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Trends in asthma and chronic obstructive pulmonary disease therapy in Canada, 1985 to 1990

**Steven Kesten, MD, Anthony S. Rebuck, MD, and
Kenneth R. Chapman, MD** *Toronto, Ontario, Canada*

Background: *In the mid and late 1980s, numerous changes were recommended in the management of obstructive lung diseases. We analyzed drug sales to determine whether these recommendations have resulted in recent changes in prescription drugs used in airway management.*

Methods: *Data on prescription sales in Canada from 1985 to 1990 were obtained from an international pharmaceutical market research organization. Data from a random sampling of physicians that reported patients seen along with the diagnosis and prescriptions given were also reviewed.*

Results: *From 1985 to 1990, there was a 38% increase in prescriptions of all airway drugs. Prescriptions increased significantly for inhaled drugs as follows: inhaled β_2 -agonists, 70%; inhaled steroids, 139%; cromoglycate, 88%; and ipratropium bromide, 204%. Theophylline prescriptions, by contrast, fell significantly, by 19%. Although theophylline was the most commonly prescribed airway medication in 1985, inhaled β_2 -agonists were the most commonly prescribed drug in 1990, and these changes in proportional use were significant. Increases in ipratropium bromide usage was accounted for by increases in prescriptions for chronic obstructive pulmonary disease. Increases in nonsteroidal antiinflammatory drugs were accounted for by asthma prescriptions.*

Conclusions: *The increase in airway medication prescriptions dispensed in Canada is consistent with an increase in the number of patients treated, an increase in the severity of disease treated, or both. (J ALLERGY CLIN IMMUNOL 1993;92:499-506.)*

Key words: *Asthma, chronic obstructive pulmonary disease, β_2 -agonist, theophylline, inhaled steroid, ipratropium bromide, cromoglycate*

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Reprint requests: Steven Kesten, MD, FRCPC, Asthma Centre of the Toronto Hospital, 399 Bathurst St., Edith Cavell Wing 4-009, Toronto, Ontario M5T 2S8, Canada.

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Reported increases in asthma mortality have prompted a reevaluation of our diagnostic and therapeutic approaches to asthma management. More than one review or consensus paper has emphasized the importance of suppressing airway inflammation with inhaled antiinflammatory drugs while stressing the need to reduce our reliance on

Abbreviation used

COPD: Chronic obstructive pulmonary disease

bronchodilator-based regimens.^{1, 2} Concurrently, there have been relatively few dramatic changes in expert recommendations for the treatment of chronic obstructive pulmonary disease (COPD). However, mortality from COPD appears to be increasing gradually and there is increasing emphasis on inhaled rather than oral bronchodilator treatment.³⁻⁵ We have, as yet, little objective evidence that such warnings have been heeded. Trends in the prescription of airway medications have been reported in Australia, New Zealand, the United Kingdom, and the United States, but only up to the mid-1980s.⁶⁻⁸ There is little information on physician responses for the past 5 years.

We undertook a review of physician prescribing habits to test the hypothesis that increased awareness of obstructive lung disease and the recognition of the role of preventive antiinflammatory care for asthma would be reflected by changes in the types of airway medications prescribed. In addition, we tested the hypothesis that if reported increases in asthma prevalence and severity were true, there would be an associated increase in prescriptions of airway medications. Finally, we examined prescription data to determine whether there were trends to reflect reported seasonal variations in asthma severity and hospital admission rates. To review physician prescribing habits, we ascertained and analyzed data on prescription airway drugs in Canada from 1985 to 1990.

METHODS

Data on prescription sales of airway drugs in Canada from 1985 to 1990 were obtained from an international pharmaceutical market research organization (IMS Compuscript; Dorval, Quebec, Canada). The data represent an audit of prescriptions recorded in pharmacy computers from a randomly selected sample of Canadian retail pharmacies. Available data are organized by drug class and by specific drug with regional and monthly breakdown. Neither the number of patients receiving these prescriptions nor their diagnoses are known.

To determine more specifically for which indications these airway medications had been prescribed, a second data collection was reviewed and analyzed. These data were collected from a random sampling of physicians who were asked to list all patients seen approximately 1 day each month and to note drugs prescribed and diagnosis for each patient. All reported prescriptions

for an airway medication were reviewed and the associated diagnosis noted.

