# Original Article

## Effect of theophylline associated with short-acting or long-acting inhaled $\beta_2$-agonists in patients with stable chronic obstructive pulmonary disease: a systematic review*

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## Abstract

**Objectives:** To determine whether, in stable patients with chronic obstructive pulmonary disease, administration of theophylline in combination with short-acting or long-acting inhaled $\beta_2$-agonists is more efficacious than is a placebo or each of these drugs used in isolation. **Methods:** A systematic review and meta-analysis were carried out. All randomized and double-blind clinical trials found in the literature were selected. **Results:** A total of eight studies were included. In comparing the effect of theophylline combined with $\beta_2$-agonists to that of a placebo, we found a statistically significant improvement in mean $FEV_1$ (0.27 L; 95%CI: 0.11 to 0.43) and mean dyspnea (–0.78; 95%CI: –1.26 to –0.29). None of the meta-analyses performed detected any difference between the results obtained using theophylline combined with $\beta_2$-agonists and those obtained using $\beta_2$-agonists alone. When the administration of theophylline combined with $\beta_2$-agonists was compared to that of theophylline alone, there was a statistically significant improvement in mean dyspnea (–0.19; 95%CI: –0.34 to –0.04). **Conclusion:** In patients with stable chronic obstructive pulmonary disease, theophylline combined with $\beta_2$-agonists is more efficacious than is a placebo in terms of improving $FEV_1$ and dyspnea. In addition, theophylline combined with $\beta_2$-agonists is more efficacious than is theophylline in improving dyspnea. Furthermore, administration of theophylline combined with $\beta_2$-agonists is no more efficacious, for any of the variables studied, than is the use of $\beta_2$-agonists in isolation.

**Keywords:** Lung diseases, Obstructive; Bronchodilator agents; Xanthines; Pulmonary disease, Chronic obstructive.

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Submitted: 4 March 2006. Accepted, after review: 18 July 2006.

## Introduction

Chronic obstructive pulmonary disease (COPD) is considered one of the major public health problems in the world.[1] It was recently defined as a disease characterized by airflow limitation, not fully reversible,[2,3] usually progressive, and accompanied by an abnormal pulmonary inflammatory response to noxious gases or particles.[4]

An efficient treatment would be one that could prevent the progression of the disease, reduce symptoms, increase exercise tolerance, prevent/treat complications, reduce mortality, and improve quality of life.[4] However, currently, there are no medications for COPD that modify the long-term decline in pulmonary function or reduce mortality. We will address, within the field of bronchodilator therapy, treatment with theophylline, as well as with short-acting and long-acting inhaled $\beta_2$-agonists.

The $\beta_2$-agonist bronchodilators, which can be short-acting or long-acting, are potent and safe. Their principal effect consists of dilating the bronchi by acting directly on the $\beta_2$ adrenoreceptors in the smooth muscle. The stimulation of these receptors causes the relaxation of the smooth muscles through a mechanism that involves an increase in the intracellular concentration of cyclic adenosine monophosphate (cAMP).

Theophylline is the most commonly prescribed oral bronchodilator.[5] It is a medication that has been used for approximately sixty years, since it reduces lung hyperinflation and, consequently, dyspnea.[6]

The relaxation effect on the smooth muscle is attributed to the inhibition of the phosphodiesterase, with a resulting increase in cAMP. This increase in cAMP also plays an important role in the inhibition of the inflammatory process.[7] In addition, it affects mucociliary clearance, increasing the ciliary beat frequency and stimulating the transport of secretion in the airway epithelium.[6]

The anti-inflammatory effect of theophylline is the object of ongoing studies. In addition to causing the nonselective inhibition of the phosphodiesterase, theophylline has been found to suppress the inflammatory response through the activation of the histone deacetylase, an enzyme that is inhibited by the oxidative stress occurring in patients with COPD. This mechanism also improves the response to treatment with corticosteroids and has the advantage of being activated even by low concentrations of theophylline (5-10 μg/mL), thereby resulting in fewer side effects.[6]

