with the methodological process of the CPG.

More than 5 years have passed since the publication of this Clinical Practice Guideline and its validity has not been reviewed

Bibliography

1. Ministerio de Sanidad y Política Social. Plan de Calidad para el Sistema Nacional de Salud. Estrategia en EPOC del Sistema Nacional de Salud. Sanidad 2009. Ministerio de Sanidad y Política Social. Disponible en: http://www.msc.es/organizacion/sns/planCalidadSNS/docs/EstrategiaEPOCSNS.pdf.2009.
2. Miravitlles M, Calle M, Soler-Cataluna JJ. Clinical phenotypes of COPD: identification, definition and implications for guidelines. Arch Bronconeumol. 2012;48:86-98.
3. Soriano JB, Zielinski J, Price D. Screening for and early detection of chronic obstructive pulmonary disease. Lancet. 2009;374:721-732.
4. Estrategia en EPOC del Sistema Nacional de Salud. Plan de Calidad para el Sistema Nacional de Salud. Ministerio de Sanidad y Política Social. 2009.
5. Global Initiative for Chronic Obstructive Lung Disease (GOLD). Global Strategy for the Diagnosis, Management, and Prevention of Chronic Obstructive Pulmonary Disease (Revised 2011). [sedeWeb]. GOLD 2011 [acceso 10-1-2012]; Disponible en: www.goldcopd.org2011.
6. Grupo de trabajo de la guía de práctica clínica sobre Atención Integral al paciente con Enfermedad Pulmonar Obstructiva Crónica (EPOC). Sociedad Española de Neumología y Cirugía Torácica (SEPAR) y Sociedad Española de Medicina de Familia (semFYC). 2010.
7. Peces-Barba G, Barberà JA, Agustí A et al. Guíaclínica de diagnóstico y tratamiento de la enfermedad pulmonar obstructiva crónica. Sociedad Española de Neumología y Cirugía Torácica (SEPAR) y Asociación Latinoamericana del Tórax (ALAT). Arch Bronconeumol. 2008;44:271-81.
8. GuyattG, Oxman AD, Akl EA et al. GRADE guidelines: 1. Introduction-GRADE evidence profiles and summary off indings tables. J Clin Epidemiol. 2011;64:383-394.
9. Marzo CM, Alonso-Coello P. Clasificación de la calidad de la evidencia y fuerza de las recomendaciones. GRADE Working Group. Aten Primaria 2006;37(1):00-00.2006;37:00.
10. Grupo de trabajo sobre GPC. Elaboración de Guías de Práctica Clínica en el Sistema Nacional de Salud. Manual Metodológico. Madrid: Plan Nacional para el SNS del MSC. Instituto Aragonés de Ciencias de la Salud-I+CS; 2007. Guías de Práctica Clínica en el SNS: I+CSNº 2006/0I. 2007.
11. Bousquet J, Kiley J, Bateman ED et al. Prioritised research agenda for prevention and control of chronic respiratory diseases. Eur Respir J. 2010;36:995-1001.
12. Pauwels RA, Buist AS, Calverley PM et al. Global strategy for the diagnosis, management, and prevention of chronic obstructive pulmonary disease. NHLBI/WHO Global Initiative for Chronic Obstructive Lung Disease (GOLD) Workshop summary. Am J Respir Crit Care Med. 2001;163:1256-1276.
13. Halbert RJ, Natoli JL, Gano A et al. Global burden of COPD: systematic review and meta-analysis. Eur Respir J. 2006;28:523-532.
14. Atsou K, Chouaid C, Hejblum G. Variability of the chronic obstructive pulmonary disease key epidemiological data in Europe: systematic review. BMC Med.2011;9:7.
15. Peña VS, Miravitlles M, Gabriel R et al. Geographic variations in prevalence and underdiagnosis of COPD: results of the IBERPOC multicentre epidemiological study. Chest. 2000;118:981-989.

More than 5 years have passed since the publication of the Clinical Practice Guideline, and its validity has not been reviewed

16. Miravitlles M, Ferrer M, Pont A et al. Characteristics of a population of COPD patients identified from a population-based study. Focus on previous diagnosis and never smokers. Respir Med. 2005;99:985-995.

17. Miravitlles M, Soriano JB, Garcia-Rio F et al. Prevalence of COPD in Spain: impact of undiagnosed COPD on quality of life and daily life activities. Thorax. 2009;64:863-868.

18. Soriano JB, Ancochea J, Miravitlles M et al. Recent trends in COPD prevalence in Spain: a repeated cross-sectional survey 1997-2007. Eur Respir J. 2010;36:758-765.

19. WHO. World health statistics 008.http://www.who.int/whosis/whostat/EN_WHS08_Full.pdf.2010.

20. Regidor E G-FJAM. Patrón de mortalidad en España, 2008. Madrid: Ministerio de Sanidad, Política Social e Igualdad, 2011. http://www.msc.es/ca/estadEstudios/estadisticas/estadisticas/estMinisterio/mortalidad/docs/Patrones_de_Mortalidad_en_Espana_2008.pdf.2011.

21. Raziel. Mortalidad por todas las causas. Área de Análisis Epidemiológico y Situación de Salud. Vigilancia de la mortalidad. Instituto Carlos III. 2012. Ref Type: Electronic Citation

22. Registro de Altas de los Hospitales Generales del Sistema Nacional de Salud. Disponible en: http://www.msc.es/estadEstudios/estadisticas/cmbd.htm.2012.

23. Ministerio de Sanidad y Política Social. Plan de Calidad para el Sistema Nacional de Salud. Estrategia en EPOC del Sistema Nacional de Salud. Sanidad 2009. Ministerio de Sanidad y Política Social. Disponible en: http://www.msc.es/organizacion/sns/planCalidadSNS/docs/EstrategiaEPOCSNS.pdf.2009.

24. Miravitlles M, Murio C, Guerrero T et al. Costs of chronic bronchitis and COPD: a 1-year follow-upstudy. Chest. 2003;123:784-791.

25. Soler-Cataluña JJ, Calle M, Cosio B G et al. Estándares de calidad asistencial en la EPOC. Arch Bronconeumol. 2009;45:361-362.

26. Celli BR, Macnee W. Standards for the diagnosis and treatment of patients with COPD: a summary of the ATS/ERS position paper. Eur Respir J. 2004;23:932-946.

27. Han MK, Agusti A, Calverley PM et al. Chronic obstructive pulmonary disease phenotypes: the future of COPD. Am J Respir Crit Care Med. 2010;182:598-604.

28. Miravitlles M. Tratamiento individualizado de la EPOC: una propuesta de cambio. Arch Bronconeumol. 2012;45:27-34.

29. Celli BR, Thomas NE, Anderson JA et al. Effect of pharmacotherapy on rate of decline of lung function in chronic obstructive pulmonary disease: results from the TORCH study. Am J Respir Crit Care Med. 2008;178:332-338.

30. Martinez-Garcia MA, Soler-Cataluna JJ, Donat SY et al. Factors associated with bronchiectasis in patients with COPD. Chest. 2011;140:1130-1137.

