

# Rates and patterns of chronic obstructive pulmonary disease exacerbations

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**BACKGROUND:** Acute exacerbations of chronic obstructive pulmonary disease (COPD) are believed to be a common occurrence in patients with COPD and are known to be associated with considerable morbidity.

**OBJECTIVE:** To describe the frequency of treated COPD exacerbations in a large population-based cohort.

**SUBJECTS AND METHODS:** A cohort of newly treated patients with COPD was formed from the administrative databases of Saskatchewan Health. The outcome was the occurrence of all moderate or severe exacerbations from 1990 to 1999. Exacerbations were defined in three ways: dispensing of a prescription for a systemic antibiotic; dispensing of both a prescription for an antibiotic and a prescription for an oral corticosteroid on the same day; and requiring a hospitalization with a primary discharge diagnosis of COPD.

**RESULTS:** There were 5645 patients who entered the COPD cohort between 1990 and 1997, of whom 4453 experienced at least one exacerbation requiring treatment during follow-up. The overall rate of acute exacerbations was 1.12/person-year. It was constant across all age groups, and was similar in both men and women (1.13/person-year versus 1.11/person-year, respectively). The rate of exacerbations was highest in the first trimester of therapy for the disease (1.39/person-year) and stabilized thereafter at 1.04 exacerbations/person-year.

**CONCLUSIONS:** The results indicate that in a population-based cohort of patients with COPD, the average rate of exacerbations was 1.12/person-year. Men and women had similar rates of exacerbations.

**Key Words:** *Chronic obstructive pulmonary disease; Pharmacoepidemiology; Rate of exacerbations*

Acute exacerbations of chronic obstructive pulmonary disease (COPD) are known to be associated with considerable morbidity and mortality (1,2), and important deficits in quality of life (3). They are a common cause of hospital admission (4), often after failed initial therapy in the community, and a frequent cause of readmission to hospital (5,6). The following factors are thought to trigger exacerbations of COPD: viral and bacterial infections, inhalation of environmental irritants, discontinuation of medications and changes in diet (7).

Economic studies suggest that the burden of exacerbations of COPD to society is considerable. American data showed that, in 1995, the total direct costs of inpatient and physician services related to the treatment of acute exacerbations of COPD were US\$1.6 billion, of which US\$1.2 billion was spent on individuals aged 65 years or older (8). In 1998, approximately 2% of all

## Taux d'exacerbations de la MPOC et modes de présentation

**HISTORIQUE :** Les exacerbations aiguës de la MPOC (maladie pulmonaire obstructive chronique) seraient fréquentes chez les patients atteints et elles sont associées à une importante morbidité.

**OBJECTIF :** Décrire la fréquence des exacerbations de MPOC traitées au sein d'une importante cohorte basée dans la population.

**SUJETS ET MÉTHODES :** Une cohorte de patients atteints de MPOC nouvellement traités a été formée à partir des bases de données administratives du ministère de la Santé de la Saskatchewan. Le paramètre mesuré était l'occurrence de toutes les exacerbations modérées ou sévères entre 1990 et 1999. Les exacerbations se définissaient de trois façons : prescription d'antibiotiques systémiques, prescription d'antibiotiques et de corticostéroïdes oraux le même jour et hospitalisation nécessaire, avec MPOC pour diagnostic principal au moment du congé.

**RÉSULTATS :** Entre 1990 et 1997, 5 645 patients ont été inclus dans la cohorte MPOC; 4 453 d'entre eux ont présenté au moins une exacerbation ayant nécessité un traitement durant le suivi. Le taux global d'exacerbations aiguës a été de 1,12 par année-personne. Ce taux est resté constant parmi tous les groupes d'âge et a été semblable chez les hommes et les femmes (1,13/année-personne versus 1,11/année-personne, respectivement). Le taux d'exacerbations a été le plus élevé au cours du premier trimestre de traitement de la maladie (1,39/année-personne) et s'est stabilisé par la suite à 1,04 exacerbations par année-personne.

