

## Pharmacological treatment of COPD

Terapêutica medicamentosa da DPOC

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Knowledge of COPD has increased in recent years, from the first American Thoracic Society/European Respiratory Society document, published in 1995,<sup>(1)</sup> to the publication of the Global Initiative for Chronic Obstructive Lung Disease recommendations.<sup>(2)</sup> The promotion of research and the processes of dissemination of new concepts developed rapidly, and the recommended treatment began to yield satisfactory results, with noticeable clinical responses and evident improvement in the quality of life of patients.

The medications used in the management of COPD cases provided us with the promise of symptom control and a reduction in the risks of COPD, with a decrease in the prevalence and severity of exacerbations, as well as in the severity of disease progression.

In this issue of the Brazilian Journal of Pulmonology, Menezes et al. present a systematic review of articles that were published in the 2005-2009 period and addressed the medications that are recommended for the treatment of COPD.<sup>(3)</sup> The review article shows us, in a practical manner, how to prepare a systematic review: the selection of data; the choice of questions; the classification of the answers obtained; and the interpretation of the data. The article also clarifies the evidence regarding the known effects of COPD medications, in order to achieve the principal objectives of COPD treatment.

In the article, the results were reviewed on the basis of the impact of COPD medications on the principal COPD markers: symptoms; pulmonary function; exacerbations; quality of life; mortality; and adverse drug effects.

Regarding COPD symptoms, the review concluded that the use of bronchodilators, in isolation or in combination, produced symptom relief, a finding that is in agreement with those reported in previous reviews of the same topic.<sup>(4-6)</sup> The finding that bronchodilators improve the symptoms is more evident in patients classified as having moderate or severe COPD. The authors found data suggesting that long-acting anticholinergics are less effective in patients with mild or moderate COPD. However, the authors

highlighted that there have been few studies investigating the topic. In addition, on the basis of the effects of  $\beta$ -adrenergic agonists and muscarinic antagonists), the authors concluded that the two classes of bronchodilators are equally effective in producing a clinical response. The use of inhaled corticosteroids in combination with long-acting bronchodilators was also shown to lessen dyspnea. The use of phosphodiesterase-4 inhibitors in combination with bronchodilators noticeably also lessened dyspnea.

An analysis of the impact that bronchodilators (used either in isolation or in combination) had on pulmonary function revealed that the drugs had an effect on FEV<sub>1</sub> and FVC, as well as reducing the progressive decline in pulmonary function. Again, the results obtained confirmed those of previously published studies.<sup>(6,7)</sup> An analysis of the use of inhaled corticosteroids, in isolation or in combination with a bronchodilator, showed that inhaled corticosteroids improved pulmonary function. This finding is in disagreement with those of other reviews of inhaled corticosteroid use in COPD. Yang et al<sup>(8)</sup> conducted a systematic review of the same theme and showed that inhaled corticosteroids had no impact on the pulmonary function of patients with COPD. The use of a phosphodiesterase-4 inhibitor in combination with bronchodilators improves FEV<sub>1</sub> when compared with the use of placebo. Neither mucolytics nor antioxidants were shown to have an effect on FVC and FEV<sub>1</sub>. It seems that muscarinic antagonists are slightly superior to  $\beta$ -adrenergic agonists in terms of reducing the rate of progressive decline in pulmonary function.

The results regarding COPD exacerbations were highly heterogeneous, which was probably due to the adoption of different definitions of exacerbation. The authors concluded that the decision to use COPD medications should be made on a case-by-case basis, treatment options including a combination of  $\beta$ -adrenergic agonists, a combination of muscarinic antagonists, and combinations of  $\beta$ -adrenergic agonists or muscarinic antagonists with inhaled

corticosteroids. Phosphodiesterase-4 inhibitors were shown to reduce COPD exacerbations in patients with frequent symptoms of cough and secretion accompanied by more than two exacerbations per year.<sup>(9)</sup>

The various studies reviewed showed no superiority of one class of medications over the others in terms of improving the quality of life of patients with COPD. The combinations involving the two classes of long-acting bronchodilators, as well as the combination of  $\beta$ -adrenergic agonists and inhaled corticosteroids, were shown to be equally effective in improving the quality of life. The authors reported that quality of life was the primary outcome measure of only one study involving the use of anticholinergics. Phosphodiesterase-4 inhibitors did not improve the quality of life.

An analysis of studies in which reduced mortality was the primary outcome measure showed negative results. In two large-scale studies,<sup>(10,11)</sup> inhaled corticosteroid use was reported to cause pneumonia. There is little or no reduction in mortality among patients with COPD that is more severe, and the effect of COPD medications on mortality among patients with COPD that is less severe should be investigated further.

The review found no differences between placebo and the medications under study in terms of their adverse effects. The most common adverse effects of phosphodiesterase-4 inhibitors were diarrhea and nausea; weight loss occurred in 6-12% of patients receiving the medications studied, being significantly greater than was that observed among patients receiving placebo. Those adverse effects occurred in the first weeks of treatment and did not require discontinuation of the drug.<sup>(12)</sup>

The systematic review by Menezes et al.<sup>(3)</sup> gave us confidence to manage our patients and underscored the fact that the results obtained corroborate the recommendations of the current guidelines for the management of COPD.<sup>(2)</sup>

The search for better treatments requires that the information available be constantly updated. A systematic review of articles published in the 2009-2010 period and addressing new classes of medications for the treatment of COPD revealed a new bronchodilator, an ultra-long-acting  $\beta$ -adrenergic agonist known as indacaterol. This bronchodilator differs from the others in

that it provides 24-h bronchodilation.<sup>(13)</sup> Studies conducted over a one-year period showed that, at the doses presented in Brazil (i.e., 150  $\mu$ g and 300  $\mu$ g), indacaterol improved FEV<sub>1</sub>, reduced the number of exacerbations, and improved the quality of life.<sup>(14,15)</sup> When compared with placebo, indacaterol did not increase the number or severity of exacerbations, and the medication had no impact on mortality.<sup>(13,15)</sup>

On the basis of the results of the review in question, we can recommend that COPD patients be treated as follows:

- Patients with mild COPD and few symptoms—use of short-acting bronchodilators or use of a long-acting bronchodilator
- Patients with moderate COPD with a greater number of symptoms—use of long-acting bronchodilators or use of a combination of bronchodilators
- Symptomatic patients with severe COPD—use of a combination of long-acting bronchodilators or use of bronchodilators in combination with inhaled corticosteroids
- Symptomatic patients with moderate or severe COPD and more than two exacerbations per year—use of a combination of long-acting bronchodilators, use of bronchodilators in combination with inhaled corticosteroids, or use of bronchodilators in combination with phosphodiesterase-4 inhibitors

These strategies can improve quality of life in this population of patients.

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