31. Patel BD, Coxson HO, Pillai SG et al. Airway wall thickening and emphysema show independent familial aggregation in chronic obstructive pulmonary disease. Am J Respir Crit Care Med. 2008;178:500-505.

32. Garcia-Aymerich J, Gomez FP, Benet M et al. Identification and prospective validation of clinically relevant chronic obstructive pulmonary disease (COPD) subtypes. Thorax. 2011;66:430-437.

33. Vidal R, Blanco I, Casas F et al. [Guidelines for the diagnosis and management of alpha-1 antitrypsin deficiency]. Arch Bronconeumol. 2006; 42:645-659.

34. Soler-Cataluña JJ, Rodriguez-Roisin R. Frequent chronic obstructive pulmonary disease exacerbators: how much real, how much fictitious? COPD. 2010;7:276-284.

More than 5 years have passed since the publication of this Clinical Practice Guideline, and its validity has not been reviewed

35. Hurst JR, Vestbo J, Anzueto A et al. Susceptibility to exacerbation in chronic obstructive pulmonary disease. N Engl J Med. 2010;363:1128-1138.

36. Bafadhel M, McKenna S, Terry Setal. Acute exacerbations of chronic obstructive pulmonary disease: identification of biologic clusters and their biomarkers. Am J Respir Crit Care Med. 2011;184:662-671.

37. Hardin M, Silverman EK, Barr RG et al. The clinical features of the overlap between COPD and asthma. Respir Res. 2011;12:127.

38. Gibson PG, Simpson JL. The overlap syndrome of asthma and COPD: what are its features and how important is it? Thorax. 2009;64:728-735.

39. Boulet LP, Lemiere C, Archambault F et al. Smoking and asthma: clinical and radiologic features, lung function, and airway inflammation. Chest. 2006;129:661-668.

40. Contoli M, Baraldo S, Marku B et al. Fixed air flow obstruction due to asthma or chronic obstructive pulmonary disease: 5-year follow-up. J Allergy Clin Immunol. 2010;125:830-837.

41. De MR, Accordini S, Cerveri I et al. Incidence of chronic obstructive pulmonary disease in a cohort of young adults according to the presence of chronic cough and phlegm. Am J Respir Crit Care Med. 2007;175:32-39.

42. Miravitlles M. The overlap síndrome between asthma and COPD: implications for management. Hot Topics Respir Med. 2011;16:15-20.

43. Soriano JB, Davis KJ, Coleman B et al. The proportional Venn diagram of obstructive lung disease: two approximations from the United States and the United Kingdom. Chest. 2003;124:474-481.

44. American Thoracic Society. Chronic bronchitis, asthma, and pulmonary emphysema, astatement by the Committee on Diagnostic Standards for Nontuberculous Respiratory Diseases. Am Rev Respir Dis. 1962;85:762-768.

45. Prescott E, Lange P, Vestbo J. Chronic mucus hypersecretion in COPD and death from pulmonary infection. Eur Respir J. 1995;8:1333-1338.

46. Kim V, Han MK, Vance GB et al. The chronic bronchitic phenotype of COPD: an analysis of the COPDGene Study. Chest. 2011;140:626-633.

47. Montes de OM, Halbert RJ, Lopez MV et al. Chronic bronchitis phenotype in subjects with and without COPD: the PLATINO study. Eur Respir J. 2012.

48. Patel IS, Vlahos I, Wilkinson TM et al. Bronchiectasis, exacerbation indices, and inflammation in chronic obstructive pulmonary disease. Am J Respir Crit Care Med. 2004;170:400-407.

49. Casanova C, Cote C, de Torres JP et al. Inspiratory-to-total lung capacity ratio predicts mortality in patients with chronic obstructive pulmonary disease. Am J Respir Crit Care Med. 2005;171:591-597.

50. Grydeland TB, Thorsen E, Dirksen A et al. Quantitative CT measures of emphysema and airway wall thickness are related to D(L)CO. Respir Med. 2011;105:343-351.

51. Han MK, Kazerooni EA, Lynch DA et al. Chronic obstructive pulmonary disease exacerbations in the COPDGene study: associated radiologic phenotypes. Radiology. 2011;261:274-282.

52. Nishimura M, Makita H, Nagai K et al. Annual change in pulmonary function and clinical phenotype in chronic obstructive pulmonary disease. Am J Respir Crit Care Med. 2012;185:44-52.

53. Miravitlles M, Calle M, Soler-Cataluña JJ. Fenotipos clínicos de la EPOC. Identificación, definición e implicaciones para las guías de tratamiento. Arch Bronconeumol. 2012;48:86-98.

54. Grupo de trabajo GESEPOC. Hacia un nuevo enfoque en el tratamiento de la EPOC. La Guía Española de la EPOC (GESEPOC). Arch Bronconeumol. 2011;47:379-381.

More than 5 years have passed since the publication of this Clinical Practice Guideline, and its validity has not been reviewed

55. Anderson DO, Ferris BG. Jr. Role of tobacco smoking in the causation of chronic respiratory disease. N Engl J Med. 1962;267:787-794.

56. Oswald NC, MedveiVC. Chronic bronchitis; the effect of cigarette-smoking. Lancet. 1955;269:843-844.

57. Fletcher C, Peto R. The natural history of chronic airflow obstruction. Br Med J. 1977;1:1645-1648.

58. Kohansal R, Martinez-Camblor P, Agusti A et al. The natural history of chronic airflow obstruction revisited: an analysis of the Framingham offspring cohort. Am J Respir Crit Care Med. 2009;180:3-10.

59. Lokke A, Lange P, Scharling H et al. Developing COPD: a 25 year follow up study of the general population. Thorax. 2006;61:935-939.

60. Ministerio de Sanidad y Consumo. Encuesta de salud de España. Disponible en: http://www.msps.es/estadEstudios/estadisticas/encuestaNacional/encuesta2006.htm. 2006.

61. Salvi SS, Barnes PJ. Chronic obstructive pulmonary disease in non-smokers. Lancet. 2009;374:733-743.

62. Ho SY, Lam TH, Chung SF et al. Cross-sectional and prospective associations between passive smoking and respiratory symptoms at the workplace. Ann Epidemiol. 2007;17:126-131.

63. Jaakkola MS, Jaakkola JJ. Effects of environmental tobacco smoke on the respiratory health of adults. Scand J Work Environ Health. 2002;28 Suppl 2:52-70.

64. Larsson ML, Loit HM, Meren M et al. Passive smoking and respiratory symptoms in the FinEsS Study. Eur Respir J. 2003;21:672-676.

65. Yin P,Jiang CQ, Cheng KK et al. Passive smoking exposure and risk of COPD among adults in China: the Guangzhou Biobank Cohort Study. Lancet. 2007;370:751-757.

66. Gonzalez Barcala FJ, Takkouche B, Valdes L et al. [Parental smoking and lung function in healthy children and adolescents]. Arch Bronconeumol. 2007;43:81- 85.

67. Hu G, Zhou Y, Tian J et al. Risk of COPD from exposure to biomass smoke: a metaanalysis. Chest. 2010;138:20-31.

68. Kurmi OP, Semple S, Simkhada P et al. COPD and chronic bronchitis risk of indoor air pollution from solid fuel: a systematic review and meta-analysis. Thorax. 2010;65:221-228.