**CONCLUSIONS :** Selon les résultats, dans une population de patients atteints de MPOC basés dans la population, le taux moyen d'exacerbations a été de 1,12 par année-personne, les hommes et les femmes ayant présenté un taux semblable d'exacerbations.

hospitalizations were attributed to COPD, and in 7% of all hospitalizations, COPD was listed as a contributing cause (9). The frequency of exacerbations among patients with COPD has been reported principally for patients from tertiary referral centres or for patients participating in clinical trials.

The expression 'frequent exacerbations' is sometimes used to endorse the use of certain medications in COPD patients, although it is not defined (10). The lack of a standard definition of acute exacerbation of COPD or of a severity grading system contributes to the difficulty in assessing the real impact of these episodes on patients with COPD and on the health care system. In 1999, an international working group proposed the following definition of a COPD exacerbation: "a sustained worsening of a patient's condition, from the stable state and beyond normal day-to-day variations, that is acute in onset and

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necessitates a change in regular medication in a patient with underlying COPD" (11). Three types of COPD exacerbation based on health care use were described (11):

- mild exacerbations, when there is an increased need for medication that is managed in the patient's usual environment;
- moderate, when the patient has an increased need for medication and seeks additional medical assistance; and
- severe, when the patient or caregiver recognizes obvious and/or rapid deterioration in the condition, requiring hospitalization.

In the present paper, we provide population-based data on the frequency of treated exacerbations in a large cohort of patients with COPD.

## METHODS

### Source population

The primary source of data was a COPD cohort that was formed from the computerized databases of Saskatchewan Health. These databases were developed to support the universal health insurance program provided to all residents of the province since 1975. These databases have been described extensively elsewhere (12). Dispensed prescriptions, use of health care services and vital status information are all recorded, and the information can be linked for each individual through his or her Health Service Number, a lifetime number issued at registration that uniquely identifies each person (12).

### COPD cohort

The COPD cohort was formed by selecting individuals aged 55 years or older, who had received at least three prescriptions for beta<sub>2</sub>-agonists, ipratropium bromide or xanthines in any one-year period on two different dates, between January 1, 1990, and December 31, 1997. Entry into the cohort was the date of the third prescription. To include only subjects with new onset of therapy for COPD, subjects who had used beta<sub>2</sub>-agonists, ipratropium bromide, xanthines, asthma medications (principally antileukotrienes and cromones), nasal corticosteroids or inhaled corticosteroids during the five years before these three prescriptions were excluded. Patients were not required to have a diagnosis of COPD and were not excluded if the diagnosis of asthma appeared in the hospitalization database.

All patients in the cohort were followed from cohort entry to the earliest of the following dates: December 31, 1999, emigration from the province or death.

### Outcome

The outcome was the occurrence of exacerbations during follow-up. Three types of exacerbations were defined:

- type 1, if there was a dispensing of a prescription for a systemic antibiotic (aminoglycosides, cephalosporins, macrolides, penicillins, fluoroquinolones, tetracycline derivatives or cotrimoxazole);
- type 2, if there was a dispensing of a prescription for a systemic antibiotic and an oral corticosteroid on the same day; and

- type 3, if there was a hospitalization with a primary discharge diagnosis of COPD (*International Classification of Diseases, 9th Revision* [13] codes 490-492 and 496).

For certain analyses, if an exacerbation occurred within 30 days of a previous exacerbation, it was considered a relapse and not a new exacerbation.

The prescription drug database of the province of Saskatchewan is submitted to numerous validation checks, and pharmacies that collect information undergo regular audits (12). Moreover, drug utilization reviews and program evaluations are ongoing within the drug plan, which also serves to validate the system.

### Statistical analysis

Crude rates of COPD exacerbations were computed by dividing the number of exacerbations by the person-time of follow-up. These rates were stratified by sex and time-dependent age (ie, the age at which an exacerbation occurred). To assess whether the burden of COPD changed over time, the rate of exacerbations that occurred in each calendar year was determined (ie, from 1990 to 1999).

