Pharmacological treatment of COPD*

Tratamento farmacológico da DPOC

Ana Maria Baptista Menezes, Silvia Elaine Cardozo Macedo, Ricardo Bica Noal, Jussara Fiterman, Alberto Cukier, José Miguel Chatkin, Frederico Leon Arrabal Fernandes; Grupo de Trabalho da Sociedade Brasileira de Pneumologia e Tisiologia, Grupo de Trabalho do Programa de Pós-Graduação em Epidemiologia da Universidade Federal de Pelotas

Resumo

Aproximadamente sete milhões de brasileiros acima de 40 anos são acometidos pela DPOC. Nos últimos anos, importantes avanços foram registrados no campo do tratamento medicamentoso dessa condição. Foi realizada uma revisão sistemática incluindo artigos originais sobre tratamento farmacológico da DPOC publicados entre 2005 e 2009, indexados em bases de dados nacionais e internacionais e escritos em inglês, espanhol ou português. Artigos com tamanho amostral menor de 100 indivíduos foram excluídos. Os desfechos sintomas, função pulmonar, qualidade de vida, exacerbações, mortalidade e efeitos adversos foram pesquisados. Os artigos foram classificados segundo o critério da *Global Initiative for Chronic Obstructive Lung Disease* para nível de evidência científica (grau de recomendação A, B e C). Dos 84 artigos selecionados, 40 (47,6%), 18 (21,4%) e 26 (31,0%) foram classificados com graus A, B e C, respectivamente. Das 420 análises oriundas desses artigos, 236 referiam-se à comparação de fármacos contra placebo nos diversos desfechos estudados. Dessas 236 análises, os fármacos mais frequentemente estudados foram anticolinérgicos de longa duração, a combinação β_2-agonistas de longa duração + corticosteroides inalatórios e corticosteroides inalatórios isolados em 66, 48 e 42 análises, respectivamente. Nas mesmas análises, os desfechos função pulmonar, efeitos adversos e sintomas geraram 58, 54 e 35 análises, respectivamente. A maioria dos estudos mostrou que os medicamentos aliviaram os sintomas, melhoraram a qualidade de vida, a função pulmonar e preveniram as exacerbações. Poucos estudos contemplaram o desfecho mortalidade, e o papel do tratamento medicamentoso nesse desfecho ainda não está completamente definido. Os fármacos estudados são seguros no manejo da DPOC, com poucos efeitos adversos.

Descritores: Doença pulmonar obstrutiva crônica/terapia; Doença pulmonar obstrutiva crônica/mortalidade; Revisão.

Abstract

Approximately seven million Brazilians over 40 years of age have COPD. In recent years, major advances have been made in the pharmacological treatment of this condition. We performed a systematic review including original articles on pharmacological treatments for COPD. We reviewed articles written in English, Spanish, or Portuguese; published between 2005 and 2009; and indexed in national and international databases. Articles with a sample size < 100 individuals were excluded. The outcome measures were symptoms, pulmonary function, quality of life, exacerbations, mortality, and adverse drug effects. Articles were classified in accordance with the Global Initiative for Chronic Obstructive Lung Disease criteria for the determination of the level of scientific evidence (grade of recommendation A, B, or C). Of the 84 articles selected, 40 (47.6%), 18 (21.4%), and 26 (31.0%) were classified as grades A, B, and C, respectively. Of the 420 analyses made in these articles, 236 were regarding the comparison between medications and placebos. Among these 236 analyses, the most commonly studied medications (in 66, 48, and 42 analyses, respectively) were long-acting anticholinergics; the combination of long-acting β_2 agonists and inhaled corticosteroids; and inhaled corticosteroids in isolation. Pulmonary function, adverse effects, and symptoms as outcomes generated 58, 54, and 35 analyses, respectively. The majority of the studies showed that the medications evaluated provided symptom relief; improved the quality of life and pulmonary function of patients; and prevented exacerbations. Few studies analyzed mortality as an outcome, and the role that pharmacological treatment plays in this outcome has yet to be fully defined. The medications studied are safe to use in the management of COPD and have few adverse effects.

Keywords: Pulmonary disease, chronic obstructive/therapy; Pulmonary disease, chronic obstructive/mortality; Review.

---

* Study carried out under the auspices of the Graduate Program in Epidemiology, Department of Social Medicine, Federal University of Pelotas School of Medicine, Pelotas, Brazil.

Correspondence to: Ana M B Menezes. Avenida Domingos de Almeida, 1146, casa 25, CEP 96085-470, Pelotas, RS, Brasil.
Tel/Fax: 55 53 3284-1300. E-mail: anamene@terra.com.br

Financial support: This study received financial support from the *Conselho Nacional de Desenvolvimento Científico e Tecnológico* (CNPq, Brazilian National Council for Scientific and Technological Development).
Submitted: 13 June 2011. Accepted, after review: 21 June 2011.

Introduction

In recent years, COPD has come to play a prominent role on the international stage. In a time series conducted in the United States between 1970 and 2002,[1] the astounding increase in mortality from COPD, when compared with the reduction in mortality from various other diseases, and the understanding that COPD had erroneously been labeled progressive, irreversible, and untreatable were some of the key points that piqued the interest of the scientific community.[2] In the last decade, a new COPD-related paradigm emerged, and the disease became the object of further studies, as well as becoming more widely recognized and identified, by health professionals, opening new possibilities for the treatment of COPD. It has been estimated that, in Brazil, COPD affects approximately seven million adults aged ≥ 40 years.[3] Nevertheless, only 2% of that population report having been diagnosed with the disease, and only 18% report being under treatment.[3] Even in the most severe cases of COPD, i.e., stage III (severe COPD) and stage VI (very severe COPD), as defined by the Global Initiative for Chronic Obstructive Lung Disease (GOLD),[4] COPD medication is used by only approximately half of the patients.[5] This worrisome finding has also been reported in high-income countries.[6,7] The lack of early, appropriate treatment for COPD has disastrous consequences for patients, including loss of pulmonary function and death.[8] In recent years, there has been an increase in the number of medications designed specifically for the treatment of COPD. Such medications act on various aspects of the pathophysiology of the disease. There has recently been an increase in the number of studies investigating the various outcomes and pharmacological treatment options. Therefore, we deemed it appropriate to conduct a systematic review of articles that were published in recent years and addressed the pharmacological treatment of COPD.

Article selection

The selection of original studies and the determination of the levels of scientific evidence were the cornerstones of the present review. The efficacy/effectiveness of the medications in producing various outcomes was evaluated with the purpose of contributing to the continuing education of health professionals, as well as to the future development of consensuses, guidelines, and algorithms for the pharmacological treatment of patients with COPD. In view of the wide variety of treatments available for COPD, we limited our search to the pharmacological treatment of the disease. Treatment components, such as the use of oxygen therapy, ventilatory support, and antibiotic therapy during exacerbations, as well as the use of vaccines and specific treatment for the prevention of smoking-related COPD, were outside the scope of the present review.

We searched five databases: PubMed; Web of Science; EMBASE; Cumulative Index to Nursing and Allied Health Literature; and LILACS. We selected articles published between 2005 and 2009, written in English, Spanish, or Portuguese. We combined COPD descriptors with the names of various COPD medications described in the literature. We applied inclusion and exclusion criteria in order to select articles that were in conformity with the principal objective of the present review. Chart 1 shows the principal drug abbreviations used in the present review. The description of the results was based on the six outcome measures of present review, namely symptoms, pulmonary function, exacerbation, quality of life, mortality, and adverse drug effects. For each outcome, we evaluated the medications used and the combinations thereof. Initially, we present the results of the comparison between the various COPD medications and placebos. Subsequently, we present the results of the comparison among the COPD medications. The results of the comparison between the medications and placebos are also presented as figures, the x axis showing the number of analyses and the y axis showing the classes of medications. The levels of scientific evidence (grade of recommendation A, B, or C) are shown in the figures, and each results section is followed by a discussion of recent evidence. The discussion sections were prepared by specialists. For each discussion section, we used, in addition to original articles, other systematic reviews, as well as meta-analyses, all of which were pertinent to the theme. The methodology employed in the present review is described in detail in the online supplement of the journal (http://www.jornaldepneumologia.com.br/english/artigo_detalhes.asp?id=1785).

The process of selection allowed us to include 84 original articles in the present review. Many of those articles addressed more than one class of medication and various outcomes, which generated 420 analyses. Of those, 236 were regarding the comparison between pharmacological treatment and placebo, and 184 were regarding the comparison of the medications used. Below, we describe the analyses of the six outcome measures evaluated in our review.