69. Po JY, FitzGerald JM, Carlsten C. Respiratory disease associated with solid biomass fuel exposure in rural women and children: systematic review and meta-analysis. Thorax. 2011;66:232-239.

70. Torres-Duque C, Maldonado D, Perez-Padilla R et al. Biomass fuels and respiratory diseases: a review of the evidence. Proc Am Thorac Soc. 2008;5:577-590.

71. Orozco-Levi M, Garcia-Aymerich J, Villar J et al. Wood smoke exposure and risk of chronic obstructive pulmonary disease. Eur Respir J. 2006;27:542-546.

72. Eisner MD, Anthonisen N, Coultas D et al. An official American Thoracic Society public policy statement: Novel risk factors and the global burden of chronic obstructive pulmonary disease. Am J Respir Crit Care Med. 2010;182:693-718.

73. Arbex MA, de Souza Conceicao GM, Cendon SP et al. Urban air pollution and chronic obstructive pulmonary disease-related emergency department visits. J Epidemiol Community Health. 2009;63:777-783.

74. Andersen ZJ, Hvidberg M, Jensen SS et al. Chronic obstructive pulmonary disease and long-term exposure to traffic-related air pollution: a cohort study. Am J Respir Crit Care Med. 2011;183:455-461.

75. University of Cologne. Web Eurad. 2012. Ref Type: Unpublished Work

76. Rushton L. Occupational causes of chronic obstructive pulmonary disease. Rev Environ Health. 2007;22:195-212.

More than 5 years have passed since the publication of this Clinical Practice Guideline, and its validity has not been reviewed

77. Rodriguez E, Ferrer J, Marti S et al. Impact of occupational exposure on severity of COPD. Chest. 2008;134:1237-1243.

78. Lam KB, Jiang CQ, Jordan RE et al. Prior TB, smoking, and airflow obstruction: across-sectional analysis of the Guangzhou Biobank Cohort Study. Chest. 2010;137:593-600.

79. Menezes AM, Hallal PC, Perez-Padilla R et al. Tuberculosis and airflow obstruction: evidence from the PLATINO study in Latin America. Eur Respir J. 2007;30:1180-1185.

80. Kohnlein T, Welte T. Alpha-1 antitrypsin deficiency: pathogenesis, clinical presentation, diagnosis, and treatment. Am J Med. 2008;121:3-9.

81. Mannino DM, Buist AS. Global burden of COPD: risk factors, prevalence, and future trends. Lancet. 2007;370:765-773.

82. Roche N, Marthan R, Berger P et al. Beyond corticosteroids: future prospects in the management of inflammation in COPD. Eur Respir Rev. 2011;20:175-182.

83. Yang IA, Relan V, Wright CM et al. Common pathogenic mechanisms and pathways in the development of COPD and lung cancer. Expert Opin Ther Targets. 2011;15:439-456.

84. Chatila WM, Thomashow BM, Minai OA et al. Comorbidities in chronic obstructive pulmonary disease. Proc Am Thorac Soc. 2008;5:549-555.

85. Calverley PM, Anderson J A, Celli B et al. Salmeterol and fluticasone propionate and survival in chronic obstructive pulmonary disease. N Engl J Med. 2007;356:775-789.

86. Soriano JB, Visick GT, Muellerova H et al. Patterns of comorbidities in newly diagnosed COPD and asthma in primary care. Chest. 2005;128:2099-2107.

87. Mannino DM, Thorn D, Swensen A et al. Prevalence and outcomes of diabetes, hypertension and cardiovascular disease in COPD. Eur Respir J. 2008;32:962-969.

88. Almagro P, Lopez GF, Cabrera FJ et al. [Study of the comorbidities in hospitalized patients due to decompensated chronic obstructive pulmonary disease attended in the Internal Medicine Services. ECCO Study]. Rev Clin Esp. 2010;210:101-108.

89. Finkelstein J, Cha E, Scharf SM. Chronic obstructive pulmonary disease as an independent risk factor for cardiovascular morbidity. Int J Chron Obstruct Pulmon Dis. 2009;4:337-349.

90. Feary JR, Rodrigues LC, Smith CJ et al. Prevalence of major comorbidities in subjects with COPD and incidence of myocardial infarction and stroke: a comprehensive analysis using data from primary care. Thorax. 2010;65:956-962.

91. Donaldson GC, Hurst JR, Smith CJ et al. Increased risk of myocardial infarction and stroke following exacerbation of COPD. Chest. 2010;137:1091-1097.

92. Rutten FH, Cramer MJ, Grobbee DE et al. Unrecognized heart failure in elderly patients with stable chronic obstructive pulmonary disease. Eur Heart J. 2005;26:1887-1894.

93. Almagro P, Calbo E, Ochoa de EA et al. Mortality after hospitalization for COPD. Chest. 2002;121:1441-1448.

94. Render ML, Weinstein AS, Blaustein AS. Left ventricular dysfunction in deteriorating patients with chronic obstructive pulmonary disease. Chest. 1995;107:162-168.

95. Barr RG, Bluemke DA, Ahmed FS et al. Percent emphysema, airflow obstruction, and impaired left ventricular filling. N Engl J Med. 2010;362:217-227.

96. Brenner DR, McLaughlin JR, Hung RJ. Previous lung diseases and lung cancer risk: a systematic review and meta-analysis. PLoS One. 2011;6:e17479.

More than 5 years have passed since the publication of this Clinical Practice Guideline, and its validity has not been reviewed

97. Young RP, Hopkins RJ, Christmas T et al. COPD prevalence is increased in lung cancer, independent of age, sex and smoking history. Eur Respir J. 2009;34:380-386.

98. Ng TP, Niti M, Tan WC et al. Depressive symptoms and chronic obstructive pulmonary disease: effect on mortality, hospital readmission, symptom burden, functional status, and quality of life. Arch Intern Med. 2007;167:60-67.

99. Yohannes AM, Baldwin RC, Connolly MJ. Depression and anxiety in elderly outpatients with chronic obstructive pulmonary disease: prevalence, and validation of the BASDEC screening questionnaire. Int J Geriatr Psychiatry. 2000;15:1090-1096.

100. Barnes PJ, Celli BR. Systemic manifestations and comorbidities of COPD. Eur Respir J. 2009;33:1165-1185.

101. Decramer M, Celli B, Kesten S et al. Effect of tiotropium on outcomes in patients with moderate chronic obstructive pulmonary disease (UPLIFT): a prespecified subgroup analysis of a randomised controlled trial. Lancet. 2009;374:1171-1178.

102. Jenkins CR, Jones PW, Calverley PM et al. Efficacy of salmeterol/fluticasone propionate by GOLD stage of chronic obstructive pulmonary disease: analysis from the randomised, placebo-controlled TORCH study. Respir Res. 2009;10:59.

103. Donaldson GC, Seemungal TA, Bhowmik A et al. Relationship between exacerbation frequency and lung function decline in chronic obstructive pulmonary disease. Thorax. 2002;57:847-852.

104. Miravitlles M. Cough and sputum production as risk factors for poor outcomes in patients with COPD. Respir Med. 2011;105:1118-1128.