The following categories of drugs are included in the analysis for this report: oral β_2 -agonists, inhaled β_2 -agonists, cromoglycate, inhaled steroids, ipratropium bromide, and theophylline products. In a separate analysis, inhaled steroids are divided into high-dose preparations (beclomethasone dipropionate 250 μ g per metered dose and budesonide 200 μ g per metered dose) in recognition of the fact that high-dose inhaled steroid preparations received Notice of Compliance from the Health Protection Branch of the Bureau of Human Prescription Drugs in 1988.

Population data were obtained from published demographics from the government of Canada. An estimate of change in prescriptions dispensed per capita per year was obtained by dividing the sample in each region by the population.

Data analysis

Least-squares linear regression was used to assess the significance of changes over time in the absolute numbers of prescriptions. Repeated-measures analysis of variance was used to assess changes in the prevalence of each diagnostic category over time. Proportions were compared by χ^2 analysis. Differences were considered significant at the $p < 0.05$ level.

RESULTS

From 1985 to 1990, there was a 38% increase in the prescriptions of pharmaceutical products with a labeled indication for asthma or COPD ($p < 0.001$), whereas the population increase of Canada during the same time period was estimated to be 5.7%. This increase was not seen in all drug categories. By category, the percent change was as follows: inhaled β_2 -agonists, 70% ($p < 0.001$); inhaled steroids, 139% ($p < 0.01$); cromoglycate, 88% ($p < 0.01$); ipratropium bromide, 204% ($p < 0.001$); theophylline preparations, -19% ($p < 0.05$); and oral β_2 -agonists, 4% ($p > 0.05$).

Theophylline and β_2 -agonists were the most commonly prescribed airway medications during the study period (Fig. 1). In 1985, the most commonly prescribed airway medication was theophylline (40.1% of prescriptions), followed closely by inhaled β_2 -agonists (38.3% of dispensed prescriptions). However, by 1990 there had been a significant shift in which β_2 -agonist prescriptions increased to 46.9% of prescriptions, whereas theophylline declined to 23.3%; this change in proportions is statistically significant ($p < 0.05$). Inhaled steroid prescriptions increased significantly from 8.5% to 14.8% of dispensed prescriptions. Prescriptions of high-dose inhaled steroid

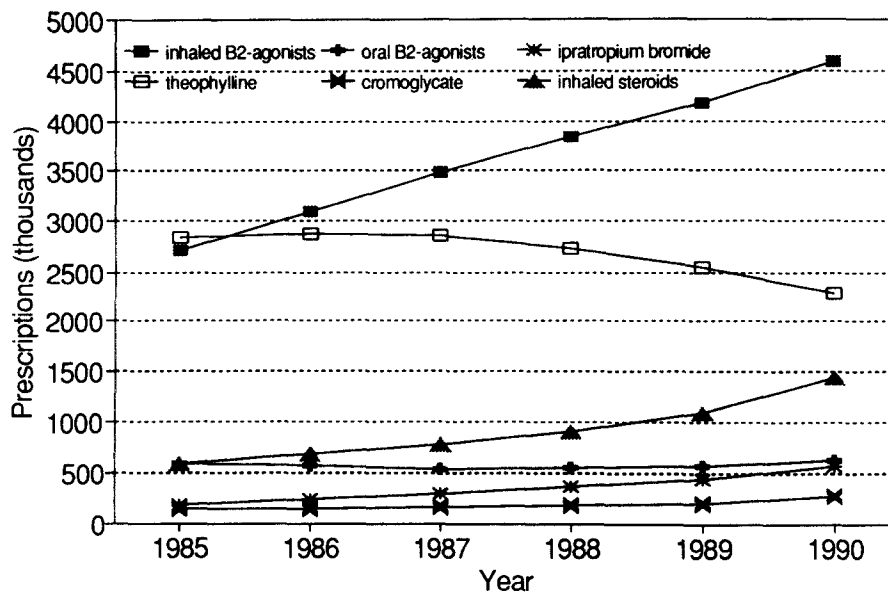


FIG. 1. Absolute number of airway medication prescriptions dispensed from 1985 to 1990 according to class of drug.