Outcome measures

Symptoms

Symptom relief is one of the immediate desires of patients with COPD. The results of the present review show that the medications for COPD symptom relief that were most commonly investigated in placebo-controlled studies were those aimed at treating moderate to severe COPD, namely LABAs, LAMAs, and ICs. Most of the studies showed that those medications, used in isolation or in combination, were effective in providing symptom relief (Figure 1). Of all studies comparing COPD medications with placebos, those involving LABAs, used in isolation or in combination with ICs, were the ones that most consistently demonstrated an improvement in the symptoms of COPD. Although LAMAs were shown to be effective in reducing COPD symptoms, 4 analyses found no beneficial effects; of those 4, 3 involved patients with mild to moderate COPD.[9-11] In four of the five studies, the use of ICs in isolation was shown to have a long-term beneficial effect on COPD symptoms. However, Vestbo et al.[12] evaluated symptom reduction at two weeks into IC treatment and found that ICs had a beneficial effect only on the patients who used them in combination with LABAs. As can be seen in Figure 1, the use of PDE4 inhibitors, as well as that of LAMAs and ICs in combination, also had a beneficial effect on COPD symptoms, as demonstrated in well-conducted studies, although there have been analyses of those medications. The comparison of medications revealed that there were no differences among the different classes of SABAs[13] or among those of LABAs[14-16] in terms of symptom reduction and the use of rescue medication. Regarding different classes of bronchodilators, Griffin et al. conducted a cohort study in which they noted a reduction in the use of rescue medications among a group of patients receiving LAMAs, when compared with a group of patients receiving the SAMA-SABA combination.[17] In patients with moderate or severe COPD, as determined by the GOLD classification, the use of salmeterol in combination with fluticasone was shown to be superior to the use of SABAs in combination with SAMAs,[18] as well as to the use of salmeterol in isolation.[19-21] In patients with severe or very severe COPD, as determined by the GOLD classification, there were no differences between the salmeterol-fluticasone and formoterol-budesonide combinations in terms of symptom

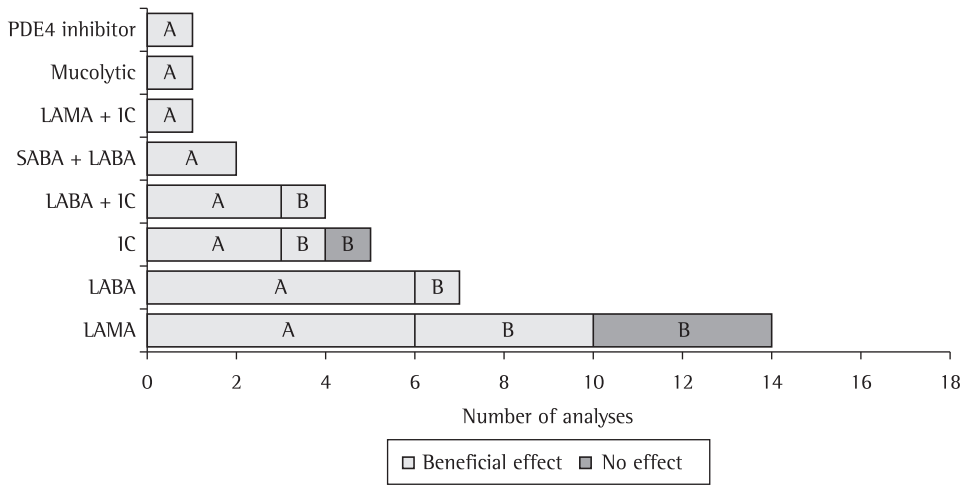

Figure 1 - Effects of the comparison between pharmacological treatment and placebo on symptoms as the outcome measure, by level of scientific evidence (grade of recommendation).

Chart 1 - Abbreviations used in the present review.

Abbreviation	Definition
LABA	long-acting β_2 agonist
SABA	short-acting β_2 agonist
SAMA	short-acting muscarinic anticholinergic
LAMA	long-acting muscarinic anticholinergic
IC	inhaled corticosteroid
PDE4	phosphodiesterase-4

reduction and rescue medication use.[22] Celik et al.[23] noted that the use of a leukotriene receptor antagonist in combination with treatment with a bronchodilator (ipratropium bromide and formoterol) produced a reduction in the dyspnea score when compared with that obtained with the use of bronchodilators in isolation. The effect of the combination of PDE4 inhibitors with LABAs and LAMAs was compared with that of other medications in a study conducted by Fabri et al.[24] In that study, PDE4 inhibitors had a beneficial effect on COPD symptoms and reduced the use of rescue medications when used in combination with LAMAs but not when used in combination with LABAs. The use of such medications, either in isolation or in combination, should be further investigated in order to define their role in relieving the symptoms of COPD.

A reduction in mortality and in the number of exacerbations, together with functional improvement, are important outcome measures of studies investigating therapeutic approaches to COPD. However, the immediate desire of patients is relief of the symptoms of dyspnea, with improvement in cough and in exercise capacity/tolerance. A medication or combination of medications that can bring these benefits to patients can also improve treatment compliance and increase patient confidence in the treatment. Although symptom relief is relevant, studies in which symptom relief is the primary outcome measure are scarce, which makes it difficult to interpret this outcome measure in the literature.

Our systematic review of the recent literature underscores the importance of long-acting bronchodilators (LABAs and LAMAs) for symptom relief in patients with COPD that is more severe. Although LABAs were shown to be more consistently effective in reducing dyspnea than were LAMAs, there is no consensus in the literature as to which class of medication is superior in terms of providing symptom relief in patients with moderate to severe COPD. It seems that the effect of LABAs, as well as that of the combination of LABAs and ICs, is a class-related effect, and no studies in the recent literature have demonstrated the superiority of any given commercial formulation. The addition of ICs to the treatment regimen seems to have a marginally positive effect in relation to monotherapy with LABAs or LAMAs, the latter having been evaluated in only one study. However, it should be taken into consideration that ICs increase the risk of side effects, such as pneumonia and oral candidiasis. Therefore, our review showed that the studies published in recent years firmly established long-acting bronchodilators (LAMAs and LABAs) as the first-line treatment for symptom relief in patients classified as having GOLD stage II, III, or IV COPD. There are knowledge gaps to be filled, including the definition of the roles that next-generation LABAs, PDE4 inhibitors, and the combination of bronchodilators with ICs and mucolytics play in reducing dyspnea. These questions can be answered by studies in which COPD symptoms are evaluated objectively and constitute the primary outcome measure.

Pulmonary function

The pharmacological treatment of COPD can affect pulmonary function in two ways. First, it increases FEV_1 and FVC, reducing the airway obstruction and air trapping seen in patients with COPD. Second, it reduces the progressive loss of pulmonary function. These two outcome measures were evaluated in 58 analyses (Figure 2). Regarding the impact of COPD medications on pulmonary function, the use of ICs, either in isolation or in combination (a total of 23 analyses), was shown to be beneficial for patients with COPD. There has been only one clinical trial—a nonrandomized trial evaluating a combination of LABAs and ICs

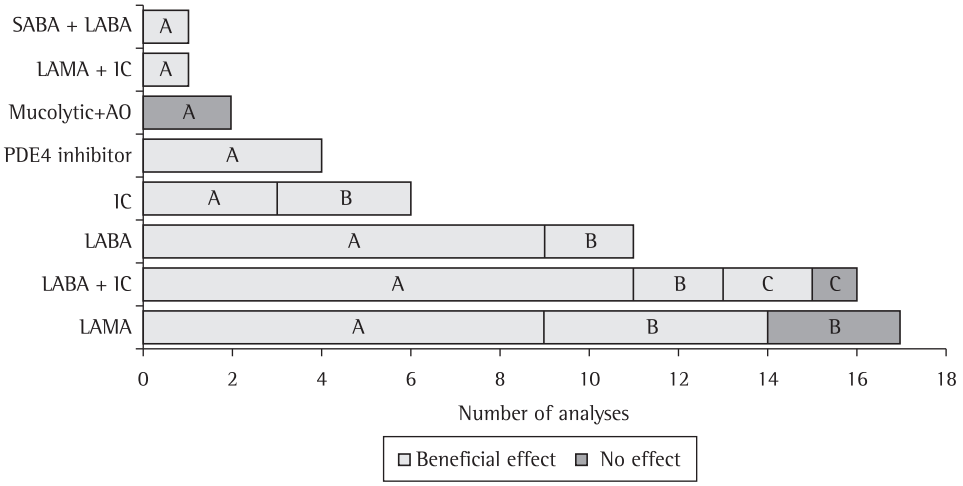

Figure 2 - Effects of the comparison between pharmacological treatment and placebo on pulmonary function as the outcome measure, by level of evidence (grade of recommendation). AO: antioxidant.

in a subgroup of patients with severe COPD—in which COPD medications were reported to have no effect on pulmonary function.[25] In 14 of the 17 analyses identified, the use of LAMAs was shown to improve pulmonary function. In 3 analyses of patients with moderate disease, LAMAs were not found to be superior to placebo.[26] Campbell et al. demonstrated that the combination of SABAs and LABAs was superior to placebo in terms of improving pulmonary function.[27] Likewise, Hodder et al.[28] found that the LAMA-IC and LABA-IC combinations were superior to placebo in terms of improving pulmonary function (FEV_1 and FVC) during a six-month study involving patients with moderate or severe COPD, as determined by the GOLD classification. The effects that a mucolytic agent[29] and an antioxidant (N-acetylcysteine)[30] have on pulmonary function have been shown to be similar to that of placebo. The effect of PDE4 inhibitors on pulmonary function was shown to be superior to that of placebo.[31] Regarding the comparison of classes of medications, two clinical trials showed that LAMAs were superior to LABAs in terms of improving pulmonary function.[28,32] However, Aaron et al. conducted a study comparing the use of LAMAs in isolation with the use of LAMAs in combination with LABAs in terms of their effects on pulmonary function and found that the LAMA-LABA combination provided no additional benefits.[33] In contrast, the use of the LAMA-LABA-IC combination was found to be superior to the use of LAMAs in isolation.[33] The combination of PDE4 inhibitors with LAMAs or LABAs was found to have a beneficial effect on pulmonary function when compared with the use of those medications in isolation.[24] A subsequent analysis in one study showed that the use of ICs, of LABAs, and of the LABA-IC combination in patients with moderate to severe COPD reduced the rate of decline in pulmonary function[34] when compared with the use of a placebo; in addition, there were no significant differences among those medications regarding their impact on the rate of decline in pulmonary function. One long-term randomized, double-blind trial showed that the use of LAMAs does not reduce the rate of decline in pulmonary function.[35] A study investigating patients with moderate COPD found a slight but significant reduction (6 mL per year) in the rate of decline in FEV_1 following bronchodilator use.[26]

