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# Effect of theophylline on the rate of moderate to severe exacerbations among patients with chronic obstructive pulmonary disease

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## WHAT IS ALREADY KNOWN ABOUT THIS SUBJECT

- Despite active research, none of the existing medications used to treat chronic obstructive pulmonary disease (COPD) has been shown to modify the long-term decline in lung function.
- Theophyllines have been recognized for their bronchodilating effects and anti-inflammatory properties, but at the same time they are associated with the risk of adverse events due to their narrow therapeutic range and potential for drug interactions.
- To our knowledge, no study has investigated the effects of theophylline on outcomes that can reflect the overall morbidity of COPD patients.

## WHAT THIS STUDY ADDS

- The use of theophyllines is associated with a reduction in the rate of COPD exacerbations compared with long-acting $\beta_2$-agonists among COPD patients.
- Theophyllines could be seen as an interesting alternative in the treatment of COPD, because they are much less expensive than long-acting $\beta_2$-agonists, and, from the patient's perspective, an oral formulation might be easier to take than an inhaled formulation.

## AIM

To determine the effectiveness of theophyllines in real clinical practice on moderate to severe exacerbations.

## METHODS

A cohort of 36 492 chronic obstructive pulmonary disease (COPD) patients aged ≥50 years was reconstructed from the health administrative databases of the province of Quebec, Canada, between 1 January 1995 and 31 December 2002 to compare users of theophyllines with users of inhaled corticosteroids (ICS) and users of long-acting $\beta_2$-agonists (LABA) on their rate of moderate to severe COPD exacerbations.

## RESULTS

Users of theophyllines were found to be less likely than users of LABA [crude rates 84 *vs.* 91 per 100 patient-years, adjusted rate ratio (RR) 0.89, 95% confidence interval (CI) 0.84, 0.95] and users of theophyllines plus ICS were found to be less likely than users of LABA plus ICS (crude rates 114 *vs.* 112 per 100 patient-years, adjusted RR 0.89, 95% CI 0.87, 0.92) to have moderate to severe COPD exacerbations. Users of theophyllines were found to be more likely than users of ICS to have a COPD exacerbation (crude rates 84 *vs.* 77 per 100 patient-years, adjusted RR 1.07, 95% CI 1.04, 1.10), and this association was even stronger among patients who had at least three exacerbations in the year prior to cohort entry (crude rates 273 *vs.* 213 per 100 patient-years, adjusted RR 1.28, 95% CI 1.19, 1.38).

## CONCLUSION

The use of theophyllines was found to be associated with a reduction in the rate of COPD exacerbations among all COPD patients, but to be less effective than ICS among patients with frequent exacerbations.

## Introduction

In Canada, chronic obstructive pulmonary disease (COPD) affects 4.3% of adults aged ≥35 years, making it the fourth most common cause of illness and death [1]. Worldwide, COPD is also the fourth leading cause of death [2] and the 12th leading cause of disability [3]. Acute exacerbations are the most frequent cause of hospital admissions and death among COPD patients [4].

Unfortunately, recent guidelines for the diagnosis, management and prevention of COPD report that none of the existing medications for COPD has been shown to modify the long-term decline in lung function [5]. Although the goals of COPD management include the prevention of disease progression and the reduction of mortality, they also include symptom relief, treatment and prevention of exacerbations and the improvement of health status [5]. The step care approach proposed by the Global Initiative for Chronic Obstructive Disease (GOLD) treatment guidelines recommends theophyllines as the third line of treatment when symptoms are still persistent despite treatment with short- and long-acting inhaled bronchodilators [5]. The recommendation for inhaled corticosteroids (ICS) use is more restricted, being recommended only for patients with frequent exacerbations, as their efficacy to improve lung function has been shown to be limited, whereas they have been shown to reduce the risk of exacerbations [6–8]. In the ISOLDE trial, the annual rate of exacerbations among moderate to severe COPD patients was 1.90 (SD 2.63) for placebo group and 1.43 (SD 1.93) for patients on ICS after 3 years of treatment [7]. In this randomized controlled trial (RCT), an exacerbation was defined as worsening of respiratory symptoms that required treatment with oral corticosteroids or antibiotics, or both [7].

Theophyllines have been recognized for their bronchodilating effects since the early 1950s, but have recently been shown also to have anti-inflammatory properties in patients with asthma [9]. Several clinical trials have shown that theophyllines improve lung function and dyspnoea [10, 11] in patients with COPD. Theophyllines may also improve mucociliary clearance [12, 13], cardiovascular function [14], gas exchange [10] and exercise capacity [14]. Despite these proven clinical benefits, the use of theophyllines in the treatment of COPD has decreased over the past years [15], mainly due to their narrow therapeutic range and potential for drug interactions [5]. At the same time, the use of ICS in the treatment of COPD has increased dramatically [16], despite the guidelines' recommendations and the lack of scientific evidence to demonstrate their efficacy to reduce disease progression [6–8, 17–19].