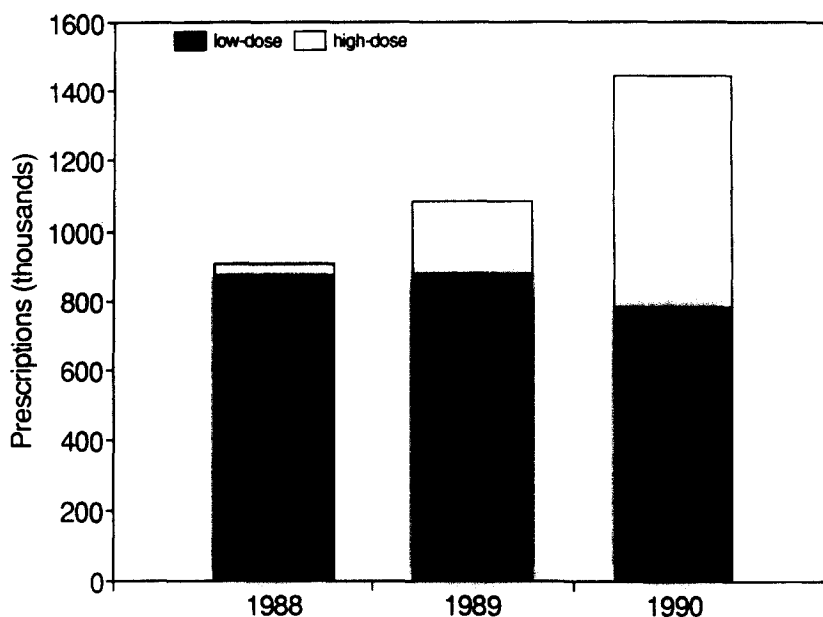


FIG. 2. Absolute number of inhaled steroid prescriptions dispensed from 1988 to 1990. Bars are divided into low- and high-dose preparations.

preparations, introduced in Canada in mid-1988, rose significantly from 19% of inhaled steroid prescriptions in 1989 to 32% in 1990 ($p < 0.001$, Fig. 2).

Examined regionally (the maritime provinces, Quebec, Ontario, the prairie provinces, and British Columbia), estimated increases in total prescriptions dispensed per capita from 1985 to 1990

occurred in each region (Fig. 3). The percent increase in prescriptions dispensed per capita per region was as follows: maritime provinces, 254%; Quebec, 26%; Ontario, 33%; prairie provinces, 32%; and British Columbia, 15%. A seasonal variation in total airway prescriptions dispensed was noted (Fig. 4). The number of prescriptions dispensed rose from August to a peak in Decem-

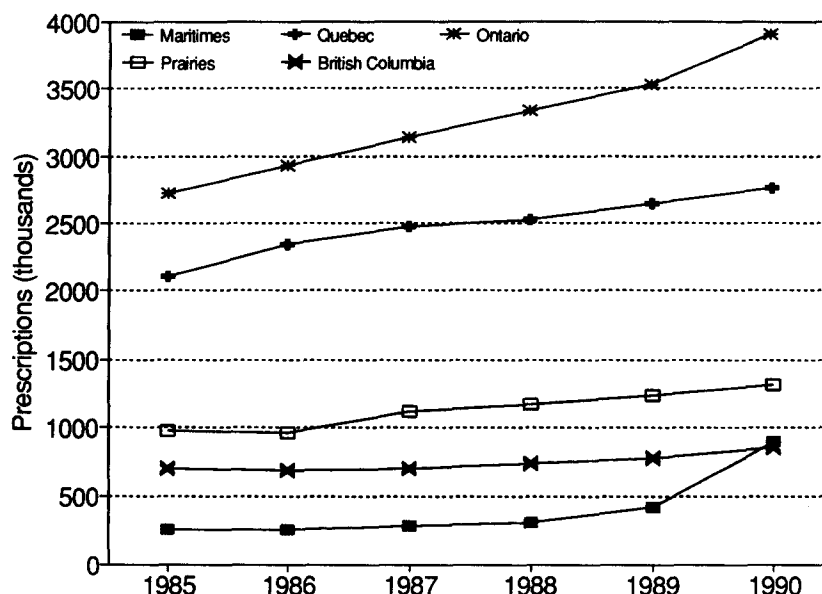


FIG. 3. Absolute number of airway medication prescriptions dispensed from 1985 to 1990 according to geographic region.