Our review of recent studies showed that the use of inhaled medications improves, although only slightly, pulmonary function parameters in patients with COPD. The use of LAMAs, LABAs, and ICs, either in isolation or in combination, was shown to increase FEV_1, which ranged from 60 mL to 190 mL over various follow-up periods (ranging from weeks to years). Considering that the recommendations of the American Thoracic Society/European Respiratory Society for standardization of spirometry[36] state that only short-term FEV_1 changes of 20% and long-term FEV_1 changes of 15% are significant, the increase in FEV_1 observed in recent studies is of borderline significance, and its clinical relevance remains

open to debate. Combination therapy with the three classes of medications apparently leads to greater functional improvement than does the use of each class of medication in isolation. The use of PDE4 inhibitors significantly increased FEV_1 when compared with the use of a placebo. In absolute terms, the increase, evaluated over 24 or 52 weeks, was slight, ranging from 24 mL to 74 mL. Clinical trials investigating this new class of medication are required in order to define the role of PDE4 inhibitors in the treatment of COPD. The results of the articles that investigated mucolytics/antioxidants and were published in the study period were negative, which reinforces the current view of national and international consensus that those classes of medications are of limited use in improving pulmonary function in patients with COPD. In COPD, the progressive decline in pulmonary function is a major prognostic marker. It seems that one way of changing the natural evolution of COPD is by addressing the rate of FEV_1 reduction. At the end of the 1990s and in the beginning of this century, various studies evaluated the effects of different therapeutic regimens on that outcome measure. Two of those studies—one evaluating the use of N-acetylcysteine[30] and the other evaluating the use of fluticasone[37]—are of note. The results of those studies with regard to the rate of decline in pulmonary function were negative, as were those of other studies.[38] Two studies differ from those published in the beginning of the decade, for two reasons[26,34]: the number of randomized patients; and the follow-up period, which was significantly longer. Post hoc analyses of those two studies showed that reduction in the decline in FEV_1 was, in the first study, 13 mL/year, in all three treatment arms,[34] and, in the second study, 6 mL/year in patients with moderate disease.[26] Those findings have been used by those who believe that the pharmacological treatment of COPD should begin early; however, there is still no definitive answer to the question of when it is appropriate to begin the treatment.[39]

Exacerbation

One of the principal objectives of COPD treatment is to prevent and treat COPD exacerbations, given that COPD exacerbations worsen the quality of life of patients, accelerate the progressive decline in pulmonary function, and increase mortality.[4,40] In the present review, 35 analyses compared the effect of the medications used in order to prevent COPD exacerbations with that of placebo (Figure 3). Most of the analyses of the effect of LAMAs—involving patients with moderate to severe COPD, as determined by the GOLD classification—have suggested that LAMAs reduce the number of exacerbations or increase the interval between episodes of exacerbation. Two groups of authors[41,42] found no beneficial effects, which might be due to the inclusion of patients with only one episode of exacerbation in the previous year or to greater losses to follow-up in the

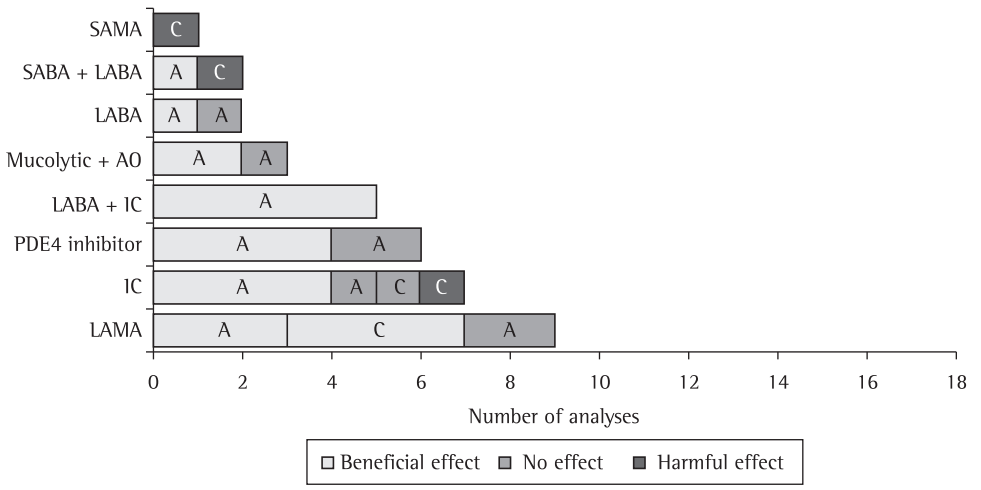

Figure 3 - Effects of the comparison between pharmacological treatment and placebo on exacerbation as the outcome measure, by level of evidence (grade of recommendation). AO: antioxidant.

untreated group. Regarding the use of LABAs, Campbell et al.[27] found no differences between patients treated with formoterol and those treated with placebo in terms of the effect of the treatment on the number of exacerbations. However, Calverley et al.[43] reported that the number of exacerbations was lower in the individuals who were treated with salmeterol than in those who received placebo; it is of note that we found only 2 analyses of the use of salmeterol. Although the combination of LABAs and SABAs was not shown to reduce the number of exacerbations, patients who received the combination required rescue medications less frequently than did those who received placebo.[27] One study reported that neither SAMAs nor the SABA-LABA combination had a beneficial effect on the number of hospitalizations[44]; however, that study received a grade C recommendation. Of the 7 analyses of the effect of ICs on COPD exacerbations, 4 found a reduction in the number of exacerbations in comparison with that seen in the placebo group. Choudhury et al.[45] reported an increase in the interval between exacerbations but observed no additional benefits. Macie et al.[44] found no differences between patients receiving ICs and those receiving placebo in terms of the number of hospitalizations (exacerbations) for cardiovascular disease, whereas Ernst et al.[46] showed that the risk of hospitalizations for pneumonia was higher in COPD patients receiving ICs. All of the analyses of the effect of the LABA-IC combination found that the number of exacerbations was lower in patients receiving the combination than in those receiving placebo. According to Rennard et al.,[47] the formoterol-budesonide combination increased the interval between exacerbations and reduced the number of exacerbations by approximately 40% in comparison with placebo. Most of the analyses of the effect of PDE4 inhibitors on the number of COPD exacerbations found that PDE4 inhibitors had a beneficial effect. In 2007, Calverley et al.[48] studied patients with severe or very severe COPD receiving PDE4 inhibitors or placebo and found no differences between PDE4 inhibitors and placebo in terms of their effect on the number of exacerbations. However, in 2009, the same group of authors[31] investigated a larger sample and found a 17% reduction in the annual rate of moderate to severe exacerbations per patient among patients receiving PDE4 inhibitors in comparison with that found among those receiving placebo, specifically in symptomatic cases. In addition, the authors noted longer intervals between exacerbations and less need for corticosteroid and antimicrobial use in order to treat COPD exacerbations. As can be seen in Figure 3, in 2 of the 3 analyses compared (all with a grade A recommendation), the use of mucolytics and antioxidants was shown to have a beneficial effect in terms of preventing exacerbations. Aaron et al.[33] conducted a study investigating the use of LAMAs in combination with other medications in patients with moderate or severe COPD, as determined by the GOLD classification. The authors noted that, among the patients receiving LAMAs in isolation, the proportion of patients who presented with exacerbations requiring the use of systemic corticosteroids or antimicrobials did not differ from that observed among those receiving the LAMA-LABA combination or the LAMA-LABA-IC combination. In contrast, the LAMA-LABA-IC combination reduced the rate of hospitalizations for COPD by nearly 40% in comparison with that observed for LAMAs in isolation. We found no studies comparing formoterol and salmeterol in terms of their effect on COPD exacerbations. Donohue et al.[16] found no significant differences between patients treated with formoterol and those treated with salmeterol regarding the number of exacerbations occurring in one year. In the analyses evaluated, the use of LABAs and ICs in combination was shown to be superior to that of LABAs or ICs in isolation for the following outcome measures[19-21,43,47]: number of exacerbations; severe exacerbations requiring hospitalization; and use of systemic corticosteroids.