These analyses were repeated for the rate of the first exacerbation. This rate was also computed over the time from onset of therapy (cohort entry) using the actuarial method. There were 1192 patients who had had an exacerbation before cohort entry excluded from this analysis (ie, subjects whose initial presentation was for the treatment of an exacerbation [including hospitalization] before having been dispensed three prescriptions for bronchodilators in any one-year period).

In all instances, it was assumed that the number of exacerbations followed a Poisson distribution, and that rates were constant within each stratum. Ninety-five per cent CIs were computed for all rates. All analyses were performed using SAS software (Version 8, SAS Institute, USA).

## RESULTS

There were 5648 patients who entered the COPD cohort between 1990 and 1997. Of these, three patients were excluded because they had no follow-up. Of the remaining 5645 patients, 53.9% were men and mean age was 73.5 years. The distribution of the COPD cohort by age groups at cohort entry, by respiratory drugs that defined cohort entry and by prescriptions for antibiotics and/or oral corticosteroids during follow-up is shown in Table 1.

A total of 34,405 possible exacerbations were identified. After exclusion of 10,373 exacerbations which occurred within 30 days of a previous exacerbation and were considered to be relapses, there were 24,032 exacerbations that occurred in 4453 patients. The overall rate of COPD exacerbation during the 10-year follow-up period was 1.12 exacerbations/person-year. Men and women had similar rates of exacerbations (1.13 versus 1.11 exacerbations/person-year, respectively), and the rate was constant across all age groups (Table 2). Table 3 shows that type 1 exacerbations (treated with antibiotics alone and not hospitalized, relapses included) accounted for most of the exacerbations. The rate of type 3 exacerbations (hospitalizations, with relapses included) was almost twice as high in men as in women (0.128/person-year versus 0.074/person-year, respectively). In addition, the rate of a first exacerbation leading to hospitalization (type 3) was also higher in men than

women (0.033 versus 0.017 exacerbations/person-year, respectively). Figure 1 shows the hazard curve for the first exacerbation of COPD. The risk for the first exacerbation was higher during the first year of follow-up and then decreased. That is, approximately nine of 10 patients will have their first exacerbation during their first year of bronchodilator treatment for COPD. For the patients who go into their second year of treatment without having had an exacerbation, their probability of having their first exacerbation in the coming year was 50%. In

**TABLE 1**  
**Demographic characteristics of the chronic obstructive pulmonary disease cohort, 1990-1999**

Cohort size, n	5645
Mean duration of follow-up, years	3.7
Age at entry in years, n (%)	
55 to 64 years	1048 (18.6)
65 to 74 years	1939 (34.3)
75 to 84 years	1814 (32.1)
≥85 years	844 (15.0)
Mean age (SD)	73.5 (9.6)
Age range, years	55 to 106
Male sex, n (%)	3041 (53.9)
Bronchodilators defining cohort entry (%)*	
Inhaled beta <sub>2</sub> -agonists	73.8
Oral beta <sub>2</sub> -agonists	10.8
Xanthines	25.3
Inhaled ipratropium bromide	32.3
Ipratropium bromide/salbutamol	2.5
Subjects with exacerbations before cohort entry, n (%)	1192 (21.1)
Total number of prescriptions dispensed during follow-up	
Oral corticosteroids	14,288
Antibiotics	31,865
Subjects with at least one prescription during follow-up, n	
Oral corticosteroids alone	164
Antibiotics alone	2825
Concomitant antibiotics and oral corticosteroids	1783
None of the above	873

\*Percentages add up to over 100 because subjects could have used up to three different drugs at cohort entry