Since bronchodilators affect different areas of the body, there are lines of research into whether the use of bronchodilators in combination presents a significant advantage over monotherapy,[8,9] since they are drugs with different mechanisms of action, areas of activity, time-to-onset characteristics, and duration of effects. Therefore, it is believed that using bronchodilator combinations can increase the degree of bronchodilation with an equivalent or lower number of side effects.[4]

It is difficult to compare the results of various studies of the use of bronchodilators in the treatment of COPD, since there are methodological differences among such studies in terms of selection criteria, sample size, drug doses, methods of drug administration, and response evaluation criteria.[10]

Comparing the three major consensus guidelines for the treatment of COPD in the literature (European Respiratory Society – 1995, American Thoracic Society – 1995, and British Thoracic Society – 1997), one author[11] concluded that many recommendations are empiric, since they are not evidence-based. However, all three guidelines recommend the use of bronchodilators as a first line of treatment, question the use of drug combinations, and agree that further studies are necessary to understand and treat such patients more effectively.

Given the importance of this topic, and with the aim of obtaining the best scientific evidence currently in existence in the literature about the therapeutic effect of theophylline combined with $\beta_2$-agonists, we carried out this systematic review of randomized clinical trials.

The objective of this review was to determine whether, in stable patients with COPD, administration of theophylline in combination with $\beta_2$-agonists is more efficacious than is that of a placebo or that of each of the two drugs used in isolation.

## Methods

The present study was approved by the Ethics Committee of the Federal University of São Paulo/Paulista School of Medicine (process no. 251/00). The randomized clinical trials included were those in which theophylline was used in combination with $\beta_2$-agonists in stable patients with COPD. The

exclusion criteria were as follows: studies with allocation concealment, inadequately described studies, studies of mixed populations (asthma and COPD patients), and studies of interventions other than those under study. Two independent reviewers evaluated the titles, abstracts, and methods sections of all identified reports of clinical trials. The studies that seemed to fulfill the inclusion criteria were selected. Subsequently, we built a collection of studies to be evaluated by the reviewers. The sources of study were as follows: the *Excerpta Medica* database, the Latin American and Caribbean Health Sciences Literature database, the Cochrane Controlled Clinical Trials Register, the Cochrane Airways Group Register of Randomized Controlled Trials, and the reference lists of the randomized clinical trials included.

The variables studied were continuous variables, which were evaluated using means and standard deviations for each of the groups. The following variables were selected for study: exercise tolerance; forced expiratory volume in one second ($FEV_1$); peak expiratory flow; maximal inspiratory pressure (MIP); quality of life; symptoms; and side effects.

The statistical analysis was carried out using the MetaView subprogram in the Review Manager software, available from the Cochrane Collaboration.

## Results

The number of articles identified from each source is shown in Figure 1. The date of the last search in the databases was January of 2005, and an article from the year 2001 was located through a handsearch.

Of the 848 articles initially selected, a total of 822 were excluded, since they did not involve the group or intervention of interest. Therefore, twenty-six studies were subjected to the inclusion and exclusion criteria previously defined, after which only eight remained. Table 1 shows the principal characteristics of the articles included.

## Quality of the studies included

In the allocation sequence, it was not mentioned how the respective sample sizes of the eight studies were calculated or if there was concern about doing so. All were double-blind studies and were adequately described. As for allocation concealment, it was mentioned in all of the texts that the studies were randomized, although the randomization procedures were not described. Only one of the studies[9] was a parallel study. The remaining seven were crossover trials.

In two of the eight studies, there were no losses.[12,13] In the remaining studies, losses ranged from 10.7 to 29.6%. The instrument known as the quality scale[14] is used to evaluate the merit of studies, taking into consideration three factors: randomization, masking, and the rate of dropouts/losses. The eight studies were randomized (although the way in which that was carried out was not described),