The management of COPD exacerbations, especially that of those requiring hospitalization, accounts for approximately half of all COPD-related treatment costs.[49] In addition, exacerbations in COPD patients can worsen quality of life, impair pulmonary function, and increase mortality.[4,40] The lack of a consensus regarding the definition of COPD exacerbation and how to grade the severity of COPD exacerbation is responsible for certain discrepancies among the results of clinical studies.[50] Therefore, some studies included only exacerbations characterized by worsening

of the symptoms for at least three days, requiring systemic corticosteroids, antibiotics, or hospitalization.[35,43] Pharmacological treatment with bronchodilators used in isolation or in combination with corticosteroids can reduce the frequency of exacerbations, increase the interval between exacerbations, or reduce the severity of the exacerbations. The studies included in our review were highly heterogeneous in terms of sample size, drug doses, drug combinations, COPD severity, length of follow-up, and parameters used in order to evaluate treatment response. The number of analyses of the use of LABAs, SAMAs, or the SABA-LABA combination was small, and the analyses yielded conflicting results, only 1 analysis having shown that the use of LABAs had a beneficial effect on COPD exacerbations. A review published in 2008 and including studies conducted before 2005 showed that the use of LABAs in isolation reduced the rate of exacerbations by 22% when compared with the use of a placebo.[51] The effect of ICs on COPD exacerbations is beneficial, although a recent review showed that the benefit is minimal and is seen only in patients with severe COPD.[52] Guidelines for COPD management recommend that ICs be used only in patients with severe COPD and two or more exacerbations per year.[4,40] Although various analyses in the present review demonstrated that the use of ICs and LABAs in combination has a greater beneficial effect on COPD exacerbations than does the use of those drugs in isolation, the clinical relevance is debatable. In comparison with the use of a placebo, the use of the LABA-IC combination resulted in a 25% reduction in COPD exacerbations,[34] whereas the use of a LAMA resulted in a 15% reduction.[26] According to Cazzola et al.,[50] such statistical differences have clinical value only when COPD exacerbations are reduced to one episode per year or when there is a ≥ 22% reduction in the number of exacerbations. Most of the studies evaluating the effects of PDE4 inhibitors have also reported beneficial effects. It is of note that PDE4 inhibitors reduced the number of COPD exacerbations only in patients with clinical characteristics of intense chronic bronchitis accompanied by chronic cough and numerous exacerbations. In the present review, there was a relatively small number of analyses from studies comparing the various COPD medications. Aaron et al. found no differences among groups of patients receiving a LAMA, a LAMA-LABA combination, or a LAMA-LABA-IC combination, in terms of the proportion of patients with exacerbations.[33] The rate of hospitalization was lower when LAMAs, LABAs, and ICs were used in combination than when LAMAs were used in isolation, although further studies are needed before definitive conclusions can be drawn. The choice of medications for reducing COPD exacerbations, as well as the decision of whether to use monotherapy or combination therapy, should be made on a case-by-case basis and should take into consideration disease severity, potential adverse drug effects, and costs.[4,40] The combination of medications with other

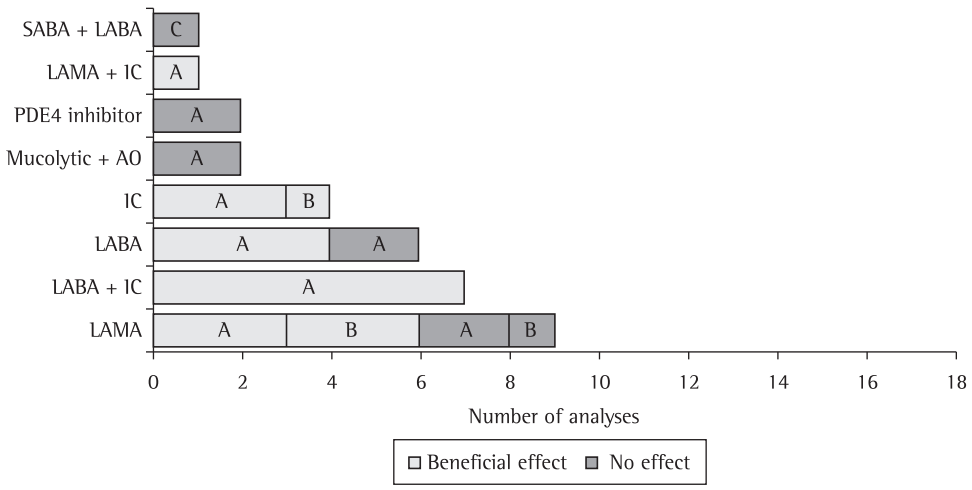

Figure 4 - Effects of the comparison between pharmacological treatment and placebo on quality of life as the outcome measure, by level of evidence (grade of recommendation). AO: antioxidant.

measures, such as pulmonary rehabilitation, vaccination, and smoking cessation, is extremely important for the success of the treatment.

Quality of life

Disability and low quality of life are conditions that have both been associated with COPD. In numerous studies in the literature, quality of life has been one of the outcome measures of COPD treatment. In the present review, the 32 placebo-controlled analyses of medications (Figure 4) showed that the use of ICs in isolation, as well as the use of LABAs and LAMAs in isolation or in combination with ICs, improved the quality of life of COPD patients, as assessed, in most cases, by the St. George's Respiratory Questionnaire (SGRQ). Neither antioxidants, mucolytics, LABA-SABA combination, nor PDE4 inhibitors had no beneficial effect on quality of life. It should be borne in mind that we evaluated only a small number of analyses of the effect that PDE4 inhibitors have on quality of life. In 6 analyses of patients with moderate to very severe COPD, the use of LAMAs was shown to have a beneficial effect on quality of life when compared with the use of a placebo.[9,26,35,41,53,54] However, two groups of authors[11,42] evaluated patients with mild to moderate COPD, as determined by the GOLD classification, and found no such effect. Only one study evaluated the effect of the LAMA-IC combination on quality of life, and it was shown to be superior to that of placebo during the six-month study period.[28] The use of LABAs in isolation was compared with the use of a placebo and was shown to have a beneficial effect on quality of life in 4 of the 6 analyses with a grade A recommendation. In the remaining 2, no beneficial effect was found. Regardless of the association studied, all of the analyses comparing the LABA-IC combination with placebo showed that the former had positive effects on quality of life. Aaron et al.[33] compared various classes of medications and found that the use of LABAs in combination with LAMAs, as well as the use of LABAs and ICs in combination with LAMAs, had beneficial effects on the quality of life of patients with moderate to severe COPD, when compared with those observed for the use of LAMAs in isolation. Similar results were reported by Welte et al.[55] when comparing the use of LAMAs in isolation with the use of LAMAs in combination with LABAs and ICs. However, Hanania et al.[56] reported that the use of LAMAs in combination with LABAs had no beneficial effects on quality of life when compared with the use of LAMAs in isolation.

Health-related quality of life has played an increasingly more important role in studies evaluating the effectiveness/efficacy of therapeutic interventions. The use of disease-specific questionnaires, such as the SGRQ, has the advantage of obtaining results with the detection of small changes in the course of the disease after interventions. Regarding the SGRQ, variations ≥ four points in any domain or in the total score are considered clinically significant. A meta-analysis comparing LAMAs with placebo[57] found that the former had a beneficial effect

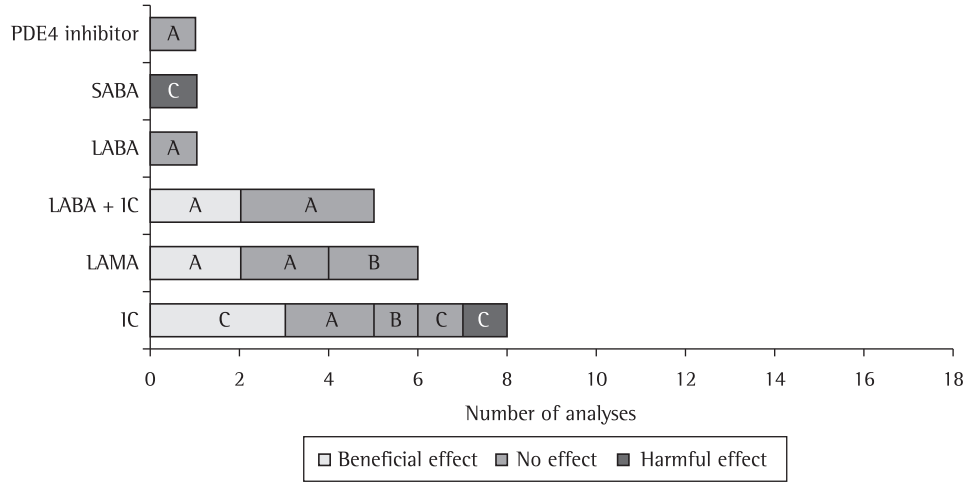

Figure 5 - Effects of the comparison between pharmacological treatment and placebo on mortality as the outcome measure, by level of evidence (grade of recommendation).

on the quality of life, as demonstrated in the studies evaluating the differences in the mean SGRQ score and in those analyzing the proportion of patients whose SGRQ scores were reduced by four points or more. In another meta-analysis, in which the effect of LABAs on COPD patients with minimally reversible obstruction was evaluated,[58] LABAs were shown to be significantly superior to placebo in terms of their effects on the quality of life of patients, as assessed by the SGRQ. However, conflicting results were obtained when quality of life was assessed by other instruments. Yang et al.[59] conducted a meta-analysis of studies comparing ICs with placebo and found a lower rate of decline in quality of life. In general, the results of that review, as well as those of other reviews, showed that the use of LABAs, LAMAs, and ICs (the last either in isolation or in combination with LABAs or LAMAs) had a beneficial effect on the quality of life of patients with COPD. However, those results should be interpreted with caution. Although statistically significant, the reduction in the mean SGRQ found in most of the studies was inferior to that which is considered clinically significant (≥ four points). Another important finding is that quality of life was not the primary outcome measure in any of the studies included, with the exception of a study conducted by Tonnel et al.[54] This underscores the need for caution when interpreting the recent data from the literature.