As in many chronic diseases, in the treatment of COPD there is an important gap between the guidelines' recommendations and the use of prescribed medications in clinical practice [16, 20]. This situation commends the evaluation of drug effectiveness in real clinical practice, since guidelines' recommendations are mainly based on the results of RCTs that might not be easily generalized into practice. To our knowledge, there is no study comparing the effectiveness of theophyllines with other available treatment options to reduce the risk of COPD exacerbations in clinical practice. We therefore conducted a large population-based cohort study to evaluate and compare the rate of moderate to severe COPD exacerbations between users of oral theophyllines, ICS and long-acting inhaled $\beta_2$-agonists (LABA) among patients aged ≥50 years.

## Methods

### *Source of data*

This study used claims data from the health administrative database of the Régie de l'Assurance Maladie du Quebec (RAMQ) and data from the MED-ECHO database from the Canadian province of Quebec. During the study period, close to 97% of elderly (>874 000 persons aged ≥65 years) and 508 000 persons aged between 50 and 64 years [21] were covered by the RAMQ medical services plan and the drug plan. The RAMQ Prescriptions Drugs Database contains information on prescriptions filled at community pharmacies, i.e. name, dose, form, quantity of medication dispensed, date and duration of prescription, as well as the identification and specialty of the prescribing physician. The RAMQ Medical Services Database contains claims data on medical services dispensed either at hospitals, emergency departments or medical clinics, i.e. date of service, where the service was dispensed, diagnosis coded with International Classification of Diseases (ICD)-9 codes, as well as specialty and identification of the treating physician. The RAMQ database also contains patients' sociodemographic data, such as age, gender and date of death, as well as a variable indicating whether a patient is receiving social assistance or a supplement added to the Old Age Security pension. The MED-ECHO database contains information on all admissions to acute care hospitals in Quebec, such as date of admission, length of stay, diagnosis coded with ICD-9 codes (admission, principal and secondary), identification of hospital and treating physician. The RAMQ and MED-ECHO databases were linked using an encrypted unique patient's identifier included in all databases. The RAMQ and MED-ECHO databases have been used extensively for epidemiological studies, and the information related to medications has been proven valid and comprehensive [22–24]. Moreover, medical diagnoses related to COPD recorded in the RAMQ Medical Services database have been found to be valid for research purposes [25].

### *Study population and design*

From the RAMQ databases a large cohort of COPD patients aged ≥50 years between 1 January 1995 and 31 December 1999 was selected. To be included in the cohort, patients should have: (i) filled at least six prescriptions of a

short-acting inhaled $\beta_2$-agonists (SABA) (epinephrine, orciprenaline, salbutamol, terbutaline, fenoterol or pirbuterol) or of an ipratropium bromide in the year preceding cohort entry (six prescriptions per year of inhaled bronchodilator correspond to 3.6 inhalations per day, on average, which is based on the recommended minimum dose of two inhalations qid when needed [5]); (ii) received at least one medical service for COPD (service billed for the following ICD-9 diagnostic codes: chronic bronchitis codes 491.0, 491.1, 491.2, 491.8 and 491.9; emphysema codes 492.0, 492.8; and chronic airway obstruction code 496) in the year preceding cohort entry; and (iii) been covered by the RAMQ drug plan for at least 1 year prior to cohort entry. Patients were excluded if they received oral corticosteroids as a continuous therapy (at least six filled prescriptions of $\geq$28 days, or at least 21 filled prescriptions regardless of duration), were hospitalized for >30 days in one hospitalization (because no information was available on medication in RAMQ database when patients were hospitalized) or received any medical service for asthma (ICD-9 codes 493) in the year preceding cohort entry. Corticosteroid-dependent patients were excluded, because this treatment might have been prescribed for a disease other than COPD and continuous use of oral corticosteroids would preclude the evaluation of our main outcome, which is based on markers of COPD exacerbations, such as a filled prescription of oral corticosteroids. Cohort entry was defined as 1 January 1996, 1997, 1998, 1999 or 2000. Patients were followed for a maximum of 7 years. Follow-up was stopped either when patients reached the end of the study period, i.e. 31 December 2002, or died. Patients were also censored if they left the RAMQ drug plan insurance, received one asthma diagnosis, were hospitalized for >30 days or started a continuous therapy of oral corticosteroids, because these events would preclude the evaluation of our main outcome. Data on medical and pharmacy services were obtained 1 year before cohort entry and during study follow-up.

## *Assessment of exposure*

Follow-up time was divided into treatment episodes. A treatment episode was defined by the number of consecutive days a patient remained under the same treatment regimen. No minimum was required for the duration of a treatment period for inclusion in the analysis. The duration of a treatment period was based on the duration of the filled prescriptions and a delay was allowed of two times the duration of the prescription between renewals before considering that a patient had stopped his treatment. Each treatment episode was classified into one of seven treatment regimens for COPD based on filled prescriptions. The first regimen was formed of SABA and/or ipratropium bromide only. For all the other regimens, there was at least one medication added to the SABA and/or ipratropium bromide and one to three adjuvant therapies, i.e. theophyllines (aminophylline, theophylline or oxtriphylline in oral formulation); ICS (beclomethasone, triamcinolone, flunisolide, budesonide or fluticasone); LABA (salmeterol or formoterol); theophyllines and ICS concurrently; ICS and LABA concurrently; and theophyllines, ICS and LABA concurrently. Patients remained in a treatment episode until they added another medication to their treatment regimen, switched, stopped a medication or reached the end of the study follow-up. Patients could thus contribute to more than one episode of treatment during the study follow-up. An example of the assessment of exposure for a patient during the entire follow-up is presented in Figure 1.