105. Vestbo J, Edwards LD, Scanlon PD et al. Changes in forced expiratory volume in 1 second over time in COPD. N Engl J Med. 2011;365:1184-1192.

106. Postma D, Anzueto A, Calverley P et al. A new perspective on optimal care for patients with COPD. Prim Care Respir J. 2011;20:205-209.

107. David K Mc Kenzie, Michael Abramson, Alan J Crockett, Nicholas Glasgow, Sue Jenkins, Christine McDonald, Richard Wood-Baker, Peter A Frith on behalf of The Australian Lung Foundation. The COPD-X Plan: Australian and New Zealand Guidelines for the management of Chronic Obstructive Pulmonary Disease2010.

108. National Institute for Health and Clinical Excellence (NICE) (2010). Chronic obstructive pulmonary disease: management of chronic obstructive pulmonary disease in adults in primary and secondary care. London: National Clinical Guideline Centre. Disponible en: http://guidance.nice.org.uk/CG101/Guidance/pdf/English 2010.

109. Qaseem A, Wilt TJ, Weinberger SE et al. Diagnosis and management of stable chronic obstructive pulmonary disease: a clinical practice guideline update from the American College of Physicians, American College of Chest Physicians, American Thoracic Society, and European Respiratory Society. Ann Intern Med. 2011;155:179-191.

110. Barr RG, Bourbeau J, Camargo CA et al. Tiotropium for stable chronic obstructive pulmonary disease: A meta-analysis. Thorax. 2006;61:854-62.

111. Agencia Española de Medicamentos y Productos Sanitarios. [sede Web]. [acceso 2-11-2011]; Disponible en: https://sinaem4.agemed.es/consaem/fichasTecnicas.do?metodo=detalleForm 2011.

112. Rodrigo GJ, Nannini LJ. Tiotropium for the treatment of stable chronic obstructive pulmonary disease: a systematic review with meta-analysis. Pulm Pharmacol Ther. 2007;20:495-502.

More than 5 years have passed since the publication of this Clinical Practice Guideline and its validity has not been reviewed

113. Vogelmeier C, Hederer B, Glaab T et al. Tiotropium versus salmeterol for the prevention of exacerbations of COPD. N Engl J Med. 2011;364:1093-1103.

114. Shukla VK, Chen S, Boucher M, Mensinkai S, Dales R. Long-acting ß2-agonists for the maintenance treatment of chronic obstructive pulmonary disease in patients with reversible and nonreversible airflow obstruction: a systematic review of clinical effectiveness [Technology report no 65]. Ottawa: Canadian Coordinating Office for Health Technology Assessment 2006.

115. Neyt M, Van den Bruel A, Gailly J, Thiry N, Devriese S. Tiotropium in the Treatment of Chronic Obstructive Pulmonary Disease: Health Technology Assessment. Health Technology Assessment(HTA). Brussels: Belgian Health Care Knowledge Centre (KCE). 2009. KCE reports 108C. D/2009/10.273/20. Disponible en:http://www.kce.fgov.be2009.

116. Kornmann O,Dahl R, Centanni S et al. Once-daily indacaterol versus twice-daily salmeterol for COPD: a placebo-controlled comparison. Eur Respir J. 2011;37:273-279.

117. Korn S, Kerwin E, Atis S et al. Indacaterol once-daily provides superior efficacy to salmeterol twice-daily in COPD: a 12-week study. Respir Med. 2011;105:719-726.

118. Dahl R, Chung KF, Buhl R et al. Efficacy of a new once-daily long-acting inhaled beta2-agonist indacaterol versus twice-daily formoterol in COPD. Thorax. 2010;65:473-479.

119. LaForce C, Aumann J, de Teresa PL et al. Sustained 24-hour efficacy of once daily indacaterol (300 mug) in patients with chronic obstructive pulmonary disease: a randomized, crossover study. Pulm Pharmacol Ther. 2011;24:162-168.

120. Magnussen H, Verkindre C, Jack D et al. Indacaterol once-daily is equally effective dosed in the evening or morning in COPD. Respir Med. 2010;104:1869-1876.

121. Vogelmeier C, Ramos-Barbon D, Jack D et al. Indacaterol provides 24-hour bronchodilation in COPD: a placebo-controlled blinded comparison with tiotropium. Respir Res. 2010;11:135.

122. Buhl R, Dunn LJ, Disdier C et al. Blinded 12-week comparison of once-daily indacaterol and tiotropium in COPD. European Respiratory Journal. 2011;38:797-803.

123. Donohue JF, Fogarty C, Lotvall J et al. Once-daily bronchodilators for chronic obstructive pulmonary disease: indacaterol versus tiotropium. Am J Respir Crit Care Med. 2010;182:155-162.

124. Rutten-van Molken MP, Oostenbrink JB, Miravitlles M et al. Modelling the 5-year cost effectiveness of tiotropium, salmeterol and ipratropium for the treatment of chronic obstructive pulmonary disease in Spain. Eur J Health Econ. 2007;8:123-135.

125. Gani R, Griffin J, Kelly S et al. Economic analyses comparing tiotropium with ipratropium or salmeterol in UK patients with COPD. Prim Care Respir J. 2010;19:68-74.

126. Naik S, Kamal KM, Keys PA et al. Evaluating the cost-effectiveness of tiotropium versus salmeterol in the treatment of chronic obstructive pulmonary disease. Clinicoecon Outcomes Res. 2010;2:25-36.

127. Oba Y. Cost-effectiveness of long-acting bronchodilators for chronic obstructive pulmonary disease. Mayo Clin Proc. 2007;82:575-582.

128. Oostenbrink JB, Rutten-van Molken MP, Monz BU et al. Probabilistic Markov model to assess the cost-effectiveness of bronchodilator therapy in COPD patients in different countries. Value Health. 2005;8:32-46.

More than 5 years have passed since the publication of this Clinical Practice Guideline and its validity has not been reviewed

129. Price D, Gray A, Gale R et al. Cost-utility analysis of indacaterol in Germany: a once-daily maintenance bronchodilator for patients with COPD. Respir Med. 2011;105:1635-1647.

130. Breekveldt-Postma NS, Koerselman J, Erkens JA et al. Enhanced persistence with tiotropium compared with other respiratory drugs in COPD. Respir Med. 2007;101:1398-1405.

131. Bourbeau J, Bartlett SJ. Patient adherence in COPD. Thorax. 2008;63:831-838.

132. Chapman KR, Fogarty CM, Peckitt C et al. Delivery characteristics and patients' handling of two single-dose dry-powder inhalers used in COPD. Int J Chron Obstruct Pulmon Dis. 2011;6:353-363.

133. Rabe KF, Timmer W, Sagkriotis A et al. Comparison of acombination of tiotropium plus formoterol to salmeterol plus fluticasone in moderate COPD. Chest. 2008;134:255-262.

134. Riemsma R, Lhachimi SK, Armstrong N et al. Roflumilast for the management of severe chronic obstructive pulmonary disease: a Single Technology Appraisal. York: Kleijnen Systematic Reviews Ltd. 2011.