Mortality

Although the available evidence demonstrates that many of the medications recommended for the treatment of COPD are effective regarding various clinically relevant aspects of the disease, the effects of COPD medications on mortality have yet to be well defined. As can be seen in Figure 5, 22 analyses evaluated the effect of pharmacological treatment on mortality in COPD patients. Of those 22 analyses, over half compared the use of a placebo with the use of ICs or LAMAs in isolation or with that of LABAs and ICs in combination. Two of the analyses showed an increase in mortality, whereas some others showed a reduction in mortality. However, most showed that the medications had no effect on mortality. In the analyses showing that the use of COPD medications reduced mortality when compared with the use of a placebo, the medications that were evaluated were ICs in isolation, LAMAs, and the LABA-IC combination. Cohort studies and case-control studies compared the use of ICs with the use of a placebo and found that the former had a beneficial effect on mortality.[60-62] Those results, however, were not confirmed by prospective clinical trials.[43,63] In a case-control study comparing an IC (fluticasone) with a placebo, Ernst et al. noted an increase in mortality from pneumonia.[46] In a clinical trial, Calverley et al. compared patients receiving placebo with those receiving a LABA-IC combination.[43] The authors found no reduction in mortality, although the difference was borderline significant ($p = 0.052$). A subsequent analysis of that study revealed that the use of salmeterol and fluticasone in combination reduced mortality in patients with moderate or severe COPD but not in those with very severe COPD.[64] Two clinical trials compared LAMAs with placebo and found that the former had no beneficial effects on mortality from COPD.[26,35] However, a subsequent analysis of one of the clinical trials revealed a reduction in mortality in patients with moderate or severe COPD, as determined by the GOLD classification; nevertheless, the reduction was not maintained 30 days after the end of the study.[65] Only one case-control study compared the regular use of SABAs in isolation with the use of a placebo and found an increase in mortality in the group of patients who received treatment.[66] Studies comparing placebo with LABAs[43] and PDE4 inhibitors[31] found that the medications had no impact on mortality in COPD patients. The evidence that is currently available is inconclusive with regard to the impact that the various bronchodilators have on COPD-related mortality. One cohort study found that mortality at post-discharge month 6 was 20% lower among those receiving LAMAs than among those receiving LABAs,[67] a result that was even more significant when LAMAs were used in combination with ICs. Another longitudinal study, however, found no such differences between LAMAs and LABAs.[68] Nevertheless, a clinical trial comparing LAMAs with the LABA-IC combination found that the latter reduced the two-year mortality.[69] Observational studies comparing the use of SABAs with the use of LABAs in isolation or in combination with ICs showed that LABAs were superior to SABAs in

terms of reducing mortality.[70,71] There is no evidence that the use of xanthines has any effect on COPD-related mortality when compared with the use of SABAs.[71]

For many years, smoking cessation and oxygen therapy for patients with severe hypoxemia were considered to be the only interventions that had any effect on COPD-related mortality. Since the late 1990s, there has been a qualitative leap in the development of medications, new treatment modalities having become available for the treatment of COPD. Although large-scale, prospective controlled studies have been conducted, mortality was the primary outcome measure in only one, and the difference between the groups under study was borderline significant (p = 0.052).[43] In the other studies, mortality was evaluated either as a secondary outcome measure or as a means of determining drug safety. Post hoc and subgroup analyses of two studies[26,34] showed that the use of LABAs and ICs in combination, as well as the use of LAMAs in isolation, had a beneficial effect on mortality, especially in patients with moderate or severe disease (GOLD stages II or III). Those data should be interpreted in view of the limitations imposed by the methods employed. It is possible that the large loss to follow-up among the controls compromised the results and made it difficult to detect that benefit among the patients who received treatment. Two recent meta-analyses compared various therapeutic regimens (ICs, LABAs, LABA-IC combinations, and LAMAs), and the various studies produced conflicting results. The first meta-analysis compared the use of LABAs in isolation with the use of LABA-IC combinations and found that the addition of ICs to the habitual therapy did not reduce mortality.[51] The second[72] concluded that only LABA-IC combinations had a beneficial effect on mortality, and that effect was small (relative risk = 0.80 [95% CI: 0.69-0.94]), a result that remained consistent even after the exclusion of patients investigated in another study included in the meta-analysis.[34] Of the 22 articles analyzed in the present systematic review, only 7 demonstrated beneficial effects on mortality. All of the positive analyses from the articles included are based on post hoc or subgroup analyses, mortality being a secondary outcome measure in most of such analyses. The two abovementioned meta-analyses and our review demonstrated that the pharmacological treatment of COPD has little or no impact on mortality. Further studies should be conducted in order to determine whether treatment at earlier stages of the disease can reduce mortality and whether it is advantageous to focus the treatment on specific phenotypes, such as patients with frequent exacerbations or those presenting with higher levels of the markers of systemic inflammation. Aggressive treatment of comorbidities, especially cardiovascular comorbidities, as well as rehabilitation and

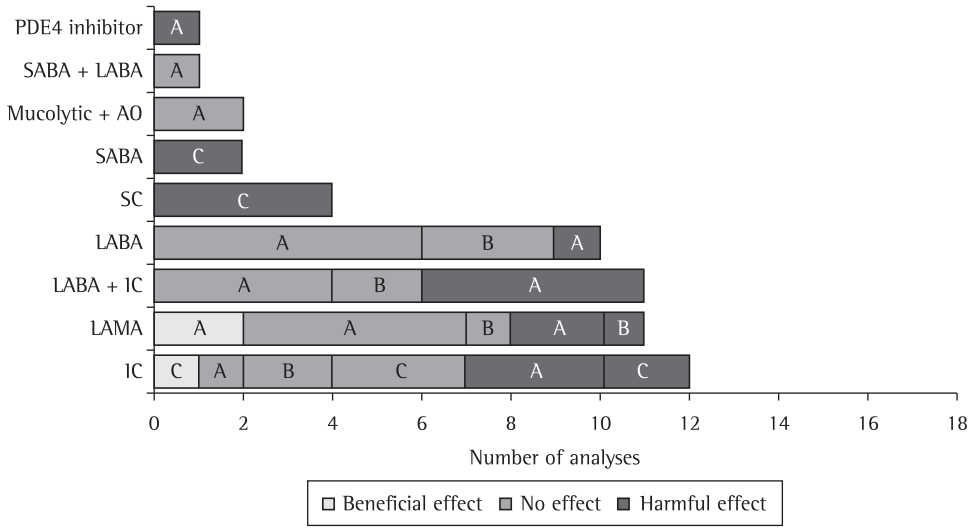

Figure 6 - Effects of the comparison between pharmacological treatment and placebo on adverse drug effects as the outcome measure, by level of evidence (grade of recommendation). AO: antioxidant; and SC: systemic corticosteroid.

therapies aimed to reduce lung volumes, together with the optimal use of medications, should also be studied as a way of reducing mortality in COPD.

Adverse drug effects

The adverse effects of the medications commonly used in the treatment of COPD were evaluated in 54 analyses, in which such medications were compared with placebo (Figure 6). Most of the adverse drug effects reported in the studies included in the present review were not severe; nevertheless, some analyses showed arrhythmias,[73] cardiac ischemic events,[74] and fractures.[75-77] Of those analyses, 21 showed that the adverse effects of COPD medications were worse than were those of placebo. Only 3 analyses—2 involving the use of LAMAs[35] and 1 involving the use of ICs[78]—showed that the medications had fewer adverse effects than did placebo. Placebo-controlled analyses of PDE4 inhibitors, SABAs, and systemic corticosteroids showed that all of the medications had harmful effects. Although 1 analysis showed that LABAs had worse adverse effects than did placebo, most of the studies found no differences between LABAs and placebo, between the SABA-LABA combination and placebo, or between mucolytics/antioxidants and placebo in terms of adverse effects. In various clinical trials, the use of ICs in isolation or in combination with LABAs increased the adverse effects, principally the risk of developing pneumonia, when compared with the use of a placebo.[43,64,79] However, a study evaluating those same drug combinations showed that the medications had no impact on the risk of developing pneumonia.[47] The use of ICs has not been shown to increase the risk of fracture,[76,77,80] except in one study.[75] However, the use of systemic corticosteroids has been shown to increase that risk.[75,76] It is of note that most of those analyses originated from observational studies, which underscores the need for specific clinical trials. The comparison among long-acting bronchodilators in terms of adverse effects was inconclusive. Briggs et al.[32] reported that the comparison between LAMAs and salmeterol in a randomized clinical trial revealed a higher prevalence of mild adverse effects, such as dry mouth, and a lower prevalence of serious adverse effects, particularly those related to the lower respiratory tract.[32] In contrast, an observational study compared those same medications and found no differences regarding cardiac ischemic events, arrhythmias, or pneumonia.[68] The use of fluticasone was compared with that of salmeterol in isolation,[19,20,43,79] as well as with that of LAMAs in isolation,[69] and was shown to increase the risk of developing pneumonia.