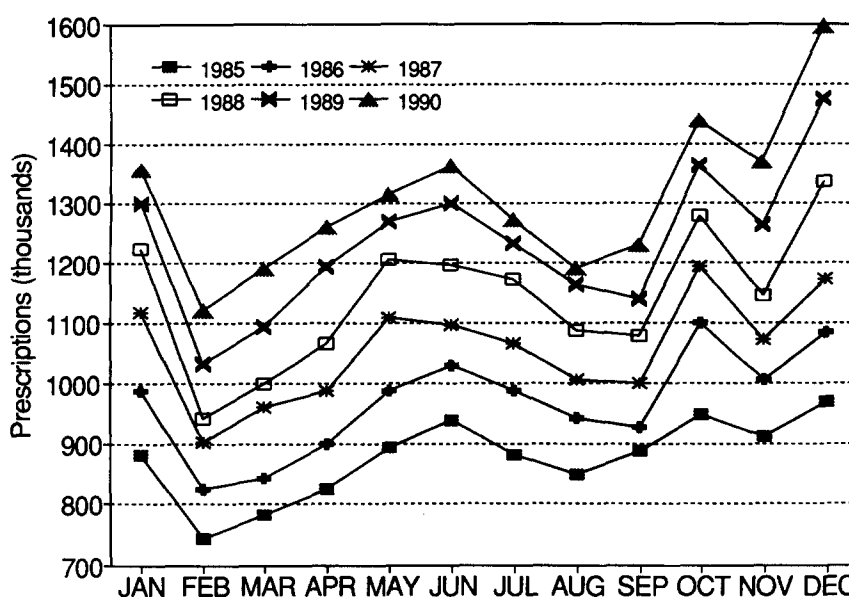


FIG. 4. Monthly variation in absolute number of airway medication prescriptions dispensed from 1985 to 1990.

ber, declined to a low in February, and then rose again to a smaller secondary peak in June. The pattern of monthly variations in prescription sales was remarkably similar for all classes of drugs.

In 1985, prescription and diagnostic information was collected on 5779 patients; in 1990, data were collected on 8053 patients. Data for oral β_2 -agonist use were not available. Table I shows the proportion of patients that received prescriptions from each of the major drug categories.

Examination of the diagnosis-specific data showed that the most common diagnosis that prompted the prescription of an airway drug was asthma, which accounted for 40.5% of all diagnoses associated with airway drugs in 1985 and 53.5% in 1990. Prescriptions for COPD were approximately one third as common as those for asthma and accounted for 14.3% in 1985 and 28.8% in 1990. The proportion of nonspecific respiratory diagnoses tended to decrease, being 45.5% in 1985

TABLE I. Proportion (%) of patients receiving prescriptions from each of the major airway drug categories

Year	Diagnosis	Inhaled β_2 -agonist	Inhaled steroid	Nonsteroidal antiinflammatory drug	Ipratropium bromide	Theophylline
1985	All	42.6	6.6	1	2.9	47.2
	Asthma	20	4.8	0.8	1.3	14
	COPD	5.6	0.9	0	0.6	7.2
	Other	17	1.3	0.2	1.0	26
1990	All	49	17.6	2.7	6.8	23.5
	Asthma	28	11	2.5	2.3	10
	COPD	11	4.8	0.1	3.7	8.7
	Other	10	1.8	0.1	0.8	4.8

and 17.5% in 1990. None of these proportions was significantly different over time when all years from 1985 to 1990 were compared.

Comparing 1985 to 1990, there was little change in the percentage of patients receiving inhaled β_2 -agonist: the proportions were 42% in 1985 and 49% in 1990. By contrast, there was a significant rise in the proportion of patients receiving inhaled steroids (6.6% versus 17.6%, $p < 0.05$) and a significant decrease in the proportion of patients receiving theophylline (47% versus 23.5%, $p < 0.05$). Although both nonsteroidal antiinflammatory drugs and ipratropium bromide were prescribed for significantly higher proportions of patients in 1990, the final percentage of patients receiving these agents remained small. When examined by diagnostic category, the increase in inhaled steroid use was evident in both asthma and COPD patient groups. By contrast, the increase in nonsteroidal antiinflammatory prescriptions was primarily in the asthma group, and the increase in ipratropium bromide usage was primarily in the COPD group.

DISCUSSION

Our data show that there has been a significant increase during the study interval in the number of asthma and COPD prescriptions dispensed in Canada. There has been a significant decline in theophylline prescriptions but a continued rise in inhaled β_2 -agonist dispensing such that in 1990 the latter were by far the most commonly prescribed airway drugs. Although inhaled steroids account for a smaller proportion of airway prescriptions, their proportional role among prescriptions has increased more rapidly than that of the inhaled β_2 -agonists.