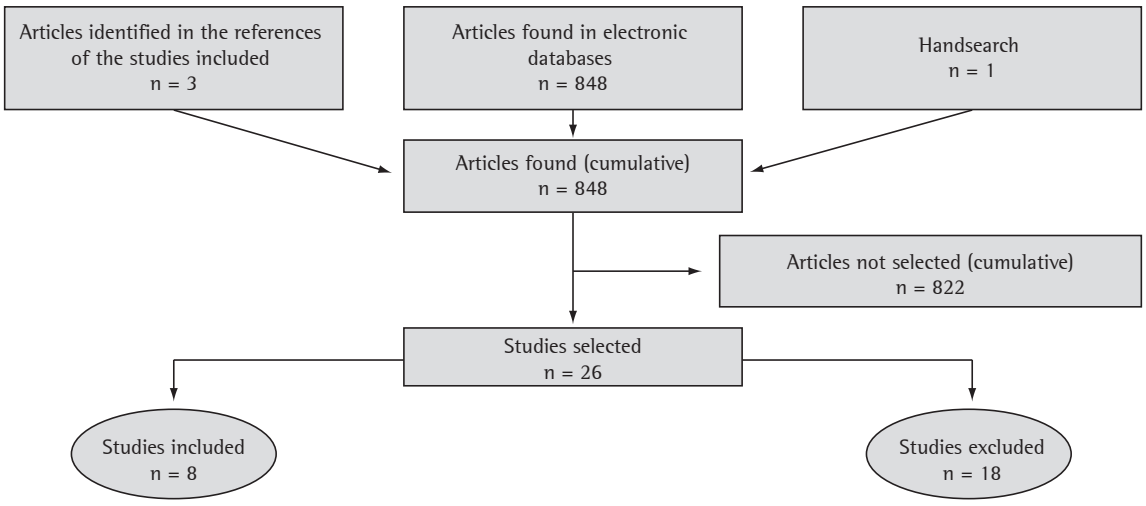


**Figure 1 -** Flowchart of the systematic review - n: number of articles.

**Table 1 -** Principal characteristics of the studies included.

| Study | Duration | Variables | Definition of COPD | Sample size | Intervention |
|---|---|---|---|---|---|
| Dullinger *et al.*[12] | 5 weeks | FVC and $FEV_1$<br>12-min walk test and incremental test<br>Dyspnea | $FEV_1$ < 1.5 L and $FEV_1$/FVC < 60% | 10 | Long-acting theophylline (10-15 µg/mL)<br>Short-acting metaproterenol (2×/day) |
| Guyatt *et al.*[30] | 8 weeks | FVC, $FEV_1$ and PEF<br>6-min walk test<br>Dyspnea and Quality of life | $FEV_1$ < 70% and $FEV_1$/VC < 0.7 | 19 | Long-acting theophylline (12.3 ± 2.9 µg/mL)<br>Short-acting salbutamol (200 µg - 4×/day) |
| Guyatt *et al.*[19] | 8 weeks | FVC and $FEV_1$<br>6-min walk test<br>Dyspnea and Quality of life | $FEV_1$ < 70% and $FEV_1$/VC < 0.7 | 24 | Long-acting theophylline<br>Short-acting albuterol (200 µg-4×/day) |
| Jaeschke *et al.*[16] | 8 weeks | FVC and $FEV_1$<br>Maximal inspiratory pressure<br>Dyspnea | $FEV_1$ < 70% and $FEV_1$/VC < 0.7 | 24 | Long-acting theophylline (12.3 ± 3.4 µg/mL)<br>Short-acting salbutamol (200 µg-4×/day) |
| Karpel *et al.*[13] | 45 days (4 regimens on 4 non-consecutive days) | FVC and $FEV_1$<br>Side effects | As defined by the American Thoracic Society | 48 | Short-acting theophylline (12-18 µg/mL)<br>Short-acting albuterol (2× 180 µg) |
| Taylor *et al.*[15] | 12 weeks | FVC, $FEV_1$ and PEF<br>Symptoms diary | Productive cough yielding sputum for 3 months for 2 consecutive years | 25 | Long-acting theophylline (10-15 µg/mL)<br>Short-acting salbutamol (200 µg-4×/day) |
| Thomas *et al.*[17] | 56 days | Spirometry and PEF<br>Symptoms diary | Patients aged 70 years or less and $FEV_1$ < 60% and $FEV_1$/FVC < 0.7 | 12 | Long-acting theophylline (10 µg/mL)<br>Short-acting salbutamol (2× 200 µg) |
| ZuWallack *et al.*[9] | 12 weeks | Spirometry and PEF<br>Dyspnea<br>Symptoms diary<br>Quality of life<br>Satisfaction with treatment | FEV1 ≥ 0.7 L, ≤ 65% and $FEV_1$/FVC ≤ 70% | 962 | Long-acting theophylline (10-20 µg/mL)<br>Long-acting salmeterol (42 µg) |