**TABLE 2**  
**Rate of exacerbations (any type) by age group and by sex**

	Age group				Total
	55 to 64 years	65 to 74 years	75 to 84 years	≥85 years	
<b>Women</b>					
Events*	1858	4092	3640	1838	11,428
Person-years†	1679.36	3639.15	3384.13	1550.81	10,253.45
Rate	1.11	1.12	1.08	1.19	1.12
95% CI	1.06 to 1.16	1.09 to 1.16	1.04 to 1.11	1.13 to 1.24	1.09 to 1.14
<b>Men</b>					
Events*	2077	4761	4150	1616	12,604
Person-years†	1837.34	4298.64	3732.41	1283.30	11,151.69
Rate	1.13	1.11	1.11	1.26	1.13
95% CI	1.08 to 1.18	1.08 to 1.14	1.08 to 1.15	1.20 to 1.32	1.11 to 1.15
<b>All</b>					
Events*	3935	8853	7790	3454	24,032
Person-years†	3516.69	7937.80	7116.55	2834.11	21,405.14
Rate	1.12	1.12	1.09	1.22	1.12
95% CI	1.08 to 1.15	1.09 to 1.14	1.07 to 1.12	1.18 to 1.26	1.11 to 1.14

\*Excluding relapses; †Excluding 30 days after each exacerbation

general, the rate of COPD exacerbations decreased over calendar time from 1.38, in 1990, to 1.03 exacerbations/person-year, in 1999 (Figure 2). Figure 3 shows that in the first three months from onset of treatment of COPD (cohort entry), the rate was 1.39 exacerbations/person-year; in the 12th month, it was 1.20/person-year, and then stabilized to approximately 1.04 exacerbations/person-year, as the duration of the disease increased.

## DISCUSSION

The overall rate of acute exacerbations of COPD in our population-based cohort was 1.12/person-year, and the mean rate of exacerbations requiring hospitalization was 0.102/person-year. Several studies have reported rates of COPD exacerbations. The different study designs, the lack of a standard definition of an exacerbation and differences in the source populations make comparison of the rates reported from different studies difficult. Anthonisen et al (14), in a trial designed to assess the role of antibiotics in the treatment of exacerbations in patients with stable COPD, reported an average of 1.3±1.5 exacerbations/patient/year. In their study, exacerbations were reported as a change in symptoms by patients. Seemungal et al (3) followed a cohort of 101 patients with moderate to severe COPD for 2.5 years (east London COPD cohort). These patients, recruited from tertiary referral centres, experienced 2.7 exacerbations/patient/year according to their symptom and peak flow diaries (3). Of note, only approximately 50% of all exacerbations had been reported to the clinical team, although patients had been instructed to do so. Therefore, many exacerbations remained untreated and would not be recognized in a prescription drug database such as ours (15).

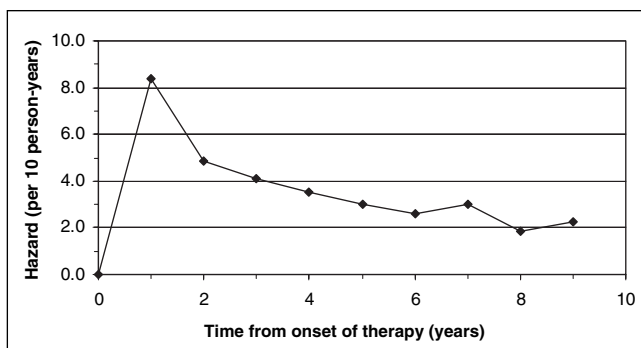
Another recent cohort study (16), in which a total of 81 patients with moderate to severe COPD were followed for 56 months, found a mean rate of 2.1 exacerbations/patient/year. In this study, exacerbations were either self-reported or reported by the physician at each monthly visit.

Among patients with COPD included in the Inhaled Steroids in Obstructive Lung Disease in Europe (ISOLDE) trial of fluticasone propionate (17), exacerbations were defined as "chest problems requiring treatment with antibiotics

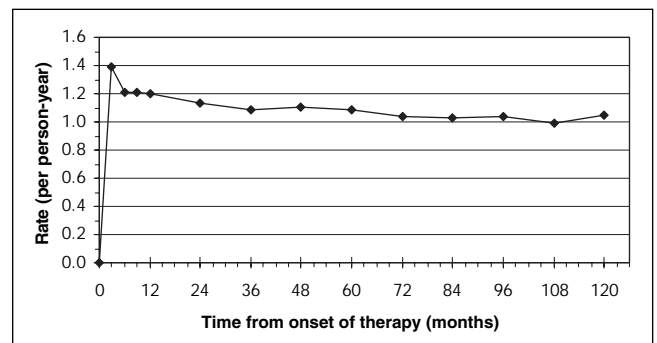
**TABLE 3**  
Rates of exacerbations per person-year by type and sex