Several reports have questioned the use of theophylline, in that it may contribute to asthma

morbidity.⁹⁻¹¹ Although theophylline was previously a mainstay of asthma therapy, it is now recognized as only a modest bronchodilator with a relatively high incidence of patient intolerance. It is not surprising then to see the significant decline in theophylline use. On the other hand, the appreciation of the role of inflammation in asthma has led to recommendations for the use of antiinflammatory therapy as first-line medication for the person who has daily symptoms of asthma.^{1, 2} Although an increase in inhaled steroid prescription sales is therefore expected, we note that antiinflammatory therapy (inhaled steroids and cromoglycate) accounted for only 17.5% of airway medications prescribed in 1990, still 25% less than theophylline. Despite their recent introduction to Canada, there has been a dramatic rise in high-dose inhaled steroid preparation prescriptions. These agents now account for 32% of the inhaled steroid prescription market and will likely soon be used preferentially over low-dose preparations if this trend continues.

The increasing use of high-dose steroid formulations would suggest that our presentation of data as number of prescriptions underrepresents the actual increase in inhaled steroid use. When compared with conventional low-dose formulations of inhaled steroids, high-dose formulations deliver approximately five times the dosage per puff yet contain the same number of puffs per canister. It would be possible to substitute up to 10 puffs per day of a low-dose formulation with one puff twice daily of a high-dose preparation. The latter prescription would be filled one fifth as often.

The drug prescription data do not distinguish between asthma and other indications for the use of "asthma" drugs such as COPD, so disease-specific conclusions cannot be drawn with cer-

tainty from these data alone. However, the survey of physician diagnoses and the accompanying prescriptions suggest that physician-diagnosed asthma accounts for the majority of airway prescriptions. Nevertheless, the small absolute but large percentage increase in overall ipratropium bromide usage is accounted for primarily by COPD prescriptions, compatible with current COPD management recommendations.^{9, 12} The increase in nonsteroidal antiinflammatory drug usage was primarily a consequence of increased asthma prescriptions. The other major trends between 1985 and 1990, including increased inhaled steroid usage, increased β_2 -agonist usage, and decreased theophylline usage, are not clearly ascribed to a single diagnostic group. This is compatible with our recently published survey of physician attitudes toward asthma and COPD management.¹³ We reported that although physicians distinguished on theoretic grounds between asthma and COPD, their prescribing habits were similar between diagnostic groups except for a small but significant tendency to use anticholinergic bronchodilators more often in COPD than in asthma.¹³ If perceptions of asthma and COPD treatment continue to diverge, it will become even more important to distinguish among diagnostic groups when analyzing trends in the prescription of airway medications. Previous papers in this field have usually failed to make this distinction.⁶⁻⁸

We note that despite a 70% increase in the number of β_2 -agonist prescriptions dispensed, the proportion of patients with airway disease who receive these medications has not changed appreciably. This suggests that a larger number of patients are being diagnosed as having airways disease or that patients prescribed β_2 -agonists are taking them more frequently, or both. By contrast, increases in inhaled steroid usage, ipratropium bromide usage, nonsteroidal antiinflammatory drug usage plus decreases in theophylline usage have been accompanied by parallel changes in the percentage of patients with respiratory disease who receive prescriptions for these compounds. This would suggest, but does not prove, that increasing β_2 -agonist sales are largely a consequence of increasing dosage per patient and that the other trends in drug sales are a consequence of more or fewer patients receiving the agent in question.

The seasonal fluctuation in airway prescriptions has not been described previously. However, there have been previous reports of seasonal changes associated with increasing numbers of asthma

exacerbations and emergency room visits, which peak in late September and October in the Northern hemisphere.^{14, 15} The reasons for this phenomenon are not known but speculation includes increasing antigen exposure to fungal spores, pollens, and other airborne agents; increasing exposure to viral illnesses; changes after summertime in airway irritability as a consequence of high pollution counts; or some combination of these. The fall exacerbations may explain a winter increase in prescriptions inasmuch as increased therapy may reflect medical intervention after 1 to 2 months of poorly controlled asthma.