The analyses in the present review showed that the medications that are currently available for COPD control are safe and have minimal adverse effects. In addition, most of the studies showed that the adverse effects of the medications did not require treatment discontinuation. However, the adverse effects of active drugs, particularly those of ICs and systemic corticosteroids, were more common than were those of placebo. Ernst et al.[46] noted an increase in the risk of hospitalization for pneumonia. A large-scale review of the topic showed that the relative risk for pneumonia in a group of patients receiving ICs was 1.57, with no increase in the mortality risk.[81] The risk of developing pneumonia was highest among elderly patients and those with COPD that was more severe. Such studies

Table 1 - Summary of the results of the principal pharmacological treatments for COPD in relation to the various outcome measures and the grade of recommendation.[a,b]

Treatments	Symptoms	Pulmonary function	Prevention of exacerbations	Quality of life	Mortality	Adverse drug effects
LABA	Yes (A)	Yes (A)	Yes (A)	Yes (A)	No (A)	Minimal
LAMA	Yes (A)	Yes (A)	Yes (A)	Yes (A)	No (B)	Minimal
IC	Yes (A)	Yes (A)	Yes (A)	Yes (A)	No (B)	Some
LABA+IC	Yes (A)	Yes (A)	Yes (A)	Yes (A)	No (B)	Some
Mucolytic+antioxidant	No (B)	No (B)	Yes (B)	No (B)	-	Minimal
PDE4 inhibitor	Yes (B)	Yes (B)	Yes (B)	No (B)	No (B)	Some

[a]"Yes" means that the drug(s) produced favorable results regarding the outcome measure, whereas "No" means that the drug(s) produced unfavorable results regarding the outcome measure. The categorization was also based on the number of analyses. [b]Grade of recommendation shown in parentheses.

raised important questions regarding the lack of a precise definition of pneumonia and the surprising absence of an increase in mortality in patients with COPD and pneumonia. One study[82] demonstrated that the use of ICs had local effects, such as oral candidiasis. Regarding the systemic effects of ICs, various prospective randomized trials have reported a higher frequency of bruising and of cataracts.[83,84] Another study[43] showed that the number of nonfatal cases of pneumonia was higher among patients who received ICs than among those who did not. It is generally accepted that the use of doses ≤ 800 mg/day of budesonide (or equivalent drugs) does not increase the risk of decreased bone density or fracture. However, that risk becomes significantly higher when doses > 1,000 mg/day of budesonide are used.[83] Studies of bone density in COPD patients treated with ICs have produced conflicting results, which might be due to the difficulty in adjusting for confounding factors, such as oral steroid use, smoking, sedentary lifestyle, diet, and type of IC. In general, the adverse effects of LABAs are of little importance.[85] For some time, the cardiovascular safety of such drugs was questioned. In two recent large-scale clinical trials—one evaluating LABAs[86] and the other evaluating LAMAs[87]—that problem was not considered to be serious, even after follow-up periods of 3 and 4 years, respectively. However, a subsequent evaluation, which corrected certain information, demonstrated that the patients who received LAMAs were at a higher risk for acute myocardial infarction and stroke. Some of the most common adverse effects of PDE4 inhibitors include diarrhea and nausea. Weight loss is also relatively common in patients receiving PDE4 inhibitors (occurring in 6-12% vs. 1-3% of those receiving placebo), the weight loss being 2 kg, on average, and most often occurring in the first months of treatment. Cazzola et al. reported that the frequency of cardiac arrhythmias and cardiovascular effects in patients receiving PDE4 inhibitors was similar to that seen in patients receiving placebo.[88] Table 1 summarizes the effects of the various medications for the treatment of COPD in relation to the principal outcomes of interest and the respective levels of scientific evidence. The summary presented in Table 1 refers to the comparisons between COPD medications and placebo, as well as to the comparisons among the various COPD medications.

Final considerations

The present systematic review included original articles that were published in the 2005-2009 period and evaluated LABAs, LAMAs, ICs, mucolytics, antioxidants, and PDE4 inhibitors, as well as the combinations thereof, in patients with COPD, the outcome measures being symptoms, pulmonary function, exacerbation, quality of life, mortality, and adverse drug effects. The 84 original articles that were selected generated 420 analyses, of which approximately 55% compared COPD medications with placebo. Of the classes of medications studied, mucolytics and antioxidants were the least studied, which is probably due to the fact that those medications play a nearly insignificant role in the treatment of COPD. The number of analyses of PDE4 inhibitors was also low, which is due to the fact that those are new drugs. Therefore, the analyses of mucolytic-antioxidant combinations and of PDE4 inhibitors received grade B recommendations. The bronchodilators that were most commonly studied were the two types of long-acting bronchodilators—LABAs and SAMAs—and there was no conclusive scientific evidence of the superiority of one over the other. The effects of ICs were positive or negative, depending on the outcome measure, and some adverse effects were observed. Mortality was the outcome measure for which there is still no conclusive evidence, and each of the medications evaluated in the present review received a grade A recommendation in that respect.

References

1. Jemal A, Ward E, Hao Y, Thun M. Trends in the leading causes of death in the United States, 1970-2002. JAMA. 2005;294(10):1255-9.
2. Celli BR. Novel concepts in the pharmacotherapy of chronic obstructive pulmonary disease. Pneumonol Alergol Pol. 2009;77(1):82-90.
3. Menezes AM, Perez-Padilla R, Hallal PC, Jardim JR, Muiño A, Lopez MV, et al. Worldwide burden of COPD in high- and low-income countries. Part II. Burden of chronic obstructive lung disease in Latin America: the PLATINO study. Int J Tuberc Lung Dis. 2008;12(7):709-12.
4. Global Initiative for Chronic Obstructive Lung Disease. Estratégia Global para Diagnóstico, Condução e Prevenção da Doença Pulmonar Obstrutiva Crônica. Bethesda: National Institutes of Health, National Heart, Lung, and Blood Institute; 2006.

5. Tálamo C, de Oca MM, Halbert R, Perez-Padilla R, Jardim JR, Muiño A, et al. Diagnostic labeling of COPD in five Latin American cities. Chest. 2007;131(1):60-7.
6. Mannino DM, Gagnon RC, Petty TL, Lydick E. Obstructive lung disease and low lung function in adults in the United States: data from the National Health and Nutrition Examination Survey, 1988-1994. Arch Intern Med. 2000;160(11):1683-9.
7. Peña VS, Miravitlles M, Gabriel R, Jiménez-Ruiz CA, Villasante C, Masa JF, et al. Geographic variations in prevalence and underdiagnosis of COPD: results of the IBERPOC multicentre epidemiological study. Chest. 2000;118(4):981-9.
8. Mannino DM, Buist AS, Petty TL, Enright PL, Redd SC. Lung function and mortality in the United States: data from the First National Health and Nutrition Examination Survey follow up study. Thorax. 2003;58(5):388-93.
9. Chanez P, Burge PS, Dahl R, Creemers J, Chuchalin A, Lamarca R, et al. Aclidinium bromide provides long-acting bronchodilation in patients with COPD. Pulm Pharmacol Ther. 2010;23(1):15-21.
10. Criner GJ, Sharafkhaneh A, Player R, Conoscenti CS, Johnson P, Keyser MT, et al. Efficacy of tiotropium inhalation powder in african-american patients with chronic obstructive pulmonary disease. COPD. 2008;5(1):35-41.
11. Johansson G, Lindberg A, Romberg K, Nordström L, Gerken F, Roquet A. Bronchodilator efficacy of tiotropium in patients with mild to moderate COPD. Prim Care Respir J. 2008;17(3):169-75.
12. Vestbo J, Pauwels R, Anderson JA, Jones P, Calverley P; TRISTSAN study group. Early onset of effect of salmeterol and fluticasone propionate in chronic obstructive pulmonary disease. Thorax. 2005;60(4):301-4.
13. Donohue JF, Hanania NA, Ciubotaru RL, Noe L, Pasta DJ, Schaefer K, et al. Comparison of levalbuterol and racemic albuterol in hospitalized patients with acute asthma or COPD: a 2-week, multicenter, randomized, open-label study. Clin Ther. 2008;30 Spec No:989-1002.
14. Baumgartner RA, Hanania NA, Calhoun WJ, Sahn SA, Sciarappa K, Hanrahan JP. Nebulized arformoterol in patients with COPD: a 12-week, multicenter, randomized, double-blind, double-dummy, placebo- and active-controlled trial. Clin Ther. 2007;29(2):261-78.
15. Cote C, Pearle JL, Sharafkhaneh A, Spangenthal S. Faster onset of action of formoterol versus salmeterol in patients with chronic obstructive pulmonary disease: a multicenter, randomized study. Pulm Pharmacol Ther. 2009;22(1):44-9.
16. Donohue JF, Hanania NA, Sciarappa KA, Goodwin E, Grogan DR, Baumgartner RA, et al. Arformoterol and salmeterol in the treatment of chronic obstructive pulmonary disease: a one year evaluation of safety and tolerance. Ther Adv Respir Dis. 2008;2(2):37-48.
17. Griffin J, Lee S, Caiado M, Kesten S, Price D. Comparison of tiotropium bromide and combined ipratropium/salbutamol for the treatment of COPD: a UK General Practice Research Database 12-month follow-up study. Prim Care Respir J. 2008;17(2):104-10.
18. Bleecker ER, Emmett A, Crater G, Knobil K, Kalberg C. Lung function and symptom improvement with fluticasone propionate/salmeterol and ipratropium bromide/albuterol in COPD: response by beta-agonist reversibility. Pulm Pharmacol Ther. 2008;21(4):682-8.
19. Anzueto A, Ferguson GT, Feldman G, Chinsky K, Seibert A, Emmett A, et al. Effect of fluticasone propionate/salmeterol (250/50) on COPD exacerbations and impact on patient outcomes. COPD. 2009;6(5):320-9.
20. Ferguson GT, Anzueto A, Fei R, Emmett A, Knobil K, Kalberg C. Effect of fluticasone propionate/salmeterol (250/50 microg) or salmeterol (50 microg) on COPD exacerbations. Respir Med. 2008;102(8):1099-108.
21. Wouters EF, Postma DS, Fokkens B, Hop WC, Prins J, Kuipers AF, et al. Withdrawal of fluticasone propionate from combined salmeterol/fluticasone treatment in patients with COPD causes immediate and sustained disease deterioration: a randomised controlled trial. Thorax. 2005;60(6):480-7.
22. Partridge MR, Schuermann W, Beckman O, Persson T, Polanowski T. Effect on lung function and morning activities of budesonide/formoterol versus salmeterol/fluticasone in patients with COPD. Ther Adv Respir Dis. 2009;3(4):1-11.
23. Celik P, Sakar A, Havlucu Y, Yuksel H, Turkdogan P, Yorgancioglu A. Short-term effects of montelukast in stable patients with moderate to severe COPD. Respir Med. 2005;99(4):444-50.
24. Fabbri LM, Calverley PM, Izquierdo-Alonso JL, Bundschuh DS, Brose M, Martinez FJ, et al. Roflumilast in moderate-to-severe chronic obstructive pulmonary disease treated with longacting bronchodilators: two randomised clinical trials. Lancet. 2009;374(9691):695-703.
25. Terzano C, Petroianni A, Ricci A, Allegra L. Combination therapy in COPD: different response of COPD stages and predictivity of functional parameters. Eur Rev Med Pharmacol Sci. 2005;9(4):209-15.
26. Decramer M, Celli B, Kesten S, Lystig T, Mehra S, Tashkin DP, 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(9696):1171-8.
27. Campbell M, Eliraz A, Johansson G, Tornling G, Nihlén U, Bengtsson T, et al. Formoterol for maintenance and as-needed treatment of chronic obstructive pulmonary disease. Respir Med. 2005;99(12):1511-20.
28. Hodder R, Kesten S, Menjoge S, Viel K. Outcomes in COPD patients receiving tiotropium or salmeterol plus treatment with inhaled corticosteroids. Int J Chron Obstruct Pulmon Dis. 2007;2(2):157-67.
29. Worth H, Schacher C, Dethlefsen U. Concomitant therapy with Cineole (Eucalyptole) reduces exacerbations in COPD: a placebo-controlled double-blind trial. Respir Res. 2009;10:69.
30. Decramer M, Rutten-van Mölken M, Dekhuijzen PN, Troosters T, van Herwaarden C, Pellegrino R, 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(9470):1552-60.
31. Calverley PM, Rabe KF, Goehring UM, Kristiansen S, Fabbri LM, Martinez FJ, et al. Roflumilast in symptomatic chronic obstructive pulmonary disease: two randomised clinical trials. Lancet. 2009;374(9691):685-94.
32. Briggs DD Jr, Covelli H, Lapidus R, Bhattycharya S, Kesten S, Cassino C. Improved daytime spirometric efficacy of tiotropium compared with salmeterol in patients with COPD. Pulm Pharmacol Ther. 2005;18(6):397-404.