	Exacerbations			First exacerbation*		
	Women (n=2604)	Men (n=3041)	Total (n=5645)	Women (n=2604)	Men (n=3041)	Total (n=5645)
Any type <sup>†</sup>	11,428	12,604	24,032	1662	1885	3547
Person-years <sup>‡</sup>	10,253.45	11,151.69	21,405.14	2910.68	3378.19	6288.87
Rate	1.11	1.13	1.12	0.57	0.56	0.56
95% CI	1.09 to 1.14	1.11 to 1.15	1.11 to 1.14	0.54 to 0.60	0.53 to 0.58	0.55 to 0.58
Type 1 <sup>§</sup>	14,830	16,701	31,531	1612	1775	3387
Rate	1.33	1.37	1.35	0.55	0.53	0.54
Type 2 <sup>  </sup>	567	873	1440	47	55	102
Rate	0.051	0.072	0.062	0.016	0.016	0.016
Type 3 <sup>**</sup>	825	1554	2379	50	110	160
Rate	0.074	0.128	0.102	0.017	0.033	0.025

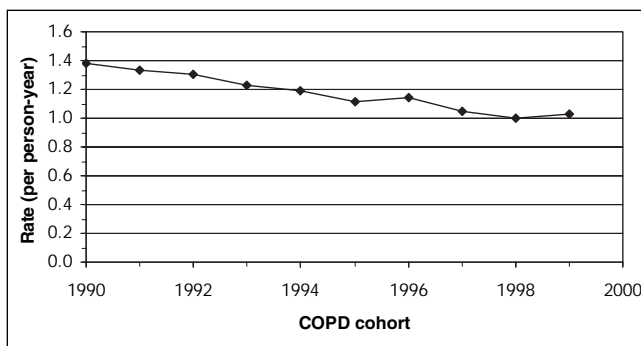
\*Patients that had had at least one exacerbation before cohort entry (n=1192) were excluded; <sup>†</sup>Includes any type of exacerbation (type 1, type 2 or type 3) but excludes 10,373 relapses (ie, any event occurring within 30 days of a previous one); <sup>‡</sup>A period of 30 days after each exacerbation was excluded to account for the relapses; <sup>§</sup>Type 1, a prescription for a systemic antibiotic, relapses were not excluded; <sup>||</sup>Type 2, same day prescription for an oral corticosteroid and a systemic antibiotic, relapses were not excluded; <sup>\*\*</sup>Type 3, hospitalization with a discharge diagnosis of chronic obstructive pulmonary disease, relapses were not excluded



**Figure 1)** Hazard curve for the first exacerbation of chronic obstructive pulmonary disease



**Figure 3)** Rate of exacerbations by time from onset of therapy



**Figure 2)** Rate of exacerbations per calendar time. COPD Chronic obstructive pulmonary disease

and/or oral corticosteroids” and were self-reported by the patient at three-month intervals. In this study, the median exacerbation rate in the combined treatment groups was significantly lower in the patients with mild COPD (0.93 exacerbations/patient/year) than in those with moderate to severe disease (1.64 exacerbations/patient/year,  $P < 0.001$ ). Moreover, the frequency of exacerbations remained unchanged throughout the three years of the study. Similarly, in patients in both the present study and in the east London COPD cohort, the frequency of exacerbations did not increase over the duration of

follow-up (18). We observed a higher rate of exacerbations in the first year of follow-up. This may relate to an initial period of stabilization required before regular therapy, follow-up and avoidance of triggers were instituted among our subjects who were identified as close as possible to the time of the initiation of therapy.