## *Outcome*

The main outcome was the rate of moderate to severe COPD exacerbations, i.e. the number of exacerbations divided by the person-days during episodes of a specific COPD treatment regimen. An episode was defined by the number of consecutive days a patient remained under the same treatment regimen. An exacerbation was defined either as a filled prescription of oral corticosteroids, a visit to an emergency department for COPD or a hospitalization for COPD (admission or principal ICD-9 codes equal to 491.x, 492.x or 496). Only a single exacerbation was considered if more than one marker of exacerbation [prescription of oral corticosteroids, Emergency Department (ED) visits for COPD or hospitalizations for COPD] occurred within a period of 15 days.

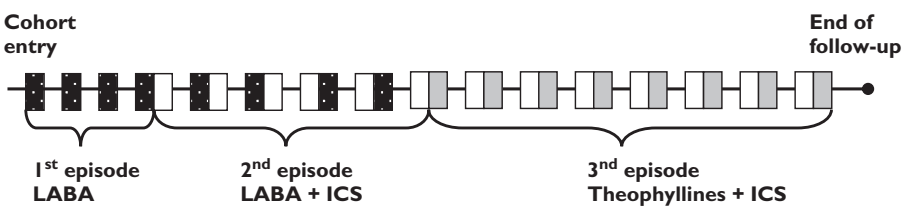


**Figure 1**

Example of assessement of exposure to chronic obstructive pulmonary disease treatment for one patient. Rx, Prescription; ICS, inhaled corticosteroids; LABA, long-acting $\beta_2$-agonists. Rx LABA, (■); Rx ICS, (□); Rx theophyllines, (▣)

### *Potential confounders*

Potential confounders included patient's age at cohort entry, gender, socio-economic status [poor (receiving social assistance or receiving Guaranteed Income Supplement added to the Old Age Security Pension) *vs.* others] and the calendar year of cohort entry (to adjust for prescribing habits that may vary over time). Potential confounders measured in the year prior to cohort entry were also included, such as a medication-based comorbidity score [26] and a medical visit-based continuity of care score [27]. Markers of COPD severity included the number of prescriptions of oral corticosteroids, ED visits for COPD and hospitalizations for COPD in the year prior to cohort entry, as well as a medical visit with a respiratory physician, the average daily dose of SABA and ipratropium bromide (one dose equals two inhalations) and the number of prescriptions of antibiotics for COPD filled in the 3 months prior to each specific treatment episode.

### *Statistical analysis*

The crude rate of moderate to severe COPD exacerbations was estimated for all treatment regimens. Poisson regression models were also performed to estimate the adjusted rate ratios of moderate to severe COPD exacerbations comparing patients who had regimens with same number of adjuvant therapies: (i) theophyllines *vs.* ICS; (ii) theophyllines *vs.* LABA; and (iii) theophyllines plus ICS *vs.* LABA plus ICS. Treatment episodes with theophyllines plus LABA were excluded from the comparison because of the small number of patients under this treatment regimen. All comparisons were performed twice, once among all COPD patients and secondly among patients who had three exacerbations of COPD or more in the year prior to cohort entry. This stratification was done to be coherent with the Canadian guidelines, which recommend regular use of ICS only in patients with moderate to severe COPD who have three or more acute exacerbations per year [28]. Other Poisson regression models were used to obtain adjusted rate ratios for COPD exacerbations in association with the average daily doses of theophyllines and ICS. All potential confounder variables were included in the models and analyses were carried out using the SAS system version 8.2 (SAS Institute Inc., Cary, NC, USA).

## Results

The cohort was formed of 36 492 COPD patients who met the eligibility criteria. The mean age at cohort entry was 73 years, 61.5% of patients were male and patients were followed on average for 2.4 years. A total of 3040 patients had three or more COPD exacerbations in the year prior to cohort entry and were followed on average for 1.5 years. The baseline characteristics of the study patients are summarized in Table 1. Among study patients, we observed that 22.9% had at least one treatment episode with theophyllines during the study follow-up and 63.7% had at least one treatment episode with ICS. The most commonly prescribed theophyllines were theophylline in long-acting formulation (84.0%) and the average daily dose of theophyllines was 346 mg (SD 204). The prescribed ICS were fluticasone (50.9%), beclomethasone (39.4%) and budesonide (17.2%), and the average daily dose of ICS was 818 µg (SD 554) beclomethasone equivalent. COPD patients had, on average, a high comorbidity score of 8.9 (SD 4.1). A total of 37.9% of patients received at least one prescription of oral corticosteroids, 29.0% had at least one visit to an ED for COPD and 19.2% were hospitalized for COPD in the year prior to cohort entry.

Similar socio-demographic characteristics were observed among patients with three or more exacerbations in the year prior to cohort entry. In this subgroup of patients, the most commonly prescribed theophylline was also in the long-acting formulation (89%) and the average daily dose was 377 mg (SD 206). The average daily dose of ICS was 1001 µg (SD 579) beclomethasone equivalent. However, these patients appeared to have severe COPD, because a larger proportion of them had prescriptions of oral corticosteroids (77.9% filled more than three prescriptions), an ED visit for COPD (70.3%) and hospitalization for COPD (54.7% had at least one hospitalization) in the year prior to cohort entry. Furthermore, they used more doses of SABA and ipratropium bromide per day and filled more antibiotics for COPD before their entry in the cohort.