$FEV_1$: forced expiratory volume in one second; VC: vital capacity; FVC: forced vital capacity; PEF: peak expiratory flow.

double-blind, and adequately described. In addition, any losses were explained. All scored three points. This scale is not used to include or exclude studies from a systematic review. However, it is possible to use it to group homogeneous studies for the sensitivity analysis portion of a meta-analysis.

## Results of the outcomes studied

### *Theophylline combined with $\beta_2$-agonists vs. placebo*

Of the 156 patients included in seven crossover clinical trials with continuous variables, 156 received theophylline combined with $\beta_2$-agonists, and 156 received placebos. The individuals allocated to the group that received theophylline combined with $\beta_2$-agonists, in comparison to those allocated to the group that received placebos, presented the following results:

$FEV_1$ (L): difference in weighted means (randomized effect model) 0.27; 95% confidence interval (0.11 to 0.43); p = 0.0007; and test of heterogeneity p = 0.96. These results are statistically significant and are based on three studies that had 48 individuals per group[15-17] (Table 2).

Dyspnea: difference in standardized means (randomized effect model) –0.78; 95% confidence interval (–1.26 to –0.29); p = 0.002; and test of heterogeneity p = 0.58. These results are statistically significant and are based on two studies that had 36 individuals per group[16,17] (Table 3).

### *Theophylline combined with $\beta_2$-agonists vs. $\beta_2$-agonists in isolation*

Of the 719 patients included in eight clinical trials, 361 received theophylline combined with $\beta_2$-agonists and 358 received $\beta_2$-agonists in isolation. There were no statistically significant differences in any of the variables studied.

### *Theophylline combined with $\beta_2$-agonists vs. theophylline in isolation*

Of the 926 patients included in eight clinical trials, 462 received theophylline combined with $\beta_2$-agonists and 464 received theophylline in isolation. The individuals allocated to the group that received theophylline combined with $\beta_2$-agonists, in comparison to those allocated to the group that received theophylline in isolation, presented the following results:

Dyspnea: difference in standardized means (randomized effect model) –0.19; 95% confidence interval (–0.34 to –0.04); p = 0.01; and test of heterogeneity p = 0.79. These results are statistically significant and are based on three studies that had a total of 336 individuals in the groups that received theophylline combined with $\beta_2$-agonists and 344 in the groups that received theophylline in isolation[9,16,17] (Table 4).

## Discussion

The results of this systematic review revealed a significant improvement in $FEV_1$ and dyspnea with the use of theophylline combined with $\beta_2$-agonists in relation to the use of a placebo, as well as an improvement in dyspnea in the group of patients who were treated with theophylline combined with

**Table 2 -** Meta-analysis of three studies comparing the effect of theophylline combined with $\beta_2$-agonists to that of a placebo in patients with COPD. Presentation of the variable $FEV_1$ (L) through the difference in weighted means and 95% confidence intervals (randomized effect model).

| Study, year | Theo + $\beta_2$ group | PL group | Difference in weighted means (95% CI) | Weight (%) | 95% CI |
|---|---|---|---|---|---|
| | n/mean ± SD | | | | |
| Theo + $\beta_2$ *vs.* PL | | | | | |
| Jaeschke *et al.*[16] | 24/1.07 ± 0.34 | 24/0.81 ± 0.36 | | 62.7 | 0.26 (0.06 to 0.46) |
| Taylor *et al.*[15] | 12/1.38 ± 0.56 | 12/1.14 ± 0.59 | | 11.6 | 0.24 (–0.22 to 0.70) |
| Thomas *et al.*[17] | 12/1.34 ± 0.42 | 12/1.03 ± 0.35 | | 25.7 | 0.31 (0.00 to 0.62) |
| Total | 48 | 48 | | 100.0 | 0.27 (0.11 to 0.43) |
| Test of heterogeneity $\chi^2$ = 0.09, df = 2, p = 0.96<br>Z-test of overall effect = 3.38, p = 0.0007 | | | -1 -5 0 5 1<br>Favorable to PL / Favorable to Theo + $\beta_2$ | | |

Theo: theophylline, PL: placebo; 95% CI: 95% confidence interval; n: number; SD: standard deviation; df: degrees of freedom; $\chi^2$: chi-square test.