33. Aaron SD, Vandemheen KL, Fergusson D, Maltais F, Bourbeau J, Goldstein R, et al. Tiotropium in combination with placebo, salmeterol, or fluticasone-salmeterol for treatment of chronic obstructive pulmonary disease: a randomized trial. Ann Intern Med. 2007;146(8):545-55.
34. Celli BR, Thomas NE, Anderson JA, Ferguson GT, Jenkins CR, Jones PW, 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(4):332-8.
35. Tashkin DP, Celli B, Senn S, Burkhart D, Kesten S, Menjoge S, et al. A 4-year trial of tiotropium in chronic obstructive pulmonary disease. N Engl J Med. 2008;359(15):1543-54.
36. Pellegrino R, Viegi G, Brusasco V, Crapo RO, Burgos F, Casaburi R, et al. Interpretative strategies for lung function tests. Eur Respir J. 2005;26(5):948-68.
37. Burge PS, Calverley PM, Jones PW, Spencer S, Anderson JA, Maslen TK. Randomised, double blind, placebo controlled study of fluticasone propionate in patients with moderate to severe chronic obstructive pulmonary disease: the ISOLDE trial. BMJ. 2000;320(7245):1297-303.
38. Soriano JB, Sin DD, Zhang X, Camp PG, Anderson JA, Anthonisen NR, et al. A pooled analysis of FEV1 decline in COPD patients randomized to inhaled corticosteroids or placebo. Chest. 2007;131(3):682-9.
39. Decramer M, Cooper CB. Treatment of COPD: the sooner the better? Thorax. 2010;65(9):837-41.
40. Sociedade Brasileira de Pneumologia e Tisiologia. II Consenso Brasileiro sobre Doença Pulmonar Obstrutiva Crônica – DPOC - 2004. J Bras Pneumol. 2004;30(Suppl 5):S1-S42.
41. Chan CK, Maltais F, Sigouin C, Haddon JM, Ford GT; SAFE Study Group. A randomized controlled trial to assess the efficacy of tiotropium in Canadian patients with chronic obstructive pulmonary disease. Can Respir J. 2007;14(8):465-72.
42. Ambrosino N, Foglio K, Balzano G, Paggiaro PL, Lessi P, Kesten S, et al. Tiotropium and exercise training in COPD patients: effects on dyspnea and exercise tolerance. Int J Chron Obstruct Pulmon Dis. 2008;3(4):771-80.
43. Calverley PM, Anderson JA, Celli B, Ferguson GT, Jenkins C, Jones PW, et al. Salmeterol and fluticasone propionate and survival in chronic obstructive pulmonary disease. N Engl J Med. 2007;356(8):775-89.
44. Macie C, Wooldrage K, Manfreda J, Anthonisen N. Cardiovascular morbidity and the use of inhaled bronchodilators. Int J Chron Obstruct Pulmon Dis. 2008;3(1):163-9.
45. Choudhury AB, Dawson CM, Kilvington HE, Eldridge S, James WY, Wedzicha JA, et al. Withdrawal of inhaled corticosteroids in people with COPD in primary care: a randomised controlled trial. Respir Res. 2007;8:93.
46. Ernst P, Gonzalez AV, Brassard P, Suissa S. Inhaled corticosteroid use in chronic obstructive pulmonary disease and the risk of hospitalization for pneumonia. Am J Respir Crit Care Med. 2007;176(2):162-6.
47. Rennard SI, Tashkin DP, McElhattan J, Goldman M, Ramachandran S, Martin UJ, et al. Efficacy and tolerability of budesonide/formoterol in one hydrofluoroalkane pressurized metered-dose inhaler in patients with chronic obstructive pulmonary disease: results from a 1-year randomized controlled clinical trial. Drugs. 2009;69(5):549-65.
48. Calverley PM, Sanchez-Toril F, McIvor A, Teichmann P, Bredenbroeker D, Fabbri LM. Effect of 1-year treatment with roflumilast in severe chronic obstructive pulmonary disease. Am J Respir Crit Care Med. 2007;176(2):154-61.
49. Miravitlles M. Avaliação econômica da doença pulmonar obstrutiva crônica e de suas agudizações: aplicação na América Latina. J Bras Pneumol. 2004;30(3):274-85.
50. Cazzola M, MacNee W, Martinez FJ, Rabe KF, Franciosi LG, Barnes PJ, et al. Outcomes for COPD pharmacological trials: from lung function to biomarkers. Eur Respir J. 2008;31(2):416-69.
51. Rodrigo GJ, Castro-Rodriguez JA, Plaza V. Safety and efficacy of combined long-acting beta-agonists and inhaled corticosteroids vs long-acting beta-agonists monotherapy for stable COPD: a systematic review. Chest. 2009;136(4):1029-38.
52. Agarwal R, Aggarwal AN, Gupta D, Jindal SK. Inhaled corticosteroids vs placebo for preventing COPD exacerbations: a systematic review and metaregression of randomized controlled trials. Chest. 2010;137(2):318-25.
53. Adams SG, Anzueto A, Briggs DD Jr, Leimer I, Kesten S. Evaluation of withdrawal of maintenance tiotropium in COPD. Respir Med. 2009;103(10):1415-20.
54. Tonnel AB, Perez T, Grosbois JM, Verkindre C, Bravo ML, Brun M, et al. Effect of tiotropium on health-related quality of life as a primary efficacy endpoint in COPD. Int J Chron Obstruct Pulmon Dis. 2008;3(2):301-10.
55. Welte T, Miravitlles M, Hernandez P, Eriksson G, Peterson S, Polanowski T, et al. Efficacy and tolerability of budesonide/formoterol added to tiotropium in patients with chronic obstructive pulmonary disease. Am J Respir Crit Care Med. 2009;180(8):741-50.
56. Hanania NA, Boota A, Kerwin E, Tomlinson L, Denis-Mize K. Efficacy and safety of nebulized formoterol as add-on therapy in COPD patients receiving maintenance tiotropium bromide: Results from a 6-week, randomized, placebo-controlled, clinical trial. Drugs. 2009;69(9):1205-16.
57. Rodrigo GJ, Nannini LJ, Rodríguez-Roisin R. Safety of long-acting beta-agonists in stable COPD: a systematic review. Chest. 2008;133(5):1079-87.
58. Appleton S, Jones T, Poole P, Pilotto L, Adams R, Lasserson TJ, et al. Ipratropium bromide versus long-acting beta-2 agonists for stable chronic obstructive pulmonary disease. Cochrane Database Syst Rev. 2006;3:CD006101.
59. Yang IA, Fong KM, Sim EH, Black PN, Lasserson TJ. Inhaled corticosteroids for stable chronic obstructive pulmonary disease. Cochrane Database Syst Rev. 2007;(2):CD002991.
60. Kiri VA, Pride NB, Soriano JB, Vestbo J. Inhaled corticosteroids in chronic obstructive pulmonary disease: results from two observational designs free of immortal time bias. Am J Respir Crit Care Med. 2005;172(4):460-4.
61. Macie C, Wooldrage K, Manfreda J, Anthonisen NR. Inhaled corticosteroids and mortality in COPD. Chest. 2006;130(3):640-6.
62. Tkacova R, Toth S, Sin DD. Inhaled corticosteroids and survival in COPD patients receiving long-term home oxygen therapy. Respir Med. 2006;100(3):385-92.
63. Bale G, Martínez-Camblor P, Burge PS, Soriano JB. Long-term mortality follow-up of the ISOLDE