The Table 2 shows the characteristics of all study patients according to compared treatment regimens. Patients using theophyllines alone or in addition to ICS had a slightly higher score of continuity of care than other patients. Patients using ICS had slightly more comorbidity than patients using other treatment regimens. Furthermore, on average, patients treated with theophyllines alone or in addition to ICS used more SABA prior to treatment initiation than those treated with other drug regimens. Patients treated with LABA alone or in addition to ICS used more ipratropium bromide and were more likely to visit a respiratory physician prior to treatment initiation than patients treated with other drug regimens. Similar patterns were observed among patients with three or more exacerbations in the year prior to cohort entry (Table 3), but they used more SABA, ipratropium bromide and antibiotics for COPD prior to treatment initiation than other patients.

Table 4 displays the crude rate of moderate to severe COPD exacerbations; this rate was found to be higher among patients with two adjuvant therapies (users of theophyllines plus ICS or users of LABA plus ICS) than patients with only one adjuvant therapy. For example, among users of theophyllines in monotherapy the rate of filled prescriptions of oral corticosteroids was 72 per 100 patient-years (4432 filled prescriptions divided by 6156 patient-years) and was lower than the rate among

## Table 1

Characteristics of all chronic obstructive pulmonary disease study patients and patients having three exacerbations or more in the year prior to cohort entry

| Variables | All patients, *n* = 36 492 | Patients with ≥3 exacerbations in year prior to cohort entry, *n* = 3040 |
|---|---|---|
| **Male (%)** | 22 430 (61.5) | 1915 (63.0) |
| **Age at cohort entry (years), mean ± SD** | 73.1 ± 8.5 | 73.0 ± 8.0 |
| **Income, *n* (%)** | | |
| **Poor to average** | 22 828 (62.6) | 1803 (59.3) |
| **Other** | 13 664 (37.4) | 1237 (40.7) |
| **Follow-up (years), mean ± SD** | 2.4 ± 1.9 | 1.5 ± 1.6 |
| **Year of cohort entry, *n* (%)** | | |
| **1996** | 10 461 (26.7) | 903 (29.7) |
| **1997** | 7 116 (19.5) | 561 (18.5) |
| **1998** | 6 991 (19.2) | 574 (18.9) |
| **1999** | 6 092 (16.7) | 497 (16.4) |
| **2000** | 5 832 (16.0) | 505 (16.6) |
| **≥1 episode(s) of treatment during follow-up, *n* (%)** | | |
| **Theophylline** | 8 371 (22.9) | 865 (28.5) |
| **ICS** | 23 262 (63.7) | 1736 (57.1) |
| **LABA** | 3 015 (8.3) | 239 (7.9) |
| **LABA plus ICS** | 5 738 (15.7) | 492 (16.2) |
| **Theophylline plus ICS** | 9 200 (25.2) | 1117 (36.7) |
| ***In the year prior to cohort entry*** | | |
| **COC index, mean ± SD** | 0.45 ± 0.29 | 0.43 ± 0.26 |
| **Comorbidity score, mean ± SD** | 8.9 ± 4.1 | 11.4 ± 3.8 |
| **Prescriptions of oral corticosteroids, *n* (%)** | | |
| **0** | 22 667 (62.1) | 109 (3.6) |
| **1** | 7 047 (19.3) | 197 (6.5) |
| **2** | 2 939 (8.1) | 365 (12.0) |
| **≥3** | 3 842 (10.5) | 2368 (77.9) |
| **Emergency department visits COPD, *n* (%)** | | |
| **0** | 25 895 (71.0) | 902 (29.7) |
| **1** | 7 814 (21.4) | 848 (27.9) |
| **≥2** | 2 783 (7.6) | 1290 (42.4) |
| **Hospitalizations for COPD, *n* (%)** | | |
| **0** | 29 468 (80.8) | 1376 (45.3) |
| **≥1** | 7 024 (19.2) | 1664 (54.7) |
| ***In the 3 months prior to cohort entry*** | | |
| **≥1 visit(s) to a respiratory physician, *n* (%)** | 6 311 (17.3) | 911 (30.0) |
| **Number of filled prescriptions of antibiotics for COPD, mean ± SD** | 0.5 ± 0.9 | 1.1 ± 1.3 |
| **Number of doses of SABA per day, mean ± SD** | 3.2 ± 2.2 | 4.3 ± 2.7 |
| **Number of doses of ipratropium bromide per day, mean ± SD** | 2.1 ± 2.3 | 3.4 ± 2.8 |

COPD, Chronic obstructive pulmonary disease; COC, continuity of care; ICS, inhaled corticosteroids; LABA, long-acting $\beta_2$-agonists; SABA, short-acting $\beta_2$-agonists.

users of theophyllines plus ICS, which was of 118 filled prescriptions of oral corticosteroids per 100 patient-years.

Among patients with three or more exacerbations in the year prior to cohort entry, the rate of moderate to severe COPD exacerbations was higher among patients treated with theophyllines (alone or in addition to ICS).