**Table 3 -** Meta-analysis of two studies comparing the effect of theophylline combined with $\beta_2$-agonists to that of a placebo in patients with COPD. Presentation of the results of the variable dyspnea through the difference in weighted means and a 95% confidence interval (randomized effect model).

| Study, year | Theo + $\beta_2$ group | PL group | Difference in weighted means (95% CI) | Weight (%) | 95% CI |
|---|---|---|---|---|---|
| | n/mean (SD) | | | | |
| Theo + $\beta_2$ *vs.* PL | | | | | |
| Jaeschke *et al.*[16] | 24/–19.40 ± 4.60 | 24/–14.6 ± 6.10 | | 65.6 | 0.87 (–1.47 to –0.28) |
| Thomas *et al.*[17] | 12/0.53 ± 0.84 | 12/1.14 ± 1.14 | | 34.4 | –059 (–1.41 to 0.23) |
| Total | 36 | 36 | | 100.0 | –0.78 (–1.26 to –0.29) |
| Test of heterogeneity $\chi^2$ = 0.31, df = 1, p = 0.58<br>Z-test of overall effect = 3.16, p = 0.02 | | | -4 -2 0 2 4<br>Favorable to Theo + $\beta_2$ / Favorable to PL | | |

Theo: theophylline, PL: placebo; 95% CI: 95% confidence interval; n: number; SD: standard deviation; df: degrees of freedom; $\chi^2$: chi-square test.

$\beta_2$-agonists in comparison to the group of patients who used theophylline in isolation.

The analysis of pulmonary function must take into account that the function tests, despite being carried out with the patient at rest and not reproducing the alterations that occur during exercise,[18] are still the gold standard for the diagnosis and evaluation of COPD, since they are the most reproducible, standardized, and objective way of measuring airflow limitation.[4]

We found statistically significant differences in $FEV_1$ (L) when we compared the effect of theophylline combined with $\beta_2$-agonists to that of a placebo.[15-17]

Other authors[15] studied the effect of theophylline and of salbutamol, used in isolation or in combination, in 25 patients with COPD and reversibility of $FEV_1 \leq 10\%$. The study was carried out in four phases of three weeks each: theophylline + salbutamol; theophylline; salbutamol; and placebo. In each phase, they evaluated pulmonary function test results (spirometry: prior to and after each intervention, and peak expiratory flow: daily), as well as the symptoms diaries kept by the patients.

**Table 4 -** Meta-analysis of three studies comparing the effect of theophylline combined with $\beta_2$-agonists to that of theophylline in isolation in patients with COPD. Presentation of the results of the variable dyspnea through the difference in weighted means and 95% confidence intervals (randomized effect model).

| Study, year | Theo + $\beta_2$ group | Theo group | Difference in weighted means (95% CI) | Weight (%) | 95% CI |
|---|---|---|---|---|---|
| | n/mean (SD) | | | | |
| Theo + $\beta_2$ *vs.* Theo | | | | | |
| Jaeschke *et al.*[16] | 24/–19.40 ± 4.60 | 24/–17.50 ± 6.50 | | 7.0 | –0.33 (0.90 to 0.24) |
| Thomas *et al.*[17] | 12/0.53 ± 0.84 | 12/0.84 ± 0.81 | | 3.5 | –0.36 (–1.17 to 0.45) |
| Zuwallack *et al.*[9] | 300/–6.40 ± 1.73 | 308/–6.10 ± 1.75 | | 89.5 | –0.33 (–0.33 to –0.01) |
| Total | 336 | 344 | | 100.0 | 0.19 (–0.34 to –0.04) |
| Test of heterogeneity $\chi^2$ = 0.46, df = 2, p = 0.79<br>Z-test of overall effect = 2.47, p = 0.01 | | | -5 -1 0 1 5<br>Favorable to Theo + $\beta_2$ / Favorable to Theo | | |

Theo: theophylline; 95% CI: 95% confidence interval; n: number; SD: standard deviation; df degrees of freedom; $\chi^2$: chi-square test.

