Analysis of Inhaled Corticosteroid and Oral Theophylline Use Among Patients With Stable COPD from 1987 to 1995*

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Study objective: To document temporal usage trends for commonly used respiratory medications in patients with COPD.

Design: We retrospectively evaluated baseline concomitant medications of 3,720 patients with COPD enrolled in 10 bronchodilator clinical trials from 1987 to 1995. The proportion of patients in each trial using inhaled corticosteroids, inhaled β-adrenergics, inhaled anticholinergics, oral theophylline, and oral corticosteroids was analyzed using the Cochran-Armitage trend test.

Patients: All patients had stable, moderate-to-severe COPD without evidence of asthma or atopy. Reversibility to β-agonists was not a requirement.

Results: The percentage of patients using inhaled corticosteroids increased significantly over time \( (p < 0.001) \) from 13.2% in 1987 to 41.4% in 1995. The percentage of patients receiving oral theophylline decreased significantly \( (p < 0.001) \) over this same time interval (63.4 to 29.0%). In addition, the percentage of patients using oral corticosteroids and the percentage using oral β-adrenergics decreased moderately \( (p < 0.05) \) (30.1 to 16.4% and 11.7 to 4.5%, respectively); the percentage of patients using inhaled anticholinergics increased slowly \( (p < 0.05) \) (48.2 to 53.8%). The percentage of patients receiving inhaled β-adrenergics did not significantly \( (p > 0.05) \) change.

Conclusions: The observed changes in use of inhaled corticosteroids and theophylline were not likely related to differences in disease severity or other patient characteristics in the evaluated trials, but related to changing prescribing and COPD management practices.

Key words: β-adrenergic receptor agonists; cholinergic antagonists; corticosteroids; COPD; drug therapy; theophylline

Abbreviation: CCS = corticosteroids

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Theophylline preparations have been used widely as bronchodilators for patients with COPD for more than 30 years. \(^1\) Treatment of patients with COPD with theophylline has been critically analyzed; the consensus is that it has, in selected cases, a beneficial effect on respiratory function, especially when combined with inhaled β-agonists. \(^2,3\) In addition, daily sustained-release preparations may have a positive effect on treatment compliance. Although inhaled corticosteroids (CCS) have enjoyed widespread acceptance for asthma management, their role in the management of COPD remains undetermined. \(^4,5\) Previous reports \(^6,7\) concluded that inhaled CCS provide little benefit for the management of COPD. Anecdotal evidence, however, suggests that inhaled CCS use is prevalent in the management of both stable and acute COPD \(^8,9\) and that theophylline use is on the decline in patients with COPD.

Trends in commonly prescribed respiratory medication have not been described recently in patients with COPD. Kesten et al \(^10\) evaluated prescription sales in Canada from 1985 to 1990 and found that the number of prescriptions for all airway medications increased over the evaluated time period and that inhaled steroids and ipratropium bromide contributed most to this increase, whereas theophylline prescriptions declined. This analysis did not, however, selectively evaluate respiratory medication use in patients with COPD. In addition to prescription sales, the authors conducted a survey of physician diagnoses and accompanying prescriptions in 1985 and 1990. The proportion of patients with COPD...
receiving prescriptions for inhaled β-agonists, CCS, and ipratropium bromide increased (5.6 to 11%, 0.9 to 4.8%, and 0.6 to 3.7%, respectively) over this time interval, and the proportion of patients with COPD receiving prescriptions for theophylline remained constant (7.2 to 8.7%). Other studies have evaluated drug sales data without specifically addressing patients with COPD.11,12 Recently, Jackevicius et al13 described the prevalence of inhaled CCS and other respiratory medication use before and during hospitalization at the tertiary care, inner city Toronto Hospital. For 1994, 26% of patients with stable COPD were receiving inhaled CCS and 10% were receiving oral theophylline. Considering the lack of data on trends for the use of respiratory medications in patients with COPD, the controversial role of CCS, and the declining popularity of oral theophylline, we elected to evaluate the usage trends of these and other commonly used respiratory medications using data collected from US clinical trials of therapeutic agents in patients with COPD.

**Materials and Methods**

We retrospectively evaluated the baseline concomitant medications of 3,720 patients with COPD enrolled in 10 bronchodilator clinical trials from 1987 to 1995. Clinical trials were selected on the basis of the sample size (>150 patients with COPD per trial) and comparability of entrance criteria (Table 1). The number of research sites per trial ranged from 8 to 34 (Table 2) with >115 different sites involved in the 10 trials. Research sites were placed throughout the US with sites located in at least 35 of the 50 states. All clinical trials were conducted according to Good Clinical Practice (the clinical practice guidelines of the International Conference on Harmonization). An institutional review board for human studies approved all protocols, and all patients provided informed written consent prior to participation.

Patient inclusion and exclusion criteria are listed in Table 1. All patients were required by protocol to have a diagnosis of COPD according to the following criteria: a relatively stable, moderate-to-severe airway obstruction with an FEV1 according to the following criteria: a relatively stable, moderate-to-severe airway obstruction with an FEV1 according to the following criteria: a relatively stable, moderate-to-severe airway obstruction with an FEV1 according to the following criteria: a relatively stable, moderate-to-severe airway obstruction with an FEV1 according to the following criteria: a relatively stable, moderate-to-severe airway obstruction with an FEV1 according to the following criteria: a relatively stable, moderate-to-severe airway obstruction with an FEV1 according to the following criteria: a relatively stable, moderate-to-severe airway obstruction with an FEV1 according to the following criteria: a relatively stable, moderate-to-severe airway obstruction with an FEV1 according to the following criteria: a relatively stable, 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The percentage of patients receiving oral theophylline decreased significantly ($p < 0.001$) over this same time interval from 63.4 to 29.0%, representing a 54.3% decline (Fig 1). The percentage of patients using oral CCS and the percentage using oral $\beta$-adrenergics decreased moderately ($p < 0.05$) during this time interval from 30.1 to 16.4% and from 11.7 to 4.5%, respectively (Fig 2). The percentage of patients using inhaled anticholinergics increased slowly ($p < 0.05$) from 48.2% in 1989 to 53.8% in 1995 (Fig 2). The percentage of patients receiving inhaled $\beta$-adrenergics did not significantly ($p > 0.05$) increase or decrease over time (Fig 2). When the analysis controlled for patient baseline disease severity and duration of disease (Table 2), the trend for inhaled CCS and theophylline use was maintained; however, the significance in the trend was greatly reduced for the use of inhaled anticholinergics, oral CCS, and oral $\beta$-adrenergics.