participants: causes of death during 13 years after trial completion. Respir Med. 2008;102(10):1468-72.
64. Jenkins CR, Jones PW, Calverley PM, Celli B, Anderson JA, Ferguson GT, 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.
65. Celli B, Decramer M, Kesten S, Liu D, Mehra S, Tashkin DP, et al. Mortality in the 4-year trial of tiotropium (UPLIFT) in patients with chronic obstructive pulmonary disease. Am J Respir Crit Care Med. 2009;180(10):948-55.
66. Corrao G, Zambon A, Faini S, Bagnardi V, Leoni O, Suissa S. Short-acting inhaled beta-2-agonists increased the mortality from chronic obstructive pulmonary disease in observational designs. J Clin Epidemiol. 2005;58(1):92-7.
67. Gershon AS, Wang L, To T, Luo J, Upshur RE. Survival with tiotropium compared to long-acting Beta-2-agonists in Chronic Obstructive Pulmonary Disease. COPD. 2008;5(4):229-34.
68. Jara M, Lanes SF, Wentworth C 3rd, May C, Kesten S. Comparative safety of long-acting inhaled bronchodilators: a cohort study using the UK THIN primary care database. Drug Saf. 2007;30(12):1151-60.
69. Wedzicha JA, Calverley PM, Seemungal TA, Hagan G, Ansari Z, Stockley RA, et al. The prevention of chronic obstructive pulmonary disease exacerbations by salmeterol/fluticasone propionate or tiotropium bromide. Am J Respir Crit Care Med. 2008;177(1):19-26.
70. Kiri VA, Bettoncelli G, Testi R, Viegi G. Inhaled corticosteroids are more effective in COPD patients when used with LABA than with SABA. Respir Med. 2005;99(9):1115-24.
71. Lee TA, Pickard AS, Au DH, Bartle B, Weiss KB. Risk for death associated with medications for recently diagnosed chronic obstructive pulmonary disease. Ann Intern Med. 2008;149(6):380-90.
72. Kliber A, Lynd LD, Sin DD. The effects of long-acting bronchodilators on total mortality in patients with stable chronic obstructive pulmonary disease. Respir Res. 2010;11:56.
73. Huerta C, Lanes SF, García Rodríguez LA. Respiratory medications and the risk of cardiac arrhythmias. Epidemiology. 2005;16(3):360-6.
74. Huiart L, Ernst P, Ranouil X, Suissa S. Oral corticosteroid use and the risk of acute myocardial infarction in chronic obstructive pulmonary disease. Can Respir J. 2006;13(3):134-8.
75. Pujades-Rodríguez M, Smith CJ, Hubbard RB. Inhaled corticosteroids and the risk of fracture in chronic obstructive pulmonary disease. QJM. 2007;100(8):509-17.
76. Vestergaard P, Rejnmark L, Mosekilde L. Fracture risk in patients with chronic lung diseases treated with bronchodilator drugs and inhaled and oral corticosteroids. Chest. 2007;132(5):1599-607.
77. de Vries F, van Staa TP, Bracke MS, Cooper C, Leufkens HG, Lammers JW. Severity of obstructive airway disease and risk of osteoporotic fracture. Eur Respir J. 2005;25(5):879-84.
78. Parimon T, Chien JW, Bryson CL, McDonell MB, Udris EM, Au DH. Inhaled corticosteroids and risk of lung cancer among patients with chronic obstructive pulmonary disease. Am J Respir Crit Care Med. 2007;175(7):712-9.
79. Crim C, Calverley PM, Anderson JA, Celli B, Ferguson GT, Jenkins C, et al. Pneumonia risk in COPD patients receiving inhaled corticosteroids alone or in combination: TORCH study results. Eur Respir J. 2009;34(3):641-7.
80. Ferguson GT, Calverley PM, Anderson JA, Jenkins CR, Jones PW, Willits LR, et al. Prevalence and progression of osteoporosis in patients with COPD: results from the TOwards a Revolution in COPD Health study. Chest. 2009;136(6):1456-65.
81. Singh S, Loke YK. Risk of pneumonia associated with long-term use of inhaled corticosteroids in chronic obstructive pulmonary disease: a critical review and update. Curr Opin Pulm Med. 2010;16(2):118-22.
82. Calverley P, Pauwels R, Vestbo J, Jones P, Pride N, Gulsvik A, et al. Combined salmeterol and fluticasone in the treatment of chronic obstructive pulmonary disease: a randomised controlled trial. Lancet. 2003;361(9356):449-56.
83. Chung KF, Caramori G, Adcock IM. Inhaled corticosteroids as combination therapy with beta-adrenergic agonists in airways disease: present and future. Eur J Clin Pharmacol. 2009;65(9):853-71.
84. Clark DJ, Grove A, Cargill RI, Lipworth BJ. Comparative adrenal suppression with inhaled budesonide and fluticasone propionate in adult asthmatic patients. Thorax. 1996;51(3):262-6.
85. Niewoehner DE, Lapidus R, Cote C, Sharafkhaneh A, Plautz M, Johnson P, et al. Therapeutic conversion of the combination of ipratropium and albuterol to tiotropium in patients with chronic obstructive pulmonary disease. Pulm Pharmacol Ther. 2009;22(6):587-92.
86. Salpeter SR, Buckley NS, Salpeter EE. Meta-analysis: anticholinergics, but not beta-agonists, reduce severe exacerbations and respiratory mortality in COPD. J Gen Intern Med. 2006;21(10):1011-9.
87. Singh S, Loke YK, Furberg CD. Inhaled anticholinergics and risk of major adverse cardiovascular events in patients with chronic obstructive pulmonary disease: a systematic review and meta-analysis. JAMA. 2008;300(12):1439-50. Erratum in: JAMA. 2009;301(12):1227-30.
88. Cazzola M, Matera MG. Emerging inhaled bronchodilators: an update. Eur Respir J. 2009;34(3):757-69.

About the authors

Ana Maria Baptista Menezes
Full Professor of Pulmonology. Department of Clinical Medicine, Federal University of Pelotas School of Medicine, Pelotas, Brazil.

Silvia Elaine Cardozo Macedo
Adjunct Professor of Pulmonology. Department of Clinical Medicine, Federal University of Pelotas School of Medicine, Pelotas, Brazil.

Ricardo Bica Noal
Doctoral Student. Graduate Program in Epidemiology, Department of Social Medicine, Federal University of Pelotas School of Medicine, Pelotas, Brazil.

Jussara Costa Fiterman
Professor. Pontifical Catholic University of Rio Grande do Sul School of Medicine, Porto Alegre, Brazil.

Alberto Cukier
Tenured Professor. Department of Pulmonology, University of São Paulo School of Medicine, São Paulo, Brazil.

José Miguel Chatkin
Full Professor of Internal Medicine and Pulmonology. Pontifical Catholic University of Rio Grande do Sul School of Medicine, Porto Alegre, Brazil.

Frederico Leon Arrabal Fernande
Attending Physician. Heart Institute, University of São Paulo School of Medicine *Hospital das Clínicas*, São Paulo, Brazil.

Brazilian Thoracic Association Work Group
Brazilian Thoracic Association Work Group: Adalberto S. Rubin, Antonio George de M. Cavalcante, Carlos Alberto Pereira, Cyntia M. S. Viana, Emilio Pizzichini, José R. B. Jardim, Julio C. Abreu, Luis Fernando Pereira, Marcelo Rabahi, Márcia Pizzichini, Marli Knorst, Oliver Nascimento, and Marina Andrade Lima.

Work Group of the Federal University of Pelotas Graduate Program in Epidemiology
Work Group of the Federal University of Pelotas Graduate Program in Epidemiology: David A. González, Maria de Fátima Maia, Fernando César Wehrmeister, Jeovany Martinez-Mesa, and Samuel C. Dumith.