135. Mills EJ, Druyts E, Ghement I et al. Pharmacotherapies for chronic obstructive pulmonary disease: a multiple treatment comparison meta-analysis. Clin Epidemiol. 2011;3:107-129.

136. Wells GA, Sultan SA, Chen L et al. Indirect Evidence: Indirect Treatment Comparisons in Meta-Analysis. Ottawa: Canadian Agency for Drugs and Technologies in Health. 2009.

137. Singh JM, Palda V A, Stanbrook MB et al. Corticosteroid therapy for patients with acute exacerbations of chronic obstructive pulmonary disease: a systematic review. Arch Intern Med. 2002;162:2527-2536.

138. Weatherall M, Clay J, James K et al. Dose-response relationship of inhaled corticosteroids and cataracts: a systematic review and meta-analysis. Respirology. 2009;14:983-90.

139. National Institute for Health and Clinical Excellence (NICE). TA244 Chronic obstructive pulmonary disease-roflumilast: guidance. [sede Web]. [acceso 19-02-2012]; Disponible en: http:/www.nice.org.uk/nicemedia/live/13649/57889/57889.pdf. 2012.

140. Merck Sharp & Dohme. Chronic obstructive pulmonary disease-roflumilast: Merck Sharp & Dohme. [Actualizado 7 Sept 2011; citado 18 Enero 2012]. Disponible en: http://guidance.nice.org.uk/TA/Wave24/13/Consultation/EvaluationReport/ManufacturerSubmissions/MSD/pdf/English. 2011.

141. Grandjean EM, Berthet PH, Ruffmann R et al. Cost-effectiveness analysis of oral N-acetylcysteine as a preventive treatment in chronic bronchitis. Pharmacol Res. 2000;42:39-50.

142. Poole P, Black PN. Mucolytic agents for chronic bronchitis or chronic obstructive pulmonary disease. Cochrane Database Syst Rev. 2010;CD001287.

143. Stey C, Steurer J, Bachmann S et al. The effect of oral N-acetylcysteine in chronic bronchitis: a quantitative systematic review. Eur Respir J. 2000;16:253-262.

144. Sutherland ER, Crapo JD, Bowler RP. N-acetylcysteine and exacerbations of chronic obstructive pulmonary disease. COPD. 2006;3:195-202.

145. Tan-Reyes MA. The role of N-acetylcysteine in reducing number of exacerbations in patients with moderate to severe chronic obstructive pulmonary disease; a meta-analysis. Respirology. 2009;14:A268.

146. Sayiner A, Aytemur ZA, Baysak A et al. N-Acetylcysteine in exacerbations of chronic obstrutive pulmonary disease associated with increased sputum [Abstract]. American Journal of Respiratory and Critical Care Medicine Am J Respir Crit Care Med. 2011;183:A3123.

More than 5 years have passed since the publication of this Clinical Practice Guideline, and it validity has not been reviewed

147. Schermer T, Chavannes N, Dekhuijzen R et al. Fluticasone and N-acetylcysteine in primary care patients with COPD or chronic bronchitis. Respir Med. 2009;103:542-551.

148. Stav D, Raz M. Effect of N-acetylcysteine on air trapping in COPD: a randomized placebo-controlled study. Chest. 2009;136:381-386.

149. Long-term oral acetylcysteine in chronic bronchitis. a double-blind controlled study. Eur J Respir Dis Suppl. 1980;111:93-108.

150. Bachh AA, Shah NN, Bhargava R et al. Effect of oral N-Acetylcysteine in COPD-a randomised controlled trial. JK-Practitioner. 2007;14(1):12+16.

151. Boman G, Backer U, Larsson S et al. Oral acetylcysteine reduces exacerbation rate in chronic bronchitis: report of a trial organized by the Swedish Society for Pulmonary Diseases. Eur J Respir Dis. 1983;64:405-415.

152. Borgia M, Sepe N, Ori-Belometti M et al. Comparison between acetylcysteine and placebo in the long term treatment of chronic bronchitis [Confronto tra acetilcisteina e placebo nel trattamento a lungo termine della bronchite cronica]. 1981.

153. British Thoracic Society Research Committee. Oral N-acetylcysteine and exacerbation rates in patients with chronic bronchitis and severe airways obstruction. Thorax. 1985;40:832-835.

154. Decramer M, Rutten-van MM, Dekhuijzen PN et al. Effects of N-acetylcysteine on outcomes in chronic obstructive pulmonary disease (Bronchitis Randomized on NAC Cost-Utility Study, BRONCUS): a randomised placebo-controlled trial. Lancet. 2005;365:1552-1560.

155. Grassi C, Morandini GC. A controlled trial of intermittent oralacetylcysteine in the long-term treatment of chronic bronchitis. Eur J Clin Pharmacol. 1976;09:393-396.

156. Hansen NC, Skriver A, Brorsen-Riis L et al. Orally administered N-acetylcysteine may improve general well-being in patients with mild chronic bronchitis. Respir Med. 1994;88:531-535.

157. Jackson IM, Barnes J, Cooksey P. Efficacy and tolerability of oral acetylcysteine (Fabrol) in chronic bronchitis: a double-blind placebo controlled study. J Int Med Res. 1984;12:198-206.

158. Meister R. Long-term therapy with acetylcysteine retard tablets in patients with chronic bronchitis: adouble-blind. placebo-controlled study. Unpublished source. 1986.

159. Nowak D, Carati L, Pirozynski M. Long-term administration of N-acetylcysteine reduces the number of acute exacerbation episodes in subjects with chronic obstructive pulmonary disease: report of the BREATHE study. European Respiratory Journal. 1999;14 Suppl:381S-382S.

160. Parr GD, Huitson A. Oral Fabrol (oral N-acetyl-cysteine) in chronic bronchitis. Br J Dis Chest. 1987;81:341-348.

161. Pela R, Calcagni AM, Subiaco S et al. N-acetylcysteine reduces the exacerbation rate in patients with moderate to severe COPD. Respiration. 1999;66:495-500.

162. Rasmussen JB, Glennow C. Reduction in days of illness after long-term treatment with N-acetylcysteine controlled-release tablets in patients with chronic bronchitis. Eur Respir J. 1988;1:351-355.

163. Grassi C, Casali L, Ciaccia A et al. Terapia intervallare con l'associazione carbocisteina-sobrerolo nella profilassi delle riacutizzazioni della bronchite cronica. Italian Journal of Chest Disease. 1994;48:17-26.

More than 4 years have passed since the publication of this Clinical Practice Guideline, and its validity has not been reviewed

164. Allegra L, Cordaro CI, Grassi C. Prevention of acute exacerbations of chronic obstructive bronchitis with carbocysteine lysine salt monohydrate: amulticenter, double-blind, placebo-controlled trial. Respiration. 1996;63:174-180.

165. Zheng JP, Kang J, Huang SG et al. Effect of carbocisteine on acute exacerbation of chronic obstructive pulmonary disease (PEACE Study): a randomised placebo-controlled study. Lancet. 2008;371:2013-2018.

166. Grillage M, Barnard-Jones K. Long-term oral carbocisteine therapy in patients with chronic bronchitis. A double blind trial with placebo control. Br J Clin Pract. 1985;39:395-398.