The results of Poisson regression analysis presented in Table 5 show that all users of theophyllines were found to be significantly (7%) more likely to have a moderate to severe COPD exacerbation than users of ICS [adjusted rate ratio (RR) 1.07, 95% confidence interval (CI) 1.04, 1.10]. However, in this model, users of theophyllines were found to be significantly (11%) less likely to have moderate to severe COPD exacerbations than users of LABA (adjusted RR 0.89, 95% CI 0.84, 0.95). A similar association was observed when theophyllines were added to ICS and compared with LABA plus ICS (adjusted RR 0.89, 95% CI 0.87, 0.92). From this Poisson regression model it was also observed that women were significantly less likely than men to have an exacerbation, that for every increase of one unit in the score of comorbidity the risk of exacerbations increased by 5% (crude RR 1.05; 95% CI 1.046,1.050), but this association was not found to be statistically significant when we adjusted for other covariables (adjusted RR 1.001; 95% CI 0.999, 1.003), whereas patients with markers of disease severity were more likely to have an exacerbation. Patients had an increased risk of having an exacerbation as they increased their daily doses of SABA taken in the 3 months prior to an episode of treatment (13% increase for two to three doses and 32% increase for more than

## Table 2

Selected patients' characteristics according to treatment regimens (36 492 patients)

| Variables | Theophyllines | ICS | LABA | LABA + ICS | Theophyllines + ICS |
|---|---|---|---|---|---|
| **Number of episode of treatment** | 19 613 | 58 916 | 5623 | 10 697 | 21 760 |
| **Duration of episode (days), mean ± SD** | 188 ± 273 | 115 ± 239 | 93 ± 163 | 185 ± 237 | 172 ± 269 |
| **Male (%)** | 67.1 | 60.6 | 64.2 | 65.1 | 66.7 |
| **Age at cohort entry (years), mean ± SD** | 72.5 ± 8.0 | 73.0 ± 8.5 | 71.7 ± 7.8 | 71.2 ± 7.9 | 72.5 ± 7.9 |
| **Income (%)** | | | | | |
| **Poor** | 63.8 | 63.2 | 57.3 | 60.8 | 64.3 |
| **Other** | 36.2 | 36.8 | 42.7 | 39.3 | 35.7 |
| **Number of COPD exacerbations per patient in the year prior to cohort entry, mean ± SD** | 0.9 ± 1.2 | 0.8 ± 1.1 | 0.8 ± 1.1 | 0.8 ± 1.1 | 1.0 ± 1.3 |
| ***In the 3 months prior to an episode of treatment*** | | | | | |
| **≥1 visit to a respiratory physician, %** | 16.0 | 14.0 | 24.2 | 27.9 | 17.9 |
| **Number of filled prescriptions of antibiotics for COPD, mean ± SD** | 0.5 ± 1.0 | 0.5 ± 0.9 | 0.6 ± 1.0 | 0.7 ± 1.1 | 0.7 ± 1.0 |
| **Number of doses of SABA per day, mean ± SD** | 3.5 ± 2.6 | 3.1 ± 2.2 | 2.9 ± 2.7 | 3.3 ± 2.8 | 3.9 ± 2.5 |
| **Number of doses of ipratropium bromide per day, mean ± SD** | 2.5 ± 2.7 | 2.1 ± 2.3 | 3.0 ± 2.8 | 3.1 ± 2.8 | 2.6 ± 2.7 |

COPD, Chronic obstructive pulmonary disease; ICS, inhaled corticosteroids; LABA, long-acting $\beta_2$-agonists; SABA, short-acting $\beta_2$-agonists.

## Table 3

Patients' characteristics according to treatment regimen, among patients with three exacerbations or more in the year prior to cohort entry (3040 patients)

| Variables | Theophyllines | ICS | LABA | LABA + ICS | Theophyllines + ICS |
|---|---|---|---|---|---|
| **Number of episode of treatment** | 1676 | 3535 | 398 | 883 | 2202 |
| **Duration of episode (days), mean ± SD** | 76 ± 159 | 162 ± 233 | 67 ± 129 | 171 ± 227 | 161 ± 251 |
| **Male (%)** | 69.0 | 61.6 | 65.3 | 62.0 | 66.7 |
| **Age at cohort entry (years), mean ± SD** | 72.2 ± 7.8 | 73.6 ± 8.0 | 72.1 ± 7.2 | 71.4 ± 7.5 | 72.3 ± 7.4 |
| **Income (%)** | | | | | |
| **Poor** | 59.2 | 61.7 | 59.0 | 60.8 | 63.3 |
| **Other** | 40.8 | 38.3 | 41.0 | 39.2 | 36.7 |
| **Number of COPD exacerbations per patient in the year prior to cohort entry, mean ± SD** | 3.7 ± 1.0 | 3.7 ± 1.0 | 3.6 ± 0.9 | 3.6 ± 0.9 | 3.7 ± 1.0 |
| ***In the 3 months prior to an episode of treatment*** | | | | | |
| **≥1 visit to a respiratory physician, %** | 24.5 | 23.5 | 32.4 | 36.1 | 26.4 |
| **Number of filled prescriptions of antibiotics for COPD, mean ± SD** | 1.0 ± 1.2 | 1.0 ± 1.2 | 1.0 ± 1.4 | 1.1 ± 1.3 | 1.1 ± 1.2 |
| **Number of doses of SABA per day, mean ± SD** | 4.4 ± 3.0 | 4.0 ± 2.7 | 3.6 ± 3.0 | 3.8 ± 2.7 | 4.8 ± 2.9 |
| **Number of doses of ipratropium bromide per day, mean ± SD** | 3.5 ± 2.9 | 3.2 ± 2.6 | 3.7 ± 3.0 | 3.8 ± 2.9 | 3.8 ± 2.9 |