The authors found that using the drugs in combination produced a significant improvement in the spirometric values ($p < 0.001$).

In other studies,[16] the samples consisted of 24 stable patients with COPD and reversibility of $FEV_1 \leq 35\%$. The authors analyzed the effects of theophylline and of salbutamol on pulmonary function and dyspnea during activities of daily living. In four two-week periods, the patients were submitted to the following treatments: salbutamol; theophylline; theophylline combined with salbutamol; and placebo. The use of theophylline combined with salbutamol was found to produce a significant increase in $FEV_1$ ($p < 0.001$) in comparison to the use of a placebo.

The last study included,[17] which contributed to the significant improvement in $FEV_1$ in this meta-analysis, analyzed 12 stable patients with COPD ($FEV_1 = 1.09 \pm 0.35$ L) and bronchodilator reversibility of $FEV_1 \leq 15\%$. The duration of the study was 56 days, divided into four two-week phases. The interventions were as follows: theophylline; salbutamol; theophylline + salbutamol; and placebo. Spirometry was performed at the end of each phase. In the patients treated with the drugs, $FEV_1$ improved by 13.5% in those receiving theophylline, 16.2% in those receiving salbutamol, and 31.3% in those receiving the two drugs in combination.. Therefore, use of the theophylline + salbutamol combination resulted in a significant improvement.

The $FEV_1$ was found to be the most common variable in the clinical trials, despite being expressed in liters in some studies[12,13,15-17,19] and as a percentage of predicted in others.[9,15] Therefore, of the eight articles included, seven studied $FEV_1$. However, certain studies were excluded from the statistical analysis because of inappropriate presentation of the data[12,19] or differences in methodology, such as that observed in one study,[13] whose authors divided the sample into patients with $FEV_1 \leq 0.5$ L and patients with $FEV_1 \geq 0.5$ L.

The analysis of the theophylline combined with $\beta_2$-agonists *vs.* theophylline in isolation groups, together with that of the theophylline combined with $\beta_2$-agonists *vs.* $\beta_2$-agonists in isolation groups, revealed that the response to the use of the drugs in combination was favorable only when compared to the response obtained with the use of theophylline in isolation.

It is important to emphasize that, in the studies that revealed no significant improvement in pulmonary function, benefits in quality of life,[20] as well as symptom improvement,[21,22,24-26] were observed.

As for dyspnea, we should bear in mind that this is one of the principal complaints of patients with COPD. This is a subjective report, which is related to various factors, from physiological to sociocultural ones. This is considered to be the most highly-valued symptom in the literature.[27]

It is believed that bronchodilators produce dilation of the small airways, with a consequent decrease in air trapping, which results in increased muscle strength, reduced dyspnea, and improved exercise tolerance in patients with COPD.[27]

We obtained statistical significance in the differences between the following pairs of groups: theophylline combined with $\beta_2$-agonists *vs.* placebo;[16,17] and theophylline combined with $\beta_2$-agonists *vs.* theophylline in isolation.[9,16,17] These findings are of great clinical importance for patients with COPD, since reduced dyspnea is directly related to improved quality of life in such patients.

In one study,[16] the principal objective was to evaluate dyspnea during activities of daily living in patients with COPD being treated with theophylline and salbutamol, in combination or not. This evaluation was carried out using one part of the Chronic Respiratory Questionnaire (CRQ), which is an instrument used to assess health-related quality of life, in which there are 5 questions on a 7-point scale (ranging from 5 to 35 points), an overall score of 1 signifying severe dyspnea and an overall score of 7 signifying no dyspnea. A significant negative correlation was found between dyspnea and $FEV_1$, as well as between dyspnea and MIP ($p < 0.001$ for both), and it was concluded that the degree of dyspnea during activities of daily living is lower, due to increased muscle strength and increased airway diameter, in patients receiving theophylline combined with salbutamol.