167. Langsetmo L, Ernst P, Bourbeau J. Underreporting exacerbation of chronic obstructive pulmonary disease in a longitudinal cohort. Am J Respir Crit Care Med. 2008;177:396-401.

168. Seemungal TAR, Donaldson GC, Paul EA et al. Effect of exacerbation on quality of life in patients with chronic obstructive pulmonary disease. Am J Respir Crit Care Med. 1998;157:1418-22.

169. Miravitlles M, Ferrer M, Pont A et al. Exacerbations impair quality of life in patients with chronic obstructive pulmonary disease. A two-year follow-up study. Thorax. 2004;59:387-95.

170. Hurst JR, Donaldson GC, Perera WR et al. Use of plasma biomarkers at exacerbation of chronic obstructive pulmonary disease. Am J Respir Crit Care Med. 2006;174:867-74.

171. Parker CM, Voduc N, Aaron SD et al. Physiologic changes during symptom recovery from moderate exacerbation of COPD. Eur Respir J. 2005;26:420-428.

172. Perera WR, Hurst JR, Wilkinson TMA et al. Inflammatory changes, recovery and recurrence at COPD exacerbation. Eur Respir J. 2007;29:527-34.

173. Miravitlles M, Murio C, Guerrero T et al. Pharmacoeconomic evaluation of acute exacerbations of chronic bronchitis and COPD. Chest. 2002;121:1449-1455.

174. Soler-Cataluña JJ, Martínez-García MA, Román-Sanchez P SE et al. Severe acute exacerbations and mortality in patients with chronic obstructive pulmonary disease. Thorax. 2005;60:925-31.

175. Walters JA, Gibson PG, Wood-Baker R et al. Systemic corticosteroids for acute exacerbations of chronic obstructive pulmonary disease. Cochrane Database Syst Rev. 2009; CD001288.

176. McCrory DC, Brown C, Gelfand SE et al. Management of acute exacerbations of COPD: a summary and appraisal of published evidence. Chest. 2001;119:1190-1209.

177. Quon BS, Gan WQ, Sin DD. Contemporary management of acute exacerbations of COPD: a systematic review and metaanalysis. Chest. 2008;133:756-766.

178. Riancho JA, Portero I, Cubian I. Eficacia de los glucocorticoides en las reagudizaciones de la enfermedad pulmonar obstructiva cronica: metaanalisis de los estudios publicados. Med Clin (Barc). 2000;114:681-684.

179. Schweiger TA, Zdanowicz M. Systemic corticosteroids in the treatment of acute exacerbations of chronic obstructive pulmonary disease. Am J Health Syst Pharm. 2010;67:1061-1069.

180. Aaron SD, Vandemheen KL, Hebert P et al. Outpatient oral prednisone after emergency treatment of chronic obstructive pulmonary disease. N Engl J Med. 2003;348:2618-2625.

181. Thompson WH, Nielson CP, Carvalho P et al. Controlled trial of oral prednisone in outpatients with acute COPD exacerbation. Am J Respir Crit Care Med. 1996;154:407-412.

More than 5 years have passed since the publication of this Clinical Practice Guideline and its validity has not been reviewed

182. Jette DU, Bourgeois MC, Buchbinder R. Pulmonary rehabilitation following acute exacerbation of chronic obstructive pulmonary disease. Phys Ther. 2010;90:9-12.

183. Marciniuk DD, Brooks D, Butcher S et al. Optimizing pulmonary rehabilitation in chronic obstructive pulmonary disease-practical issues: a Canadian Thoracic Society Clinical Practice Guideline. Can Respir J. 2010;17:159-168.

184. Ries AL, Bauldoff GS, Carlin BW et al. Pulmonary Rehabilitation: Joint ACCP/AACVPR Evidence-Based Clinical Practice Guidelines. Chest. 2007;131:4S-42S.

185. Puhan MA, Gimeno-Santos E, Scharplatz M et al. Pulmonary rehabilitation following exacerbations of chronic obstructive pulmonary disease. Cochrane Database Syst Rev. 2011;CD005305.

186. Seymour JM, Moore L, Jolley CJ et al. Outpatient pulmonary rehabilitation following acute exacerbations of COPD. Thorax. 2010;65:423-428.

187. Murphy N, Bell C, Costello RW. Extending a home from hospital care programme for COPD exacerbations to include pulmonary rehabilitation. Respir Med. 2005;99:1297-1302.

188. Man WD, Polkey MI, Donaldson N et al. Community pulmonary rehabilitation after hospitalisation for acute exacerbations of chronic obstructive pulmonary disease: randomised controlled study. BMJ. 2004;329:1209.

189. Ghanem M, Elaal EA, Mehany M et al. Home-based pulmonary rehabilitation program: Effect on exercise tolerance and quality of life in chronic obstructive pulmonary disease patients. Ann Thorac Med. 2010;5:18-25.

190. Clini EM, Crisafulli E, Costi S et al. Effects of early inpatient rehabilitation after acute exacerbation of COPD. Respir Med. 2009;103:1526-1531.

191. Fiore MC, Jaén CR, Baker TG et al. Treating tobacco use and dependence: 2008 Update. Clinical Practice Guideline. Rockville, MD: US Department of Health and Human Services, Public Health Service. 2008.

192. Anthonisen NR, Skeans MA, Wise RA et al. The effects of a smoking cessation intervention on 14.5-year mortality: a randomized clinical trial. Ann Intern Med. 2005;142:233-239.

193. Godtfredsen NS, Lam TH, Hansel TT et al. COPD-related morbidity and mortality after smoking cessation: status of the evidence. Eur Respir J. 2008;32:844-853.

194. Hylkema MN, Sterk PJ, de Boer WI et al. Tobacco use in relation to COPD and asthma. Eur Respir J. 2007;29:438-445.

195. Wagena EJ, van der Meer RM, Ostelo RJ et al. The efficacy of smoking cessation strategies in people with chronic obstructive pulmonary disease: results from a systematic review. Respir Med. 2004;98:805-815.

196. Jiménez Ruiz CA, de Granda Orive JI, Riesco Miranda JA. Abordaje diagnóstico y terapéutico del tabaquismo en EPOC. En: R Güell y P de Lucas eds. Tratado de rehabilitación respiratoria. Madrid, Ars Medica. 2005.

197. Cabezas C, Robledo de Dios T, Marqués F et al. Recomendaciones sobre el estilo de vida. Aten Primaria. 2007;39(Supl3):27-46.

198. Sundblad BM, Larsson K, Nathell L. High rate of smoking abstinence in COPD patients: Smoking cessation by hospitalization. Nicotine Tob Res. 2008;10:883-890.

199. Wang D, Connock M, Barton P et al. 'Cut down to quit' with nicotine replacement therapies in smoking cessation: a systematic review of effectiveness and economic analysis. Health Technol Assess. 2008;12:iii-xi, 1.

More than 5 years have passed since the publication of this Clinical Practice Guideline, and its validity has not been reviewed

200. Christenhusz L, Pieterse M, Seydel E et al. Prospective determinants of smoking cessation in COPD patients within a high intensity or a brief counseling intervention. Patient Educ Couns. 2007;66:162-166.