COPD, Chronic obstructive pulmonary disease; ICS, inhaled corticosteroids; LABA, long-acting $\beta_2$-agonists; SABA, short-acting $\beta_2$-agonists.

three doses). Also, patients were more likely to have an exacerbation if they used two or more doses of ipratropium bromide per day (24% for two to three doses and 34% for more than three doses) or filled antibiotic prescriptions for COPD in the 3 months prior to an episode of treatment.

Among patients with three or more COPD exacerbations in the year prior to cohort entry, ICS were associated with a reduced risk of COPD exacerbations compared with theophyllines (adjusted RR 0.78, 95% CI 0.72, 0.84; Table 3). No other significant difference was found for the other treatment comparisons.

Poisson regression models were performed to investigate the effect of the daily dose of theophyllines and ICS on the rate of exacerbations. The dose was not found to be significantly associated with the risk of exacerbations

**Table 4**

Crude rate of moderate to severe COPD exacerbations during the study follow-up according to treatment regimens

| Treatment | All patients | | | | | ≥3 moderate to severe exacerbations in the year prior to cohort entry | | | | |
|---|---|---|---|---|---|---|---|---|---|---|
| | Patient-years | Rate* of OCS prescriptions | Rate* of ED visits for COPD | Rate* of hospitalizations for COPD | Rate* of exacerbations† | Patient-years | Rate* of OCS prescriptions | Rate* of ED visits for COPD | Rate* of hospitalizations for COPD | Rate* of exacerbations† |
| **Theophyllines** | 6 156 | 72 | 39 | 32 | 84 | 350 | 271 | 126 | 102 | 273 |
| **ICS** | 30 413 | 75 | 30 | 21 | 77 | 1568 | 237 | 85 | 57 | 213 |
| **LABA** | 1 426 | 89 | 30 | 24 | 91 | 73 | 261 | 68 | 52 | 230 |
| **LABA + ICS** | 5 414 | 126 | 33 | 26 | 112 | 415 | 292 | 68 | 49 | 233 |
| **Theophyllines + ICS** | 10 283 | 118 | 46 | 33 | 114 | 974 | 305 | 106 | 75 | 268 |

*Rate per 100 patient-years. †An exacerbation was defined either as a prescription of oral corticosteroids filled, a visit to an ED for COPD or hospitalization for COPD. Only one single exacerbation was considered if more than one marker of exacerbation (prescription of oral corticosteroids, ED visits for COPD or hospitalizations for COPD) occurred within a period of 15 days. COPD, Chronic obstructive pulmonary disease; ED, emergency department; ICS, inhaled corticosteroids; LABA, long-acting $\beta_2$ -agonists; OCS, oral corticosteroids.

when theophyllines were prescribed in monotherapy, but was when theophyllines were added to ICS (adjusted RR 0.87, 95% CI 0.80, 0.94, 201–300 mg *vs.* ≤200 mg; adjusted RR 0.78, 95% CI 0.74, 0.83, >300 mg *vs.* ≤200 mg). On the other hand, the dose of ICS (≤1000 *vs.* >1000 μg per day in beclomethasone equivalent) was not found to be significantly associated with the risk of exacerbations when ICS were given in monotherapy (adjusted RR 0.99, 95% CI 0.96, 1.0) but was when ICS were given in addition to theophyllines (adjusted RR 1.04, 95% CI 1.01, 1.07).

## Discussion

In the entire cohort, COPD patients treated with theophyllines (either alone or in addition to ICS) were found to be less likely to have moderate to severe COPD exacerbations than patients treated with LABA (either alone or in addition to ICS). However, users of theophyllines, particularly those with frequent past COPD exacerbations, were found to be more at risk of exacerbations than users of ICS.

A review of 20 RCTs concluded that oral theophyllines improve lung function because they increase central respiratory drive, respiratory muscle performance, arterial blood gas tensions and ventilatory capacity [29]. This systematic review also reported that patients preferred theophyllines to placebo and concluded that theophyllines remain an important option in the management of COPD, but their benefits have to be weighed against their risk of adverse effects [29]. Although many RCTs have shown that theophyllines are relatively weak bronchodilators, an advantage of theophyllines is that their systemic administration may have effects on small airways, may reflect in a reduction of the hyperinflation, a reduction in dyspnoea and an improvement in exercise performance [30]. Theophyllines can also improve mucociliary clearance, and this beneficial action may complement their effects on bronchoconstriction and respiratory muscle dysfunction in patients with chronic bronchitis [12, 13]. Theophyllines are also nonselective phosphodiesterase (PDE) inhibitors. This effect may account in part for their efficacy [31]. Moreover, theophyllines may increase responsiveness to ICS, avoid steroid resistance and allow ICS to suppress chronic inflammation in COPD patients [32]. This might explain why theophyllines added to ICS were more effective then LABA added to ICS in reducing the rate of exacerbations. However, RCTs have shown that patients treated with LABA [33, 34] or LABA plus ICS [35] have a significant greater improvement in lung function [forced expiratory volume in 1 s ($FEV_1$), forced vital capacity and morning peak expiratory flow], a higher percentage of symptom-free (cough, wheezing and shortness of breath) days and use less rescue medications (salbutamol or albuterol) than patients treated with theophyllines [33, 34, 36] or theophyllines plus ICS [35].