The differences in populations studied and in the way of determining exacerbations likely explain the somewhat lower rates observed among patients with COPD drawn from the whole population, among whom exacerbations were identified only if they led to a change in therapy or hospitalization. The definitions of an exacerbation that we used correspond to the definitions of moderate and severe COPD exacerbations proposed by an international working group (11). No attempt was made to identify milder exacerbations because this would unlikely be reliable when using only computerized records. For moderate exacerbations, we required that a subject be dispensed an antibiotic with or without a concomitant prescription for oral corticosteroids. We did not use the dispensing of a prescription for oral corticosteroids alone in defining exacerbations because of the difficulty in distinguishing prescriptions for a burst of corticosteroids from prescriptions for regular maintenance therapy with these medications. In addition, we were concerned that oral corticosteroids might be prescribed differentially according to sex or the presence of comorbid conditions such as diabetes. The frequency of moderate exacerbations may

have been overestimated if the antibiotics dispensed were prescribed for reasons other than a COPD exacerbation. As discussed previously, our definition of an exacerbation required a patient to obtain a prescription from a physician, and we, therefore, will not have detected untreated exacerbations. However, the definitions used assure that the exacerbations included are clinically relevant and associated with morbidity and costs.

In the present study, we were interested in assessing the effect of sex and age on the risk of acute exacerbations in a population-based cohort of patients with COPD. The effect of sex in COPD has been disputed by several authors. COPD has historically occurred more frequently in men, which has been attributed to sex-related differences in smoking patterns worldwide. More recently, men were shown to report more respiratory symptoms than women, even after adjusting for smoking (19). Nevertheless, a few studies (20-22) on sex-related differences and lung function have suggested that smoking is more detrimental for women. In our study, the rate of exacerbations did not differ appreciably between the sexes, although severe exacerbations requiring hospitalization were more common in men. To explain why exacerbations might lead more frequently to hospitalization in men, we might speculate that the disease was, on average, more severe in men during the period of the study but this is difficult to verify without measures of lung function.

Our definition of a severe exacerbation requiring a primary discharge diagnosis of COPD assumes an accurate recording of the discharge diagnosis. Rawson and Malcolm (23) studied the validity of the recording of several conditions, including COPD, in the Saskatchewan hospital database and concluded that, for COPD, there was exact agreement between computerized hospital data and the discharge diagnosis in medical charts in 94.2% of the cases.

A strength of our study was the use of a population-based cohort of patients with COPD, which provides a more representative picture of what happens in the community, rather than among participants in clinical trials or among patients followed in specialized centres. However, it might be argued whether the patients in the present study truly have COPD given the absence of clinical information such as lung function and smoking history. We believe that limiting our study to subjects with more than casual use of bronchodilators (we required the dispensing of at least three bronchodilator prescriptions over a one-year period) starting at the age of 55 years or older for most patients assures that the great majority of subjects has

recognized COPD. While asthma may also appear after 55 years of age, this remains unusual (24). Furthermore, 43% of patients in the present cohort had a primary or secondary discharge diagnosis of COPD at some point in time, supporting the likelihood that the subjects in the present cohort did indeed suffer from COPD (25). The selection of patients starting regular therapy (incident cases) assures us that all treated patients were included, not just those patients who have survived the initial stages of the disease.

## CONCLUSIONS

Our findings suggest that in a population-based cohort of patients with COPD, approximately 79% of subjects will experience moderate or severe exacerbations during an average period of 3.7 years of follow-up. The average rate in the present population-based study was 1.12 exacerbations/person-year. The rate of severe exacerbations requiring hospitalization was 12.8 exacerbations/100 person-years for men and 7.4 exacerbations/100 person-years for women. From a public health perspective, this is an important finding because it provides an indication of how resources will be used for patients with COPD.

COPD has been rising in prevalence (26), and this trend is expected to continue. It has been estimated that by the year 2020, COPD will be the fifth highest cause of burden of disease worldwide, and will rank third among the most common causes of death (27). The frequency of exacerbations has been shown to be related to long-term decline in lung function in patients with moderate to severe disease (28). Therefore, efforts should be made to develop new strategies to encourage smoking cessation and new ways to stabilize the disease.

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**DISCLAIMER:** This study was based on de-identified data provided by the Saskatchewan Department of Health. The interpretation and conclusions contained herein do not necessarily represent those of the government of Saskatchewan or the Saskatchewan Department of Health.

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