201. Crowley TJ, Andrews AE, Cheney J et al. Carbon monoxide assessment of smoking in Chronic Obstructive Pulmonary Disease. Addictive Behaviors. 1989;14:493-502.

202. Crowley TJ, Macdonald MJ, Walter MI. Behavioral anti-smoking trial in chronic obstructive pulmonary disease patients. Psychopharmacology (Berl). 1995;119:193-204.

203. Hilberink SR, Jacobs JE, Breteler MH et al. General practice counseling forpatients with chronic obstructive pulmonary disease to quit smoking: impact after 1 year of two complex interventions. Patient Educ Couns. 2011;83:120-124.

204. Monninkhof E, van d, V, van der PJ et al. The effect of a minimal contact smoking cessation programme in out-patients with chronic obstructive pulmonary disease: apre-post-test study. Patient Educ Couns. 2004;52:231-236.

205. Pederson LL, Wanklin JM, Lefcoe NM. The effects of counseling on smoking cessation among patients hospitalized with chronic obstructive pulmonary disease: a randomized clinical trial. Int J Addict. 1991;26:107-119.

206. Turner SA, Daniels JL, Hollandsworth JG. The effects of a multicomponent smoking cessation program with chronic obstructive pulmonary disease outpatients. Addict Behav. 1985;10:87-90.

207. Wilson JS, Fitzsimons D, Bradbury I et al. Does additional support by nurses enhance the effect of a brief smoking cessation intervention in people with moderate to severe chronic obstructive pulmonary disease? A randomised controlled trial. Int J Nurs Stud. 2008;45:508-517.

208. Tonnesen P, Mikkelsen K, Bremann L. Nurse-conducted smoking cessation in patients with COPD using nicotine sublingual tablets and behavioral support. Chest. 2006;130:334-342.

209. van Schayck CP, Kaper J, Wagena EJ et al. The cost-effectiveness of antidepressants for smoking cessation in chronic obstructive pulmonary disease (COPD) patients. Addiction. 2009;104:2110-2117.

210. Hoogendoorn M, Feenstra TL, Hoogenveen RT et al. Long-term effectiveness and cost-effectiveness of smoking cessation interventions in patients with COPD. Thorax.2010;65:711-8.

211. Berlin I, Jacob N, Coudert M et al. Adjustment of nicotine replacement therapies according to saliva cotinine concentration: the ADONIS* trial-a randomized study in smokers with medical comorbidities. Addiction. 2011;106:833-843.

212. Strassmann R, Bausch B, Spaar A et al. Smoking cessation interventions in COPD: a network meta-analysis of randomised trials. Eur Respir J. 2009;34:634-640.

213. Berlin I. Therapeutic strategies to optimize the efficacy of nicotine replacement therapies. COPD. 2009;6:272-276.

214. Moore D, Aveyard P, Connock M et al. Effectiveness and safety of nicotine replacement therapy assisted reduction to stop smoking: systematic review and meta-analysis. BMJ. 2009;338:b1024.

215. Richmond R, Zwar N. Review of bupropion for smoking cessation. Drug Alcohol Rev. 2003;22:203-220.

216. Tashkin D, Kanner R, Bailey W et al. Smoking cessation in patients with chronic obstructive pulmonary disease: adouble-blind, placebo-controlled, randomised trial. Lancet 2001;357:1571-1575.

More than 5 years have passed since the publication of this Clinical Practice Guideline and its validity has not been reviewed

217. Wagena EJ, Knipschild PG, Huibers MJ et al. Efficacy of bupropion and nortriptyline for smoking cessation among people at risk for or with chronic obstructive pulmonary disease. Arch Intern Med. 2005;165:2286-2292.

218. Bolin K, Wilson K, Benhaddi H et al. Cost-effectiveness of varenicline compared with nicotine patches for smoking cessation-results from four European countries. Eur J Public Health. 2009;19:650-654.

219. Ebbert JO, Wyatt KD, Zirakzadeh A et al. Clinical utility of varenicline for smokers with medical and psychiatric comorbidity. Int J Chron Obstruct Pulmon Dis. 2009;4:421-430.

220. Mohanasundaram UM, Chitkara R, Krishna G. Smoking cessation therapy with varenicline. Int J Chron Obstruct Pulmon Dis. 2008;3:239-251.

221. Tashkin DP, Rennard S, Hays JT et al. Effects of varenicline on smoking cessation in patients with mild to moderate COPD: a randomized controlled trial. Chest. 2011;139:591-599.

222. Nota informativa del 9 de enero de 2008 de la Agencia Española de Medicamentos y Productos Sanitarios sobre la revisión de la información de seguridad de la vareniclina en Europa. [sede Web]. [acceso 5-1-2012]; Disponible en: http://www.aemps.gob.es/informa/notasInformativas/medicamentosUsoHumano/seguridad/2008/NI_2008-01_vareniclina.htm 2008.

223. Hansen EC, Walters J, Baker RW. Explaining chronic obstructive pulmonary disease (COPD): perceptions of the role played by smoking. Soc Sci Health Illn. 2007;29:730-749.

224. Schofield I, Kerr S, Tolson D. An exploration of the smoking-related health beliefs of older people with chronic obstructive pulmonary disease. J Clin Nurs. 2007;16:1726-1735.

225. Wilson JS, Elborn JS, Fitzsimons D. 'It' s not worth stopping now': why do smokers with chronic obstructive pulmonary disease continue to smoke? A qualitative study. J Clin Nurs. 2011;20:819-827.

226. Winstanley L, Daunt M, Macfarlane J. Doctors' attitude towards current smokers with chronic obstructive pulmonary disease and its impact on delivering smoking cessation advice. Journal of Smoking Cessation. 2008;3(2):133-135.

227. Zhang MW, Ho RC, Cheung MW et al. Prevalence of depressive symptoms in patients with chronic obstructive pulmonary disease: a systematic review, meta-analysis and meta-regression. Gen Hosp Psychiatry. 2011;33:217-223.

228. Hill K, Geist R, Goldstein RS et al. Anxiety and depression in end-stage COPD. Eur Respir J. 2008;31:667-677.

229. Bosley CM, Corden ZM, Rees PJ et al. Psychological factors associated with use of home nebulized therapy for COPD. Eur Respir J. 1996;9:2346-2350.

230. Garrod R, Marshall J, Barley E et al. Predictors of success and failure in pulmonary rehabilitation. Eur Respir J. 2006;27:788-794.

231. Coultas DB, Edwards DW, Barnett B et al. Predictors of depressive symptoms in patients with COPD and health impact. COPD. 2007;4:23-28.

232. McCathie HC, Spence SH, Tate RL. Adjustment to chronic obstructive pulmonary disease: the importance of psychological factors. Eur Respir J. 2002;19:47-53.

233. Management of COPD Working Group. VA/DoD clinical practice guideline for the management of outpatient chronic obstructive pulmonary disease. Washington (DC): Department of Veterans Affairs, Department of Defense 2007.