## Table 5

Crude and adjusted rate ratios of moderate to severe COPD exacerbations comparing theophyllines, ICS and LABA

| | All patients | | | Patients with ≥3 exacerbations in the year prior to cohort entry | | |
|---|---|---|---|---|---|---|
| | Crude RR | Adjusted* RR | 95% CI | Crude RR | Adjusted* RR | 95% CI |
| **Theophyllines/ICS** | 1.09 | 1.07 | 1.04, 1.10 | 1.28 | 1.28 | 1.19, 1.38 |
| **Theophyllines/LABA** | 0.92 | 0.89 | 0.84, 0.95 | 1.19 | 1.07 | 0.90, 1.26 |
| **Theophyllines + ICS/LABA + ICS** | 1.02 | 0.89 | 0.87, 0.92 | 1.15 | 1.02 | 0.95, 1.10 |
| **Female *vs.* male** | 0.88 | 0.94 | 0.93, 0.96 | 0.93 | 0.96 | 0.92, 1.00 |
| **Age (5 years' difference)** | 1.01 | 1.02 | 1.02, 1.03 | 0.97 | 0.99 | 0.98, 1.00 |
| **Socio-economic status (poor/others)** | 0.97 | 0.99 | 0.98, 1.01 | 0.99 | 1.01 | 0.97, 1.05 |
| **COC index (0.1 difference)** | 0.98 | 1.00 | 0.99, 1.00 | 0.99 | 0.99 | 0.99, 1.00 |
| **Comorbidity score (1 difference)** | 1.05 | 1.00 | 1.00, 1.00 | 0.99 | 1.00 | 0.99, 1.00 |
| **Year of cohort entry (1997 as the reference)** | | | | | | |
| **1996** | 1.08 | 1.00 | 0.98, 1.02 | 1.04 | 1.00 | 0.95, 1.06 |
| **1998** | 1.05 | 0.96 | 0.94, 0.98 | 1.02 | 1.01 | 0.95, 1.07 |
| **1999** | 0.94 | 0.85 | 0.83, 0.88 | 0.87 | 0.89 | 0.84, 0.95 |
| **2000** | 0.93 | 0.80 | 0.77, 0.82 | 0.91 | 0.91 | 0.85, 0.97 |
| ***Markers of disease severity in the year prior to cohort entry*** | | | | | | |
| **Prescriptions of oral corticosteroids (0 reference):** | | | | | | |
| **1** | 1.76 | 1.39 | 1.36, 1.42 | | | |
| **2** | 2.44 | 1.66 | 1.61, 1.71 | | | |
| **≥3** | 4.09 | 2.37 | 2.32, 2.44 | †1.38 | †1.32 | 1.26, 1.39 |
| **Emergency department visits COPD, y/n** | 1.99 | 1.24 | 1.22, 1.26 | 0.96 | 0.97 | 0.93, 1.01 |
| **Hospitalizations for COPD, y/n** | 2.08 | 1.12 | 1.10, 1.15 | 1.13 | 1.13 | 1.09, 1.18 |
| ***Markers of disease severity in the 3 months prior to an episode of treatment*** | | | | | | |
| **Visit to a respiratory physician, y/n** | 1.72 | 1.22 | 1.20, 1.25 | 1.23 | 1.09 | 1.04, 1.14 |
| **Number of filled prescriptions of antibiotics for COPD (0 reference):** | | | | | | |
| **1** | 1.81 | 1.51 | 1.49, 1.54 | 1.29 | 1.23 | 1.18, 1.29 |
| **2** | 2.51 | 1.78 | 1.74, 1.83 | 1.50 | 1.40 | 1.33, 1.48 |
| **≥3** | 3.25 | 2.01 | 1.95, 2.07 | 1.79 | 1.60 | 1.51, 1.70 |
| **Doses of SABA per day (<2 reference):** | | | | | | |
| **2–3** | 1.33 | 1.13 | 1.10, 1.17 | 1.27 | 1.26 | 1.17, 1.36 |
| **>3** | 2.02 | 1.32 | 1.29, 1.35 | 1.45 | 1.30 | 1.22, 1.38 |
| **Doses of ipratropium bromide per day (<2 reference):** | | | | | | |
| **2–3** | 1.48 | 1.24 | 1.21, 1.27 | 1.07 | 0.96 | 0.90, 1.03 |
| **>3** | 2.12 | 1.34 | 1.31, 1.36 | 1.23 | 1.00 | 0.95, 1.05 |

*Adjusted for all variables in the table. †The reference was less than three exacerbations in the year prior to cohort entry. COPD, Chronic obstructive pulmonary disease; COC, continuity of care; ICS, inhaled corticosteroids; LABA, long-acting $\beta_2$ -agonists; SABA, short-acting $\beta_2$ -agonists; RR, rate ratio; CI, confidence interval.