**DISCUSSION**

This retrospective analysis documented that inhaled CCS use by patients with COPD increased from 1987, whereas the use of theophylline in the same population declined. These observed changes in medication use were likely not related to differences in disease severity or other characteristics of patients in the evaluated trials, but related to chang-

![Figure 1. Percentage of patients using inhaled CCS and oral theophylline: November 1987 to March 1995. Closed circles, oral theophylline; open circles, inhaled CCS. The range of standard error for the percentages was 1.6 to 3.8%.](http://journal.publications.chestnet.org/pdfaccess.ashx?url=/data/journals/chest/21909/ on 06/21/2017)
ing prescribing and COPD management practices. Individual trial characteristics, such as differences in inclusion and exclusion criteria, test substance, and duration of the trial, were not specifically controlled for in the analysis, but based on the uniformity of all measured patient characteristics, they likely had minimal influence on the trial population and subsequent medication use.

Current treatment standards for patients with COPD note the clear utility of bronchodilators, including selective roles for theophylline, and that insufficient documentation exists supporting the use of inhaled CCS. Nonetheless, we found that > 40% of the evaluated patients with COPD used inhaled CCS in 1995, which was in far excess of the proportion of patients with COPD in Canada in 1990 who were prescribed inhaled CCS and considerably greater than that found in 1994 in stable hospitalized patients with COPD in Toronto.

While ongoing trials are addressing the effect of inhaled CCS on the natural history of COPD, the implications of their increased use and the declining use of theophylline need to be critically addressed. We hypothesize that the observed usage trends for these medications are potentially related to their use in the treatment of asthma, particularly the increased and successful use of inhaled CCS. One survey of primary care practitioners in Canada concluded that, while physicians displayed discrimination in the diagnosis asthma and COPD, treatment regimens for the two disorders were often similar. A recent analysis of 6-month pharmacy claims for 5,173 asthmatic patients in 1996 in the US observed that, on average, 41.3% of the patients received inhaled CCS and 17.0% received theophylline. While significant differences exist between the two evaluated populations, the proportion of asthmatic patients receiving inhaled CCS in 1996 is strikingly similar to that found in this analysis of patients with COPD in 1995 (41.4%). The large proportion of patients with COPD using inhaled CCS is an indication of their wide acceptance in this population. Possibly, physicians perceive a benefit of inhaled CCS use in COPD that has not been definitively detected in clinical trials or the use of inhaled CCS represents a hopeful attempt to affect the diminishing lung function of COPD, which as of yet has not been alterable.

While theophylline once was the principal bronchodilator for COPD, recent advances in β₂-agonists and the introduction of anticholinergics have displaced this medication as a third option for the treatment of COPD. Current guidelines recognize the bronchodilatory effect of theophylline and recommend their administration in less compliant or capable patients. In spite of the selective therapeutic advantages to treatment with theophylline, the use of this medication has declined to much below that of inhaled CCS, which have not been proven efficacious in COPD.

Inhaled β-adrenergics and anticholinergics were the most prevalently used medications in patients with COPD in this survey, and oral CCS and β-
adrenergics were the least frequently used. Inhaled β-adrenergics and anticholinergics have been well accepted as the principal therapeutic agents in COPD, and the relatively stable, high rate of use was not unexpected. The oral forms of CCS and β-adrenergics have been associated with significant side effects and the inhaled route is often preferred. While minor trends in the proportion of patients using oral CCS, oral β-adrenergics, and inhaled β-adrenergics were observed, patient factors such as baseline disease severity and duration of disease may have influenced trends. The observation of a relatively high proportion of patients receiving oral CCS (30.1 to 30.6%) in the early portion of the observed period (1987 and 1988) cannot be accounted for by trial-specific inclusion or exclusion criteria and the relevance of this observation is not clear.

The limitations to the analysis included the inability to evaluate dosage and frequency of use. Inhaled CCS were not divided into high or regular dose, nor was theophylline separated into long- and short-acting preparations. In addition, no trials were available for analysis from October 1990 to May 1993. Not all pulmonary medications were recorded for all trials, therefore, only those that were consistently recorded were analyzed. However, these medications do represent the most commonly used medications in COPD. While the investigators of the clinical trials were all primarily in specialty practice, the participating patients were drawn from both the involved practice and the community and likely were representative of patients with stable, moderate-to-severe COPD.

This study clearly demonstrated that medication usage by patients with COPD did not reflect current treatment standards. Most notably, inhaled CCS were used by a significant proportion of the analyzed population in spite of the lack of evidence supporting their use in the management of stable COPD. While inhaled CCS have been associated with few serious side effects, they represent a significant expense and multiple therapies can lead to decreased treatment compliance. Physicians caring for patients with COPD need to critically evaluate each patient’s therapeutic regimen and determine the true benefit of each medication prescribed.

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