More than 5 years have passed since the publication of this Clinical Practice Guideline and its validity has not been reviewed

234. National Collaborating Centre for Mental Health. Depression in adults with a chronic physical health problem: treatment and management. National Institute for Health and Clinical Excellence (NICE) (2009) clinical guideline 91. Disponible en: http://www.nice.org.uk/guidance/CG91.RefType: Generic

235. Gift AG, McCrone SH. Depression in patients with COPD. Heart Lung. 1993;22:289-297.

236. Yesavage JA. Depression in the elderly. How to recognize masked symptoms and choose appropriate therapy. Postgrad Med. 1992;91:255-8,261.

237. Eiser N, Harte R, Spiros K et al. Effect of treating depression on quality-of-life and exercise tolerance in severe COPD. COPD. 2005;2:233-241.

238. Lacasse Y, Beaudoin L, Rousseau L et al. Randomized trial of paroxetine in end-stage COPD. Monaldi Arch Chest Dis. 2004;61:140-147.

239. Silvertooth EJ, Doraiswamy PM, Clary GL et al. Citalopram and quality of life in lung transplant recipients. Psychosomatics. 2004;45:271-272.

240. Light RW, Merrill EJ, Despars J et al. Doxepin treatment of depressed patients with chronic obstructive pulmonary disease. Arch Intern Med. 1986;146:1377-1380.

241. Borson S, McDonald GJ, Gayle T et al. Improvement in mood, physical symptoms, and function with nortriptyline for depression in patients with chronic obstructive pulmonary disease. Psychosomatics. 1992;33:190-201.

242. Usmani ZA, Carson KV, Cheng JN et al. Pharmacological interventions for the treatment of anxiety disorders in chronic obstructive pulmonary disease. Cochrane Database Syst Rev. 2011;11:CD008483.

243. Baraniak A, Sheffield D. The efficacy of psychologically based interventions to improve anxiety, depression and quality of life in COPD: a systematic review and meta-analysis. Patient Educ Couns. 2011;83:29-36.

244. Hynninen MJ, Bjerke N, Pallesen S et al. A randomized controlled trial of cognitive behavioral therapy for anxiety and depression in COPD. Respir Med. 2010;104:986-994.

245. Lamers F, Jonkers CC, Bosma H et al. Improving quality of life in depressed COPD patients: effectiveness of a minimal psychological intervention. COPD. 2010;7:315-322.

246. Coventry PA, Hind D. Comprehensive pulmonary rehabilitation for anxiety and depression in adults with chronic obstructive pulmonary disease: Systematic review and meta-analysis. J Psychosom Res. 2007;63:551-565.

247. Paz-Diaz H, Montes de OM, Lopez JM et al. Pulmonary rehabilitation improves depression, anxiety, dyspnea and health status in patients with COPD. Am J Phys Med Rehabil. 2007;86:30-36.

248. Yohannes AM, Connolly MJ, Baldwin RC. A feasibility study of antidepressant drug therapy in depressed elderly patients with chronic obstructive pulmonary disease. Int J Geriatr Psychiatry. 2001;16:451-454.

249. Hutton W. Putting the public at the heart of the NHS. BMJ. 2007;334:69-70.

250. Health literacy: report of the Council on Scientific Affairs. Ad Hoc Committee on Health Literacy for the Council on Scientific Affairs, American Medical Association JAMA. 1999;281:552-557.

251. Selden CR ZMRS. Health literacy. Acceso el 4 de abril de 2012: http://www.nlm.nih.gov/archive//20061214/pubs/cbm/hliteracy.pdf. 2012. Ref Type: Report

More than 5 years have passed since the publication of this Clinical Practice Guideline, and its validity has not been reviewed

252. Dewalt DA, Pignone MP. The role of literacy in health and health care. Am Fam Physician. 2005;72:387-388.

253. Easton P, Entwistle VA, Williams B. Health in the 'hidden population' of people with low literacy. A systematic review of the literature. BMC Public Health. 2010;10:459.

254. Powers BJ, Trinh JV, Bosworth HB. Can this patient read and understand written health information? JAMA. 2010;304:76-84.

255. Roberts NJ, Ghiassi R, Partridge MR. Health literacy in COPD. Int J Chron Obstruct Pulmon Dis. 2008;3:499-507.

256. Davis TC, Wolf MS. Health literacy: implications for family medicine. Fam Med. 2004;36:595-598.

257. Kit de visita médica. http://www.universidadpacientes.org/kitdevisitamedica/elkit/index.php?pag=descarga Acceso el 4 de abril de 2011. 2012. Ref Type: Report

258. Bourbeau J, van der PJ. Promoting effective self-management programmes to improve COPD. Eur Respir J. 2009;33:461-463.

259. Bodenheimer T MKSC. Helping Patients Manage Their Chronic Conditions. Oakland, CA, California Healthcare Foundation, 2005. 2012. Ref Type: Report

260. Mauksch LB, Dugdale DC, Dodson S et al. Relationship, communication, and efficiency in the medical encounter: creating a clinical model from a literature review. Arch Intern Med. 2008;168:1387-1395.

261. Langewitz W, Denz M, Keller A et al. Spontaneous talking time at start of consultation in outpatient clinic: cohort study. BMJ. 2002;325:682-683.

262. Hanson JL. Shared decision making: have we missed the obvious? Arch Intern Med. 2008;168:1368-1370.

263. Bourbeau J, Julien M, Maltais F et al. Reduction of hospital utilization inpatients with chronic obstructive pulmonary disease: adisease-specific self-management intervention. Arch Intern Med. 2003;163:585-591.

264. De VB, rling-Fisher C, Thomas AC et al. Implementation and outcomes of group medical appointments in an outpatient specialty care clinic. J Am Acad Nurse Pract. 2008;20:163-169.

265. Jaber R, Braksmajer A, Trilling JS. Group visits for chronic illness care: models, benefits and challenges. Fam Pract Manag. 2006;13:37-40.

266. Bischo ff EW, Hamd DH, Sedeno M et al. Effects of written action plan adherence on COPD exacerbation recovery. Thorax. 2011;66:26-31.

267. Lorig KR, Ritter PL, Dost A et al. The Expert Patients Programme online, a1-year study of an Internet-based self-management programme for people with long-term conditions. Chronic Illn. 2008;4:247-256.

268. Martí M, Fabrellas N, Chicote S et al. Llamada al autocuidado. Seguimiento telefónico a enfermedades crónicas. Revista de Innovación Sanitaria y Atención Integrada. 2009;1:Article 7.

269. Marshall A, Medvedev O, Antonov A. Use of a smartphone for improved self-management of pulmonary rehabilitation. Int J Telemed Appl. 2008;753064.

270. Toledo P de, Jiménez S, Pozo F del et al. Telemedicine experience for chronic care in COPD. IEEE TransactionsonInformationTechnology in Biomedicine. 2006;10:573.

More than 5 years have passed since the publication of this Clinical Practice Guideline, and its validity has not been reviewed

271. Torrente E, Escarrabill J, and Martí T. Impacto de las redes sociales de pacientes en la práctica asistencial. Revista de Innovación Sanitaria y Atención Integrada. 2010;2.

272. Tapscott D WD. Wikinomics. London: AtlanticBooks; 2006. 2012.

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