In 1985, the use of theophylline in the United States and Canada was similar.⁸ In that same year, there was more use of oral β_2 -agonist and less use of inhaled corticosteroids in the United States. In the United States from 1977 to 1985 there was an increase in drugs dispensed in the following categories: inhaled β_2 -agonist, oral β_2 -agonist, and sustained-release theophylline preparations. There was a decrease in the use of immediate-release theophylline preparations and combination medications. Inhaled steroids were seldom used and showed virtually no increase from 1981 to 1985. Data since 1985 have not as yet been published. In Australia, for the years 1980 to 1986, there was an increase in β_2 -agonist and sustained-release theophylline prescriptions along with a smaller rate of rise in inhaled steroid prescriptions.⁷ Again, data beyond 1986 are not as yet available in the published literature. Other countries have not reported regional breakdowns. We can only speculate and do not have an adequate explanation for why the maritime region in Canada had a disproportionate increase in airway medication use, particularly during 1989 and 1990. However, the maritime region is relatively small with fewer respondents than other regions. It is possible that the data were skewed by a few "outliers" in the region. Data on the prevalence of asthma in Canada do not suggest marked regional differences up to 1987 although this does not rule out more recent changes.¹⁶

Perhaps the greatest concern from the data presented is the apparent reliance on inhaled β_2 -agonists, usage of which has increased rapidly since 1985. Several studies have demonstrated either tolerance to the bronchodilator response of these agents or a possible increase in hyperresponsiveness with prolonged use of these agents.¹⁷⁻¹⁹ A recent study by Sears et al.¹⁷ suggests that regular scheduled use of inhaled β_2 -agonists may be responsible for increasing symp-

toms of asthma when compared with intermittent as-needed use.¹⁷ Although cause and effect has not been demonstrated, there appears to be an association between high use of these agents and risk of death from asthma.²⁰

Some limitations of our data must be addressed. First, we have dealt with prescriptions dispensed but we cannot be certain of patient compliance with these agents. Nonetheless, we doubt that dramatic changes occurred in patient characteristics during the 5-year interval studied and doubt that this accounts for our observations, including increased prescription rates. Second, we cannot be sure that physicians did not change prescribing habits with respect to the number of doses dispensed per visit and therefore the number of prescriptions recorded. However, we are unaware of any such changes in prescribing habits. Finally, we do not know the accuracy of the diagnoses reported by practicing physicians. However, our review was intended to examine the treatment strategies used by physicians and not the correctness of their diagnoses.

One is struck by the marked increase in airway prescriptions in a 5-year interval. Our study was not designed to determine the factors responsible for such trends, but several hypotheses may be entertained. First, it has been reported that asthma had been underdiagnosed in the recent past.^{21, 22} However, recent lay publicity and attention in the medical literature to rising asthma death rates may have increased the rate of diagnosis. Although we have no direct data to verify this hypothesis, anecdotal observation in large urban areas of Canada suggests that asthma is being diagnosed more readily and earlier, particularly in the pediatric population. The rate of false-positive diagnoses may also be rising. Indirect support for this hypothesis is available from our data: there was a nonsignificant trend toward fewer nonspecific respiratory diagnoses. Second, patients may be receiving more combined drug regimens than previously. Third, increases in total population plus the aging of the population may increase the numbers of patients available for treatment. Fourth, an increase in the number of physicians and a decrease in patient to physician ratio may contribute to increasing numbers of prescriptions. Finally, changes in the provision of medical care and medications could alter prescribing practices. However, government-sponsored universal health care insurance has long been available in Canada, as have drug benefits for the poor and the elderly. These and other

factors to explain increasing airway prescription trends warrant further investigation.

In summary, prescriptions of airway drugs have increased significantly during the past 5 years in Canada and have risen in excess of the population increase. There continues to be a rapid rise in inhaled β_2 -agonist use along with a significant decrease in theophylline prescriptions. The data presented indicate a trend toward inhaled rather than oral medications and a trend toward increasing use of inhaled antiinflammatory medications, although the latter continue to be used less than either inhaled β_2 -agonists or theophylline. Increased inhaled steroid prescriptions for asthma, decreased theophylline prescriptions, preference of inhaled versus oral medication, and increased anticholinergic medication prescriptions for COPD are in keeping with present recommendations for the treatment of obstructive lung disease. The increase in airway medication prescription sales in Canada is consistent with an increase in the number of patients treated or an increase in the severity of disease treated, or both.

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