One group of authors,[17] using a 5-point symptoms diary scale (0 = none, and 4 = intolerable), described the following symptoms: dyspnea, cough, secretion, and bronchoconstriction. The use of theophylline + salbutamol resulted in a significant decrease in dyspnea, as well as a significant improvement in bronchoconstriction. No differences were found between groups regarding cough or production of secretion.

A randomized, double-blind, parallel-group study[9] of 962 stable patients with COPD evaluated the efficacy of theophylline and salmeterol in improving pulmonary function and symptoms as well as in preventing exacerbations. The duration of the study was twelve weeks, and the patients were divided into three groups: salmeterol; theophylline; and theophylline + salmeterol. The patients were instructed to keep a diary to record peak expiratory flow values and symptoms scores. Health-related quality of life questionnaires were applied by professionals during the evaluations made at the clinic at weeks 4, 8, and 12. Dyspnea was evaluated using two indexes: the baseline dyspnea index (BDI) and the transitional dyspnea index (TDI). The use of theophylline combined with salmeterol resulted in a significant improvement in symptoms ($p = 0.023$). As for dyspnea, the biggest difference was found in relation to the group that used theophylline in isolation ($p < 0.048$).

All three studies demonstrated a significant decrease in dyspnea after the use of theophylline combined with $\beta_2$-agonists in comparison to the other interventions. We had great difficulty in analyzing this variable due to the variations among the methods used. However, its evaluation was possible through statistical standardization, taking into account the significance of the results found in each study.

According to one study,[28] dyspnea can be measured during activities of daily living and during specific tests (for example, after the walk test). The forms of measurement accepted by the American Association of Cardiovascular and Pulmonary Rehabilitation are as follows: for activities of daily living, the BDI and the TDI, as well as the dyspnea portion of the CRQ; and for specific tests, the 0-10 Borg scale or the visual analog scale.

In the studies already described, we found the use of the CRQ and the use of the dyspnea indexes (the TDI and the BDI). However, some authors[17] used another scale to evaluate this variable. Although another two studies[12,30] evaluated dyspnea, they could not be used in the statistical analysis since their results were not adequately described. We can compare the results of one study[12] with those of this systematic review, since we found no statistically significant differences in the comparison between the group treated with theophylline + $\beta_2$-agonists and the group treated with $\beta_2$-agonists in isolation.

Given the large number of scales and indexes, it seems that there is great interest in studying dyspnea in patients with COPD. However, as was observed, there is considerable variation among studies in terms of the approach taken in evaluating dyspnea, and this hinders the comparative analysis, making it difficult to reach a conclusion on this subject.

As for peak expiratory flow and MIP, due to the small number of studies found, there is no convincing evidence that the use of theophylline combined with $\beta_2$-agonists results in improvement in these parameters.

Another two variables that are important for patients with COPD are exercise tolerance and quality of life. Exercise tolerance was studied using the 6-minute walk test,[19,30] the 12-minute walk test, and the incremental test on a cycle ergometer.[12] Quality of life was determined, by one group of authors,[19,30] using the CRQ. All of these variables are accepted in the literature. Unfortunately, we could not use them in our statistical analysis since they were not adequately described, having been published without the standard deviations.

The side effects of the use of the drugs were reported in the studies but were not described in terms of any clinical or statistical significance. The most commonly cited study[9] emphasized the deleterious effect of theophylline on the gastrointestinal tract, and nausea was the principal complaint. In all of the studies, the authors mentioned that the use of the drugs in combination has the benefit of minimizing side effects.

The present systematic review allows us to conclude the following regarding in stable patients with COPD: administration of theophylline combined with $\beta_2$-agonists is more efficacious than is a placebo in terms of improving $FEV_1$ and dyspnea; administration of theophylline combined with $\beta_2$-agonists is more efficacious than is the use of theophylline in isolation in terms of improving dyspnea; and administration of theophylline combined with $\beta_2$-agonists is no more efficacious, for any of the variables studied, than is the use of $\beta_2$-agonists in isolation.

However, in clinical decision making, the data in the literature constitute only one of the aspects that, in conjunction with clinical experience and the status/responses of individual patients, ultimately define the approach to treatment.

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