Our study is the first to investigate the association between theophyllines and moderate to severe COPD exacerbations as the primary outcome. To our knowledge, only one RCT has evaluated and compared the frequency of moderate to severe COPD exacerbations as a secondary efficacy outcome between formoterol and oral, slow-release theophylline [33]. In this RCT, the mean percentage of patients receiving additional therapy for COPD exacerbations (corticosteroids, antibiotics or oxygen) during follow-up was lower among patients receiving theophyllines (20%) than among those receiving 12 µg of inhaled formoterol (32%) or 24 µg of inhaled formoterol (23%). The number of COPD-related hospitalizations was also lower among the theophylline group ($n = 6$) than in the 12 µg inhaled formoterol group ($n = 10$), but was similar to the number found in the 24 µg inhaled formoterol group ($n = 5$). In our study, we found a 11% reduction in the risk of moderate to severe exacerbations comparing users of theophyllines with users of LABA.

Our results on the effectiveness of ICS in reducing moderate to severe exacerbations, particularly among patients with frequent past exacerbations, confirm the results of previous RCTs [10, 11]. In the ISOLDE trial, Burge *et al.* found a significant reduction of 25% in the rate of exacerbations comparing users of fluticasone propionate (ICS) with placebo ($P = 0.026$) among patients with moderate to severe COPD. In our study, we found a 22% reduction in the risk of moderate to severeexacerbations comparing users of ICS with users of theophyllines among patients with frequent past exacerbations. Our data support the recommendations of the GOLD treatment guidelines indicating that ICS should be considered in patients with moderate to severe COPD who experience frequent exacerbations [5].

This study has several strengths, namely a large sample size, a cohort representative of the population of COPD patients, a long follow-up of up to 7 years and details about pharmacological treatments taken during all these years. It also avoids recall bias by the use of administrative database. On the other hand, the study has some limitations inherent in the use of administrative databases. First, the diagnosis of COPD was not confirmed with spirometric measures ($FEV_1$). Consequently, we assumed that patients had COPD at cohort entry if they received at least one medical service for COPD and filled at least six bronchodilator prescriptions in the year preceding cohort entry. However, given that bronchodilator treatments are also commonly used for asthma, all patients who received a medical service for asthma in the year preceding cohort entry were excluded. A previous validation study has shown that the RAMQ databases were accurate in distinguishing COPD from asthma [25]. Second, the diagnosis for hospitalizations and emergency visits were based on the diagnoses recorded in the RAMQ and MED-ECHO databases, and were not validated with the medical chart. Third, the exposure to treatment was based on dispensed prescriptions, which might not correspond exactly to the intake of the medications. Fourth, we censored patients with a hospital stay of >30 days because in the RAMQ database there is no information on prescriptions dispensed in hospital and it is thus not possible to measure drug use. We also censored patients who initiated a continuous therapy with oral steroids, because it would have been difficult to evaluate our primary outcome, COPD exacerbations, which is defined, at least in part, on the use of oral corticosteroids. However, a hospital stay of >30 days or the beginning of continuous oral steroids therapy might reflect the development of more severe disease. To investigate whether censoring of patients had an impact on the study results, a sensitivity analysis was conducted in which censoring was not applied. The uncensored analysis gave similar results to the censored analysis presented in this study, revealing the robustness of the results (data available on request). Finally, we cannot rule out completely the presence of confounding due to unmeasured variables such as cigarette smoking and clinical measures of disease severity. However, in order to minimize residual confounding patients were compared who had equal numbers of adjuvant therapies. Patients with theophyllines only were compared with ICS or LABA only and patients using theophyllines plus ICS were compared with patients using LABA plus ICS. Moreover, we adjusted in the analysis for the use of SABA and ipratropium bromide in the 3 months prior to each treatment episode.

Lastly, theophylline is associated with adverse gastrointestinal effects as well as serious cardiovascular (tachycardia and arrhythmias) and central nervous system side-effects attributed to nonselective inhibition of PDE, even at therapeutic doses [31]. In this study, we observed that 86% of theophylline users renewed their prescription at least once during follow-up. Moreover, theophylline users filled 11 prescriptions per year, on average, suggesting that they tolerated their medication well and that our cohort might be over-represented by patients who tolerate theophyllines well. Moreover, the average daily dose of theophyllines used by study patients did not exceed the maximun recommanded daily dose of 800 mg [5].

Theophyllines, as the only adjuvant therapy or in addition to ICS, were found to be more effective than LABA in avoiding moderate to severe exacerbations. However, among patients with frequent past exacerbations, ICS were found to be more effective than theophyllines in avoiding moderate to severe exacerbations, and no significant difference was observed between theophyllines and LABA. Theophyllines are much less expensive medications than ICS and LABA, and oral formulations have been shown to increase patient adherence compared with inhaled formulations in asthma [37]. In conclusion, theophyllines could be seen as an effective therapy in selected COPD patients who tolerate this medication well. Further study, based on outcomes that can measure overall morbidity, will be required to evaluate whether the benefits observed in this study outweigh the potential risk of adverse reactions of theophyllines.

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